Viral Hepatitis in Non-Hepatic Solid Organ Transplant Recipients

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1. Introduction

Hepatotropic viral infections are frequent in solid organ allograft recipients and may be caused by a number of different viruses. Of these, the most important infectious agents are hepatitis B virus (HBV), with and without Hepatitis D virus (HDV), and hepatitis C virus (HCV). In addition, Hepatitis E virus (HEV) is emerging as an increasing cause of chronic hepatitis and cirrhosis in solid organ transplant recipients in industrialized countries (1–4). This chapter will focus primarily on the epidemiology, transmission, clinical presentation and management of the primary hepatitis viruses: HBV + HDV, HCV, and HEV, following solid organ transplantation.

2. Risk factors for the development of viral hepatitis post-transplant

The risk of viral hepatitis following solid organ transplant varies over time and is closely related to modifications in immunosuppression. There are three time frames, influenced by surgical factors, the level of immunosuppression, and environmental exposures, during which infections of specific types most frequently occur. These include the first month; the second through sixth months, and the late posttransplant period (beyond the sixth month)(5). With few exceptions, most viral hepatitis occurs during the middle to late periods following solid organ transplant, often due to reactivation within a recipient. However, both donor and recipient-derived infections can present early in the posttransplant period.

- **Epidemiologic exposures**

Epidemiologic exposures, including donor–derived and recipient–derived transmission, play an integral role in the timing and severity of viral hepatitis. Mandatory reporting of transplantation–associated infections has increased awareness of donor–associated infection, and all transplant centers perform screening for common types of infections in order to reduce donor transmission. In addition, pre–transplantation screening of recipients for common causes of viral hepatitis helps to prevent reactivation posttransplant. Finally, nosocomial transmission via blood transfusions or hemodialysis has been reported rarely in solid–organ transplant recipients.

- **Donor-derived infections and screening recommendations**

Transplanted organs can facilitate transmission of hepatitis from organ donors. Most often, these infections are latent in the transplanted tissues, although active donor infection (e.g. viremia) may also cause viral hepatitis. HBV, HCV and CMV are the most commonly reported hepatotropic viruses transmitted during solid organ transplant, though the incidence has decreased over the last decade due to improvements in screening and vaccination practices. Recently, HEV infection has been added as an emergent cause of chronic hepatitis in organ transplantation(4).

The screening of transplant donors for infections is limited by the available technology and by the short period during which organs from deceased donors can be used. Currently, the evaluation of donors for viral hepatitis relies on an epidemiologic history for common modes of transmission (e.g. intravenous drug use) and serologic testing for antibodies to common hepatotropic viruses such as HBV (hepatitis B surface antigen (HBsAg), antibodies against hepatitis B surface antigen (anti–HBs)), HCV, CMV, EBV, and
VZV. In certain situations (e.g. history of intravenous drug use or known exposure to a hepatotropic virus) special testing using nucleic acid assays may be performed. Since seroconversion may not occur during acute infections and the sensitivity of these tests is not 100%, some active infections may remain undetected.

The ‘window period’ for a pathogen is the interval of time between infection by a pathogen and detection of that pathogen by a specific testing method. Nucleic acid testing (NAT) shortens the window period for HIV, HCV and HBV relative to serology and therefore may decrease the risk of transmitting disease from a serologically negative donor(6). For example, NAT for HBV can detect infections 21.8–36 days earlier when compared to standard serologic assays(7). Although routine NAT of potential organ donors may seem logical, it has not been rigorously studied. NAT is costly and may be logistically challenging. Most importantly, false–positive results may lead to unnecessary loss of uninfected organs (6). A 2008 survey of the 58 U.S. organ procurement organizations (OPOs) documented that 47% performed NAT on all potential donors(8). Another 28% performed NAT on a subset of donors, usually based on the identification of behaviors thought to increase the risk of infection. OPOs tested for different pathogens using different assays, platforms and confirmatory algorithms with varied turn–around times and testing volumes. Some OPOs also noted geographic challenges in NAT accessibility, thus contributing to the varied practices observed. The turnaround time for NAT is also highly variable, ranging from 12–36 hours. Time is critical in organ donation, since delays in organ recovery and prolongation of cold–ischemic time affects organ utilization and posttransplant function. Current guidelines states that there is insufficient evidence to recommend routine NAT for HIV, HCV and HBV as the standard of care for screening all potential organ donors (level III evidence), but should be considered to reduce the risk of disease transmission and potentially increase organ utilization in increased–risk donors (level II evidence) (6).

Organs from donors with specified known viral hepatitis can be considered for specific recipients. For example, donors infected with HBV who are positive for IgG antibodies against hepatitis B core antigen (anti–Hbc) can be used for some recipients who have been vaccinated, who were previously infected with HBV, or under antiviral prophylaxis provided this is available (9–11). The use of organs infected with HCV can generally be used in other HCV–infected recipients, although this practice remains somewhat controversial(12).

Recipient-derived infections and screening recommendations

Active viral hepatitis in solid organ transplant recipients is common and efforts should be made to detect and eradicate the infection prior to transplantation. Prior to the era of antiviral prophylaxis (late 1980s), 80% of patients experienced HBV reinfection after liver transplantation(13). However, with the advent of hepatitis B immunoglobulin (HBIG) and the first oral antiviral agent for HBV, lamivudine, in the mid–late 1990s, graft reinfection has become the exception rather than the rule (14, 15). For HCV, liver disease can progress with increased immunosuppression, with outcomes determined by the viral strain and the response to antiviral therapy(16, 17).

Similar to donor screening, recipient screening is based on the epidemiologic history and serologic testing of the recipient. At our institution, all potential solid organ transplant recipients are screened with serologic testing for antibodies to CMV, EBV, HSV, VZV, HBV (HBsAg, anti–HBs), and HCV. In addition, special serologic testing using nucleic acid assays based on risk factors and recent exposures is performed (e.g. HBV or HCV viral load).
Nosocomial-derived infections

Although rare, patients waiting for organ transplantation may become infected with hepatitis viruses via blood transfusion or hemodialysis. A 2010 study on HBV in donated blood suggests that the risk is about 1 in every 350,000 units or less (18). The transmission of HCV via transfusion currently stands at about a rate of 1 in 2 million units (19).

In the hemodialysis setting for those awaiting renal transplantation, cross-contamination to patients via environmental surfaces, supplies, equipment, multiple-dose medication vials and staff members is mainly responsible for both HBV and HCV transmission. The incidence and prevalence of HBV in hemodialysis centers have dropped markedly as a result of isolation strategies for HBsAg positive patients, the implementation of infection control measures and the introduction of HBV vaccine (20). The incidence and prevalence of HCV infection among hemodialysis patients remain higher than the corresponding general population.

Role of immunosuppression

Several immunosuppressant protocols are associated with an increased risk of viral activation. For example, induction therapy with T-lymphocyte-depleting antibodies such as the CD25-receptor antibodies (Interleukin-2 (IL-2) receptor antagonists, basiliximab or daclizumab) are associated with increased reactivation of HHV–6 (21). In addition, alemtuzumab (Campath–1H, anti–CD52 monoclonal antibody) induction has been associated with rapidly progressive HCV recurrence, mostly in hepatic transplantation, in addition to an increased risk of viral infections posttransplant compared to controls (22, 23). Finally, OKT3, a murine-depleting monoclonal anti–CD3 antibody is currently used in the setting of steroid-resistant rejection and has been associated with a higher risk of development post–transplant lymphoproliferative disorder (PTLD) and HCV recurrence or progression (24).

3. Common causes of viral hepatitis in solid organ transplant recipients

In addition to the primary viral hepatitis infections—HBV (+/− HDV), HCV and HEV— a variety of other systemic viral infections, such as the herpesviruses, CMV, EBV, and VZV can have toxic effects on the liver in the posttransplant recipient. This chapter will focus on the primary viral hepatitis infections. The issues related to viral hepatitis in non–hepatic organ transplant recipients are complex, and the approach to management is highly dependent on the organ transplanted.

Hepatitis B in Non-Hepatic Solid Organ Patients

HBV is a DNA virus that is transmitted parenterally, sexually, and perinatally, and leads to chronic infection in 1.25 million persons in the United States and 350 to 400 million persons worldwide. HBV infection accounts annually for 4000 to 5500 deaths in the United States and 1 million deaths worldwide from cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (25). Chronic HBV infection can be divided into several phases (26). Initially, there is an immune tolerance phase, in which HBV replicates actively but host immune responses to the virus are minimal. After 20–30 years, an immune clearance phase occurs in which HBV-specific cellular immunity becomes active, leading to inflammation and damage of hepatocytes. Levels of HBV viremia decrease drastically after this phase, and HBV infection then becomes residual. Nevertheless, the infection may reactivate in some patients (26). HBV replication correlates with the presence of hepatitis Be antigen (HBeAg), although eAg negative disease at lower viral loads can cause
chronic hepatitis and fibrosis. Prolonged HBeAg sero-positivity or high HBV viral load is associated with prolonged liver injuries and a higher risk of HCC (27). The immune responses during HBV infection are responsible to the injuries in the liver (28).

**Epidemiology & specific risk factors**

With current infection control practices and the institution of widespread vaccination, the prevalence of chronic HBV in patients on hemodialysis has declined in developed countries and ranges between 0% and 7%(29). In addition, acquisition of HBV on dialysis is now uncommon. In contrast, the epidemiology of HBV among dialysis patients in the less–developed world is not well known. There are scattered reports, typically single–center surveys, with rates of chronic HBsAg carriers ranging between 2% and 20%(30–33). The higher HBV infection rates within dialysis units in the developing world can be attributed to several factors, such as the higher background prevalence of HBV in the general population, difficulties following infection control strategies against HBV such as “standard” precautions, vaccination against HBV, and blood screening. Many of these deficiencies are often attributable, at least in part, to a lack of financial and other resources(34). Iatrogenic transmission of HBV has also been reported after transplantation of two stored vessel conduits from hepatitis–seropositive donors into seronegative kidney transplant recipients(35). The prevalence of chronic HBV in other nonhepatic transplant candidates has not been well studied, but likely mirrors the population prevalence(36). Interestingly, in cardiac allograft recipients, HBV contamination can occur after transplantation and has been related to nosocomial infection associated with the use of cardiac myotomes for myocardial biopsies. On the other hand, nosocomial transmission of HBV via blood transfusion is rare given the systematic screening of blood products for HBV, but, nevertheless, HBV is still the most frequent blood–borne infection (1/700,000)(37).

Chronic HBV infection (HBsAg–positive) has been associated with an increased risk of death in renal transplant patients and is attributed to both progressive HBV–related disease as well as an increased risk of septic events (38). Increased mortality, if it occurs, is usually seen >10 years following renal transplantation. Contradictory results concerning the long–term outcomes of HBV infection in heart transplant recipients have been reported. Some authors have described poor outcomes, with cirrhosis occurring in more than 55% of patients within the first decade after transplantation, and 17% of patients dying of liver failure(36). Others have reported little impact on short– or long–term survival (39). However, more recent studies in renal and cardiac transplantation have demonstrated excellent outcomes in HBsAg–positive patients managed with nucleos(t)ide analogue therapy(40–43).

In nonhepatic SOT recipients with markers of past HBV infection (HBsAg–negative; anti–HBe positive), there is a low risk (<5%) of HBV reactivation(44). Although uncommon, when present, reactivation has been associated with rapid progression to cirrhosis and death (45). Thus, prevention by prophylaxis or early diagnosis and treatment before clinical disease are essential.

HBV uninfected, nonimmune, patients undergoing SOT may acquire donor derived HBV. The HBsAg–positive donor carries a high risk of transmission to recipients although satisfactory outcomes have been described with prophylaxis (see prevention/prophylaxis). The risk of HBV transmission from an anti–HBe–positive nonhepatic donor is significantly lower (<5%) than that of hepatic donors. Organs from anti–HBe–positive donors can be safely used with informed consent and appropriate strategies to prevent transmission (46).

**Diagnosis**

The diagnosis of HBV in nonhepatic SOT relies on the same serological and nucleic acid assays used in the nontransplant population(26). Liver biopsy should be considered in the evaluation of older renal...
transplant candidates with HBsAg because it is difficult, on clinical grounds alone, to estimate the severity of liver disease in uremic patients (34). Administration of desmopressin acetate (DDAVP) at the time of biopsy should be considered to lessen the risk of bleeding caused by platelet dysfunction. A decision concerning transplant candidacy in HBsAg–positive patients should be based on both liver histology and evaluation of HBV replication by serum markers (i.e., HBeAg and HBV DNA). The absence of serum markers of replication before transplantation, however, does not preclude reactivation of HBV posttransplant and all patients should receive HBV prophylaxis (see Prophylaxis/Prevention).

**Treatment**

Non–hepatic SOT candidates with chronic HBV should be evaluated to determine the need for therapy prior to transplantation. If active replication is present (i.e., positive HBV DNA or HBeAg), antiviral therapy should be started to slow the progression of liver disease and should be based on published guidelines for the treatment of HBV(47, 48). If the initial histology shows more advanced fibrotic changes, a comprehensive evaluation should attempt to determine the likelihood of progression to decompensated cirrhosis. Although conventional wisdom has been that the presence of cirrhosis is an absolute contraindication to isolated non–hepatic SOT, an argument can be made that with effective antiviral therapy it is possible to abort progression of liver disease and presumably prevent hepatic decompensation post–transplant (34).

Although antiviral therapy is not generally recommended for acute HBV in immunocompetent individuals given the extremely high (>85%) rate of spontaneous resolution, treatment of acute HBV is appropriate and essential in immunosuppressed individuals following transplant (49). For reactivation of HBV, treatment with a potent nucleos(t)ide analogue, adjusted for renal function as needed, is preferred to limit the potential for future resistance. IFN–based therapy should be avoided as it is generally poorly tolerated in those with comorbid medical conditions, can lead to organ rejection, and is associated with a low rate of response in immunocompromised hosts.

As discussed previously, nucleos(t)ide analogues like ETV or TDF are recommended in the general population for the treatment of chronic HBV infection. They are more potent and have a higher genetic barrier than LAM or ADF. However, while the risk of resistance to ETV is extremely low in treatment–naive patients, it may be as high as 50% at five years in LAM–resistant patients. TDF is more effective than ADF in the non–renal transplant population, is effective in LAM–resistant patients and does not lead to resistance after five years of treatment (50, 51). TDF has a much lower renal toxicity than ADF and should be preferred in kidney transplant recipients.

**Prevention/prophylaxis**

HBV uninfected, nonhepatic SOT candidates who are nonimmune should be vaccinated for HBV as early in the course of their disease as possible (46). However, vaccine immunogenicity is low in dialyzed patients (around 70%) and even lower in renal transplant recipients (30%) as compared to 90% in the general population (52). Additionally, seroconversion rates decrease with declining renal function (53). When the standard protocol is ineffective, the use of intensified protocols or intradermal injections can reinforce immunogenicity in hemodialyzed patients (54, 55). Finally, booster vaccinations can play an important role in improving immunogenicity, even in the absence of response to primary immunization (56). There are limited data with regard to the efficacy of HBV vaccination in heart and lung transplant candidates; however small series suggest seroconversion rates of 45%–53% (57, 58).

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that all HBsAg–positive kidney transplant candidates and recipients receive prophylaxis with TDF, ETV or LAM to prevent
reactivation; however, TDF and ETV are preferable to LAM to minimize the development of drug resistance (59). Antiviral therapy should be continued indefinitely posttransplant.

In those with markers of past HBV infection (anti-HBc-positive), there is a low risk (<5%) of HBV reactivation(45). Either antiviral prophylaxis or regular serologic monitoring should be employed to limit the risk associated with HBV reactivation(46). If nucleos(t)ide analogues are not used, recipients should undergo testing for HBsAg, HBV DNA and ALT every 1–3 months with antivirals initiated if HBsAg becomes positive or if HBV DNA rises.

**Anti-HBc positive donors**

Recipients of an organ from a HBsAg positive donor, regardless of immune status, should receive a nucleos(t)ide analogue indefinitely(60). In recipients of an organ from an anti-HBc positive donor, the risk of transmission is essentially eliminated if the recipient is immune and no further prophylaxis is needed (46). In HBV nonimmune recipients of an anti-HBc positive organ, prophylaxis with LAM (or other antiviral therapy) should be initiated. An assessment of HBV DNA in the donor may be used to further guide prophylaxis. If the donor HBV DNA is positive or unknown, prophylaxis should be continued with LAM or other prophylaxis for at least 12 months (Chung, Feng et al. 2001; Levitsky and Doucette 2009). If the donor is HBV DNA is negative, prophylaxis can be discontinued, but routine monitoring should continue with transaminases, HBsAg and HBV DNA every 3 to 6 months(46).

**Hepatitis C in Non-Hepatic Organ Transplant Patients**

Hepatitis C Virus (HCV) affects more than 4 million people in the United States and more than 170 million people globally(61). The institution of blood-screening measures in developed countries has decreased the risk of transfusion–associated hepatitis to a negligible level, but new cases continue to occur mainly as a result of injection–drug use and, to a lesser degree, through other means of percutaneous or mucous–membrane exposure. Progression to chronic liver disease occurs in the majority of HCV-infected persons.

HCV is an RNA virus that belongs to the flaviviridae family, hepaciviridae genius; the most closely related flaviviruses viruses are hepatitis G virus, yellow fever virus, and dengue virus(62). The natural targets of HCV are hepatocytes and, possibly, B lymphocytes (63, 64). Viral replication is extremely robust, and it is estimated that more than 10 trillion virion particles are produced per day, even in the chronic phase of infection(65). Replication occurs through an RNA–dependent RNA polymerase that lacks a “proofreading” function, which results in the rapid evolution of diverse but related virions within an infected person and presents a major challenge with respect to immune–mediated control of HCV(61). Six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular relatedness. In the United States and Western Europe genotypes 1a and 1b are most common, followed by genotypes 2 and 3. The other genotypes are common in other areas, such as Egypt in the case of genotype 4, South Africa in the case of genotype 5, and Southeast Asia in the case of genotype 6. Knowledge of the genotype is important because it has predictive value in terms of the response to antiviral therapy, with better responses associated with genotypes 2 and 3 than with genotype 1 and 4(66). That said, newer agents (protease, replicon, polymerase inhibitors) have increased genotype 1 response rates to that of non–genotype 1 infections.

**Epidemiology & specific risk factors**

The prevalence of HCV infection in candidates for nonhepatic SOT varies by organ group. HCV infection is more frequent in renal transplant recipients and dialysis patients than in the general population and has a
significant impact on the survival of these patients (67). The annual incidence of HCV infection in hemodialysis ranges from 0% to 2.4% with a prevalence ranging between 10% and 65% according to the geographical zone(68). HCV transmission is predominantly related to failure to comply with universal hygiene rules; compliance with universal hygiene rules has eliminated nosocomial transmission of HCV, and transmission by dialysis equipment per se is today anecdotal(69, 70). Isolation of HCV–infected patients or the use of dedicated dialysis machines are not recommended(71). In heart transplant patients, the prevalence of HCV – mainly transmitted by transfusion or heart donation – is about 11–16% and appears to approximate the population prevalence(39).

The impact of HCV on transplant outcomes has been studied most extensively in renal transplant recipients. In this group, the rate of HCV–related fibrosis progression has been shown to be accelerated when compared to immunocompetent individuals(72). HCV infection decreases both patient and graft survival post renal transplant, with the greatest impact occurring >5 years following transplant (73). The 10–year survival is approximately 15% lower in HCV+ compared to HCV– renal transplant recipients. Overall, however, survival is improved compared to those patients who remain on dialysis and poor outcomes primarily occur in those with advanced fibrosis/cirrhosis at transplant. Renal transplant candidates and recipients with mild to moderate (METAVIR stage F2 or less) liver disease at baseline have a low risk of progression of liver disease (74). HCV+ recipients of a renal allograft also have an increased risk of posttransplant diabetes, graft dysfunction and proteinuria(75).

There are no long–term studies regarding the impact of HCV on outcomes of thoracic organ, small bowel or pancreas recipients. However, current studies in these populations suggest that patient and graft survival is not as affected by HCV status(39, 76, 77). Based on the renal transplant literature, there is likely an increased risk of HCV–related death beyond 5 years posttransplant in other nonhepatic SOT; however, further studies are needed to clarify the risk. On the other hand, posttransplant renal disease is common among HCV–positive recipients of any organ.

### Diagnosis

The diagnosis of HCV infection relies on the same serologic and nucleic acid testing investigations used in the nontransplant population. Initial screening for antibody to HCV should be done at the time of initial transplant assessment using a third–generation enzyme immunoassay (EIA). However, in transplant candidates or recipients with negative HCV serology and persistent unexplained liver enzyme abnormalities, qualitative HCV RNA testing to rule out false negative testing should be considered. In those with positive HCV serology, qualitative HCV RNA and genotype tests should be used to confirm current infection (see Treatment). Abdominal ultrasound is used for identification of complications of HCV–related disease such as ascites, portal hypertension and hepatocellular carcinoma (HCC).

In chronic HCV infection, the liver biopsy remains the "gold standard" for assessing the degree of hepatic inflammation and fibrosis as well as the prognosis of the disease. Specifically, transjugular liver biopsy with hepatic venous pressure gradient (HVPG) measurement is recommended over percutaneous liver biopsy. Biopsy is recommended in the assessment of nonhepatic SOT candidates with chronic HCV to guide antiviral treatment decisions, identify those who may be considered for combined (with liver) transplant and those who are ineligible for nonhepatic SOT due to advanced liver disease(78).

### Treatment

**Pretransplant:** Eradication of HCV before transplantation has several theoretical benefits. HCV is associated with worse patient and graft survival as well as an increased risk for post–transplant diabetes mellitus and de novo glomerulopathy. Eradication of HCV before transplant might mitigate some of these adverse outcomes(79, 80). Furthermore, IFN therapy after transplantation is associated with reduced treatment response rates, a greater incidence of organ rejection, and impairment of renal function(81). Thus, it is best if treatment can be undertaken before solid organ transplantation.
Results of treatment of HCV in patients who are on dialysis varies, with reasonable SVR rates ranging from 16% to 68% with PEG or standard IFN (82). Patients with bridging fibrosis or compensated cirrhosis should undergo IFN-based therapy and can be listed for transplant if an SVR is achieved. Those with decompensated cirrhosis are generally not considered candidates for isolated renal transplant but may be considered for simultaneous liver–kidney (SLK) transplant. For HCV–infected patients on maintenance hemodialysis, the KDIGO guidelines suggest monotherapy with interferon that is dose–adjusted for a GFR of <15 ml/min per 1.73 m² (KDIGO71). Importantly, ribavirin remains contraindicated in patients with a GFR < 50 mL/min, despite small studies that have suggested that with close monitoring and dose reduction, it may be safe for use (83, 84).

In heart transplant candidates, HCV therapy is contraindicated due to the adverse effect profile (i.e. worsening anemia, risk of heart failure, myocardial infarction, arrhythmia). Although there are no published data on the outcome of lung transplant in HCV–positive recipients, only one small series has shown that selected lung transplant candidates can safely and effectively be treated for HCV prior to transplant (78).

Posttransplant: IFN therapy is generally contraindicated in recipients of SOT due to a high risk of precipitation of organ rejection (85, 86). There is well–documented evidence to support the theory that the liver allograft provides some level of immunologic protection to the kidney allograft (87, 88). As such, recent reports have demonstrated successful HCV treatment with Peg–IFN and ribavirin in liver–kidney recipients without development of renal rejection on therapy, although data are limited to small numbers of patients (89–91).

Due to the risk of precipitating rejection, IFN–based therapy should therefore be avoided in life–sustaining (e.g. heart, lung) transplants. However, successful therapy has been reported post–renal transplant and may be considered on a case–by–case basis (i.e. hepatic cirrhosis in a patient with an already–failed renal transplant) in those with severe disease following careful review of the potential risks and benefits.

There are no current data on using protease inhibitors (approved: telaprevir or boceprevir) in combination with PEG/RBV prior to or after SOT. These and other agents (replicon and polymerase inhibitors) are very attractive in the SOT setting in the potential to not require IFN for HCV clearance when used in combination. It is likely that non–IFN approaches that could be used off–label in non–hepatic SOT patients will be available in the next 2–3 years.

Prevention/prophylaxis

The prevalence of HCV infection has decreased significantly since the introduction of various preventive measures: systematic screening of blood and organ donations, use of erythropoietin and compliance with universal hygiene rules. No HCV vaccine is available at the present time.

As discussed previously, serologic screening of all SOT candidates should be performed prior to transplant. In those candidates who are positive for HCV, a liver biopsy should be performed to assess underlying disease activity and the stage of HCV–related liver disease, which is not predicted well by biochemical tests. This information can help to guide expected response rates as well as the aggressiveness of therapy. IFN therapy is associated with reasonable response rates in patients who are on dialysis, with frequent maintenance of response after renal transplantation. Given the lower patient and graft survival rates after renal transplantation in patients who are HCV positive compared with patients who are HCV negative, IFN should be considered for candidates for renal transplantation who have HCV, active viral replication, and advanced fibrosis (but compensated disease). Those with decompensated cirrhosis should be considered for liver–kidney transplant.
There are little available data regarding the management of heart and lung transplant candidates with chronic HCV; therefore the principles and data from the renal transplant population should be used to guide management. As mentioned previously, HCV therapy is contraindicated in heart transplant candidates due to the adverse side effect profile. Those with mild-to-moderate disease (METAVIR stage F0–F2) may be listed for transplant, while those with advanced HCV-related fibrosis or cirrhosis are generally not considered ideal candidates for cardiac transplantation (92). In lung transplant, HCV positivity is generally considered a contraindication to transplant, however one small series has shown that selected lung transplant candidates can safely and effectively be treated for HCV prior to transplantation (93).

**Hepatitis D in the Non-Hepatic Solid Organ Patient**

Hepatitis delta virus (HDV) is a small, defective RNA virus that can only replicate in an individual who has coexistent HBV, either after simultaneous transmission of the two viruses (co-infection), or via superinfection of an established HBV carrier (94). The distribution pattern of this virus, investigated by seroprevalence studies of anti–HDV in HBsAg-positive patients, is worldwide but not uniform (95). For example, 90% of HBV carriers are infected with both viruses in the Pacific Islands, whereas the rates decline to 8% in Italy and 5% in Japan. Current estimates suggest that 15–20 million people are infected with HDV (96).

Like HBV, HDV is transmitted via the parenteral route through exposure to infected blood or body fluids (i.e. intravenous drug users and those with high risk sexual activities) (97). Perinatal transmission of HDV is uncommon. Because of blood product screening, new infections in hemophiliacs, transfusion recipients, and patients on hemodialysis are no longer seen in developed countries.

The development of anti–HDV antibodies is universal in individuals with HDV; therefore, every patient who is HBsAg positive should be tested for anti–HDV IgG antibodies, which persist even after the patient has cleared HDV infection. Although active HDV infection was diagnosed historically by anti–HDV IgM antibodies, it is now confirmed by the detection of serum HDV RNA with a commercially available sensitive real–time PCR assay (98).

The goal of treatment pre and post–transplant is to eradicate HDV together with HBV. HDV is considered eradicated when both HDV RNA in the serum and HDAg in the liver become persistently undetectable. However, it is only with HBsAg clearance that complete and definitive resolution is attained. Standard treatment is usually with IFN–α and has been shown to improve long–term clinical outcome and survival (99). However, Peg–IFNα is still insufficient to cure the majority of chronic hepatitis D patients. In a prospective trial, only 21% of patients achieved HDV RNA negativity (100). Alternative treatments have been tested, also with limited results. Antivirals such as lamivudine, adefovir dipivoxil, famciclovir and entecavir, have been shown to have some efficacy against HBV but no efficacy against HDV either in monotherapy or in combination with IFNα (101–104). Ribavirin has been shown to inhibit HDV replication in vitro but is ineffective in vivo, even if associated with Peg–IFNα (100, 105, 106). Most transplant centers use a peri- and post–LT protocol that includes the use of HBIG and a nucleos(t)ide analogue to minimize the risk of HBV reactivation, although these two treatments will have no effect on HDV replication outside of suppressing sAg. There are currently no published reports of HDV recurrence following solid organ transplant.

**Hepatitis E in the Non-Hepatic Solid Organ Patient**

**Epidemiology & specific risk factors**

Hepatitis E, caused by hepatitis E virus (HEV), was identified in 1980 in India with 275 clinical cases in small villages from a common water source (107). The virus has four genotypes; of these, genotypes 1 and
2 are known to infect only humans, whereas genotypes 3 and 4 primarily infect other mammals, particularly pigs, but occasionally cause human disease on ingestion of infected meat (108). In the initial years after its discovery, it was believed to be a common cause of sporadic and epidemic waterborne acute hepatitis in only developing countries, primarily in Asia and Africa (109, 110). However, in non–endemic regions, chronic infection with genotype 3 HEV has been reported among immunosuppressed hosts— including heart, kidney, kidney–pancreas and liver transplant recipients (3, 4). Anti–HEV IgG antibodies are present in 16.6% of blood donors in France and in 6–16% of renal transplant recipients (111). Approximately 60% of SOT patients infected with HEV can develop chronic hepatitis, and up to 15% will develop cirrhosis (112). The use of tacrolimus rather than cyclosporine A has been reported as the main independent factors associated with chronic HEV infection after SOT (112). Host factors, in particular pregnancy, age, pre–existing liver disease, and immune response clearly appear to be important in progression (113). All patients with chronic HEV infection reported to date have been related to genotype 3 virus; no cases of chronic hepatitis E caused by infection with genotypes prevalent in high–endemic countries, namely genotype 1 and 2, have been described.

There are no published reports of HEV in lung or small bowel transplant recipients. In persons with pre–existing chronic liver disease, HEV superinfection can present as acute–on–chronic liver disease and can lead to liver decompensation and death.

Diagnosis

The diagnosis of HEV infection in immunosuppressed individuals is not straightforward. Most patients have no symptoms, and clinically evident jaundice is rare. Immunosuppressed SOT recipients also have a lower degree of transaminase elevation (ALT 100 to 300 IU/L). The diagnosis of HEV infection is confirmed by serology and/or molecular techniques. However, diagnosis of HEV is limited by the lack of high sensitivity commercial assays for detecting HEV RNA and reliance on anti–HEV immunoglobulin M (IgM) antibody testing (114). Serologic testing for anti–HEV antibodies has a false–negative rate in immunosuppressed patients, so negative results should be treated with caution (112). No serologic tests to diagnose HEV infection have been approved for commercial use in the United States though several tests are available for research purposes (115).

Treatment

Data are currently lacking regarding the treatment of chronic HEV infection in SOT recipients. Peg–IFN seems to have some efficacy but must be used with caution because of the risk of graft rejection (116). Reduction of immunosuppression may be helpful. In one study nearly one–third of patients who were chronically infected with HEV achieved viral clearance after reduction in immunosuppressive therapy (112). Small studies have reported that ribavirin has promising efficacy in immunocompromised patients with chronic HEV infection, including kidney and heart recipients (117–119).

Prevention/prophylaxis

Two recombinant vaccine candidates, the rHEV vaccine expressed in baculovirus and the HEV 239 vaccine, expressed in Escherichia coli, have been successfully evaluated in Phase II/III trials (120, 121). The HEV 239 vaccine remains under development and is based on HEV genotype 1, the endemic form of HEV. However, no data are yet available on the safety and efficacy of HEV 239 in patients with chronic liver disease and in immunocompromised individuals. The vaccine has not been investigated for immunity against genotype 3 infection, which currently represents the main clinical challenge to immunocompromised patients in Europe and the USA (122). The prevention of transmission of HEV is based on respect of hygiene rules, including the adequate cooking of meat. There is no systematic screening of HEV infection for blood donation. Although cases of blood–borne transmission of HEV have been described, the risk of parenteral
transmission appears to be very low (123). Of note, following successful clearance of HEV, no reactivation has been observed following SOT (124).

Conclusion

Viral hepatitis has a significant impact on transplantation outcomes. HBV and HCV are the most common causes of viral hepatitis following SOT and HEV is emerging as a significant cause of chronic hepatitis in industrialized nations. The interaction of infection and immunosuppression is central to understanding of risk and pathogenesis of various hepatotropic viruses. Future studies to address prevention and improved treatment modalities both pre- and post-SOT are needed.

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