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Special Article

Viral Hepatitis in Solid Organ Transplantation

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Abbreviations: FCH, fibrosing cholestatic hepatitis; HAV, hepatitis A virus; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV-R, HCV recurrence; HDV, hepatitis D virus; HEV, hepatitis E virus; HVPG, hepatic venous pressure gradient; IgM, immunoglobulin M; LADR, low accelerated dose regimen; LAM, lamivudine; IFNα, interferon alfa; PegIFNα, pegylated interferon alfa; PI, protease inhibitor; RBV, ribavirin; SOT, solid organ transplant; SVR, sustained virologic response.

Introduction

A number of hepatotrophic viruses affect organ transplant candidates and recipients. The most important agents causing acute and chronic hepatitis are hepatitis B virus (HBV), with or without hepatitis delta virus (HDV), and hepatitis C virus (HCV). In addition, hepatitis E virus (HEV), previously thought to only cause acute, self-limited infection in the developing world, is emerging as an increasing cause of chronic hepatitis in transplant recipients in industrialized countries. Management of viral hepatitis in transplant candidates and recipients is complex and highly depends on the organ transplanted, particularly for HBV and HCV, and the donor/recipient status. This chapter will focus primarily on the epidemiology, diagnosis, treatment and prevention of the primary hepatotrophic viruses (A-E) after hepatic and nonhepatic organ transplantation.

Hepatitis A Virus (HAV)

HAV is a nonenveloped RNA virus and a member of the picornavirus family. It is largely transmitted person-to-person by the fecal–oral route, although blood borne transmission can occur (1,2). High-income regions of the world have very low HAV endemicity levels and a high proportion of nonimmune adults, whereas in low-income regions with high endemicity most adults are immune on the basis of prior infection (3). Worldwide, approximately 1.4 million cases of hepatitis A are reported each year; however, the true incidence is estimated to be 3–10 times higher. HAV vaccines have been licensed since 1992 and vaccination of susceptible, at-risk individuals (e.g. pre- and postorgan transplantation) is advised based on national guidelines (4).

Acute HAV infection is generally self-limited, but the risk of fulminant hepatic failure increases with age (5). Young children are frequently asymptomatic, whereas older children and adults may develop a range of clinical manifestations from mild anicteric infection to fulminant hepatic failure. Those with underlying chronic liver disease of any etiology are at increased risk of fulminant disease and those who are nonimmune should be vaccinated (4).

The estimated fatality rate for HAV is low (<1.5%). Among those who develop fulminant hepatic failure, 35–40% will spontaneously recover, whereas others usually survive after liver transplantation (LT) (6,7). Rarely, HAV recurs after transplantation (8,9).

Recommendations:

- All hepatic transplant candidates and all nonhepatic transplant candidates with chronic liver disease, or other known risk factors for HAV (e.g. men who have sex with men, travel to endemic region, sanitation workers and hemophiliacs), should be tested for HAV-IgG and if negative offered vaccination. Ideally, vaccination should be performed before LT, but it may also be given afterwards (II-1).
- Patients with fulminant hepatic failure due to acute HAV should be assessed for LT (II-2).

Hepatitis B Virus (HBV)

Hepatic transplantation

Epidemiology and risk factors: HBV is a DNA hepadnavirus transmitted parenterally, sexually and vertically. Worldwide, it infects ~400 million individuals and causes over one million deaths per year (10,11). The prevalence can be high (≥8%), intermediate (2–7%) or low (<2%) depending on the geographic region (12). With an increase in immigrants from endemic countries, it is now estimated that >2 million HBV-infected individuals reside in the United States, of which ~5000 per year die from

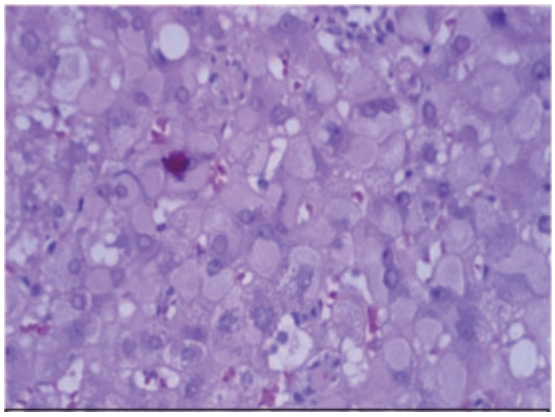

Figure 1: Ground-glass hepatocytes filled with HbsAg.

complications (13). However, the ability to effectively prevent HBV infection by immunization and treat the disease with antiviral therapy represent major advances of modern medicine. Even so, HBV infection still remains an important indication for LT.

Before the early 1990s and available HBV prophylaxis, untreatable recurrent HBV disease occurred in most recipients undergoing LT for this indication (14–16). Some developed a rapid, fibrosing cholestatic hepatitis (FCH) variant that led to poor early survival rates (17–20). A dramatic shift occurred in the mid-late 1990s with the advent of hepatitis B immunoglobulin (HBIG) and the first oral antiviral drug for HBV, lamivudine (LAM). Combination therapy (HBIG + LAM), without graft reinfection, became the rule resulting in advances in survival that now supersede other indications (21,22). More recently, nucleos(t)ide analogues (tenofovir, TDF; entecavir; ETV) with high barriers to resistance have been shown to rescue patients from liver failure and need for LT, as well as allow for excellent outcomes without recurrence post-LT (23–27). Even with risk factors, e.g. high viral load at OLT ($>2 \times 10^4$ IU/mL; HBeAg positivity), recurrence is now exceedingly rare. When recurrence occurs, the typical causes are noncompliance to antiviral therapy and/or HBIG, or resistance if an older agent (LAM; adefovir, ADV) is used as monotherapy (28–30). Patients with fulminant HBV or concurrent HDV have a low incidence of recurrence, given their characteristic low viral loads (31–34).

Diagnosis: HBV recurrence has been historically defined as the reappearance of HBsAg after LT, although patients on antiviral prophylaxis and not HBIG may develop HBsAg positivity without actual recurrence (DNA undetectable, normal biochemistry and histology). The reverse may also occur, i.e. low levels of viremia in the absence of HBsAg positivity, either spontaneously or due to HBsAg escape mutants during HBIG therapy (35–37). The histology of recurrence is similar to that of pretransplant HBV (Figure 1), with the exception of FCH. This now uncommon entity is defined as rapidly progressive cholestasis, fibrosis and multi-organ failure (38).

All patients should be followed post-LT by a clinician (hepatologist, infectious disease, other) experienced in the management of HBV infection. Although monitoring protocols for HBV recurrence vary among centers, HBsAg and DNA should be performed at least every 3 months within the first year and every 6 months thereafter even with prophylaxis. In patients receiving HBIG, it is typical to follow anti-HBs titers with a predose goal of >100 or >500 IU/L in those with low or high DNA at LT, respectively. More frequent anti-HBs titers and dosing intervals should be performed if levels remain below these thresholds.

Recommendations:

- Every 3–6 month monitoring of HBsAg and HBV DNA should be performed in HBV positive liver transplant recipients, regardless of treatment or prophylaxis regimen (III).
- Anti-HBs titers should be measured before HBIG doses, with a goal of 100 IU/L or higher depending on the risk of HBV recurrence (i.e. HBV DNA and eAg status at LT) (III).

Treatment: Central to the prevention of HBV recurrence post-LT is adequate pre-LT viral control (Table 1). Although seven drugs are licensed for HBV therapy, including interferon alfa (IFNα), pegylated interferon alfa-2a (PegIFNα-2a), telbivudine, LAM, ADV, TDF and ETV, only the latter two are advisable in patients with hepatic decompensation, due to high efficacy and low resistance. HBV DNA reduction to undetectable, or at least $<1 \times 10^5$ IU/mL, with a potent nucleos(t)ide analogue having high barrier to resistance (TDF, ETV) reduces the risk of HBV recurrence (39–42). Combination nucleoside/nucleotide [i.e. TDF/emtricitabine (FTC); TDF+ETV; LAM+ADV] therapy is often used by centers pre- and post-LT but the published data do not support any benefit of this approach over potent monotherapy. Rarely, antiviral therapy can lead to mitochondrial dysfunction and lactic acidosis requiring urgent discontinuation (43,44). Entecavir needs to specifically be taken on an empty stomach. A more detailed review of HBV therapy pre-LT can be found in current national guidelines (45).

HBV recurrence after LT is the result of failed prophylaxis (see below), either due to noncompliance or the development of drug/HBIG resistance. LAM resistance may occur in up to 50% of LT recipients and predisposes patients to ETV resistance long-term (46). Resistance to ADV is seen in up to 30% at 5 years before LT, although this has not been shown to lead to a higher rate of TDF resistance or loss of efficacy (47). However, the typical strategy is to either switch classes of drugs with high barrier to resistance or add the other class agent, resulting in combination therapy (48–54). The latter combination approach

Table 1: Suggested hepatitis B virus prophylaxis for hepatic and nonhepatic transplantation

Donor		Recipient					
HBcAb	HBsAg	HBcAb	HBsAg	HBsAb	HBIG?	Antiviral prophylaxis?	Vaccinate?[2]
Hepatic[1]							
(−)	(−)	(+)	(−)	(−) or (+)	No	No	Consider if sAb (−) or lost
(−) or (+)	(−) or (+)	(+)	(+)	(−)	Yes[3]	Yes	No
(+)	(−)	(−) or (+)	(−)	(+)	No	Yes, unless sAb persists	Consider if sAb lost
(+)	(−)	(−) or (+)	(−)	(−)	No	Yes, unless sAb persists after vaccination[4]	Yes
(+)	(+)	(−) or (+)	(−)	(−) or (+)	[5]	[5]	Consider if sAb (−) or lost
Nonhepatic[1]							
(−)	(−)	(+)	(−)	(−) or (+)	No	No	Consider if sAb (−) or lost
(−) or (+)	(−) or (+)	(+)	(+)	(−)	No	Yes	No
(+)	(−)	(−) or (+)	(−)	(+)	No	Yes, unless sAb persists	Consider if sAb (−) or lost
(+)	(−)	(−) or (+)	(−)	(−)	No	Yes, unless sAb persists after vaccination[4]	Yes
(+)	(+)	(−) or (+)	(−)	(−) or (+)	[5]	[5]	Consider if sAb (−) or lost

[1]All patients posttransplant: HBV sAg/DNA and liver function tests every 3–6 months and follow-up with an HBV provider.
[2]Typically vaccinate at 1 year posttransplant. Consider high-dose vaccine (40 mg) at 0, 7 and 28 days and assess HBsAb >1 month after.
[3]If HBV DNA (–) at transplant, consider short-term HBIG therapy; If HBV DNA (+) at transplant, consider long-term or indefinite HBIG.
[4]If donor HBV DNA is performed and negative, no prophylaxis is required, although close monitoring for HBV recurrence is recommended.
[5]Transplant typically contraindicated but may consider in select, "desparate" cases, in the setting of indefinite antiviral prophylaxis and close monitoring.

is often practiced anecdotally but again not proven to be more effective. HBIG is typically discontinued in patients with recurrent HBV. The nucleotide agents ADV and TDF may cause proximal renal tubular injury in a small percentage of patients, although this has mainly been seen in HIV infected populations (55,56). Renal function should be monitored and dose adjustments made for all agents.

Prevention/Prophylaxis: Many centers still use combination therapy with HBIG and LAM that effectively prevents HBV recurrence (Table 1; Refs.57–62). However, LAM resistance and the cost and inconvenience of intravenous HBIG have motivated a recent trend toward alternative preparations or HBIG withdrawal in conjunction with potent oral antivirals. Intramuscular HBIG is less expensive and represents an acceptable alternative to IV, particularly in patients with low HBV DNA at LT (34,59,63–67). In this group, HBIG can be safely withdrawn postoperatively (6–12 months) in conjunction with continued oral antiviral therapy (21,68). Similar low recurrence rates have also been reported with combination therapy (LAM + ADV) before and after OLT, even without HBIG therapy (48,69). Others have reported the use of newer, potent antiviral agents (TDF, ETV) ± HBIG, even in patients who are viremic at OLT (70–75). That being said, it is still currently recommended to give, at minimum, a short course of HBIG in combination with indefinite antiviral therapy with high barriers to resistance. One recent interesting study showed patients with undetectable HBV DNA at LT and no evidence of latent intrahepatic total and cccDNA may safely undergo full weaning of prophylaxis, although larger studies are needed before recommending this biopsy-driven approach (76). Vaccination as a strategy to allow discontinuation of HBIG or antivirals has yielded unreliable results and is not advisable. Antiviral prophylaxis is not necessary for anti-HBc positive "alone" recipients (i.e. sAg and HBV DNA negative), unless perhaps in situations of intense immunosuppressive therapy (i.e. lymphodepletion) (77–80).

Recommendations:

- HBsAg positive LT recipients should be treated indefinitely with nucleos(t)ide analogue therapy having high barriers to resistance + at minimum short-term HBIG (II-1).
- The choice of antiviral regimen should be based on the successful approach used pre-LT, factoring in prior exposures, resistance, potential drug interactions and side effects (II-1).

Anti-HBc positive donors and recipients: Anti-HBc positive donors have been increasingly used to expand the donor pool, although without prophylaxis they pose a 34–86% risk of transmitting HBV infection to unexposed (HBsAg negative) LT recipients (81). Oral antiviral therapy ± HBIG is effective prophylaxis for recipients who are HBsAg negative ± anti-HBc positive (Table 1). Lamivudine may be more effective than HBIG (82) and is preferred by many centers for logistical ease and cost. Although not standard of care, the available data suggest that discontinuation of prophylaxis can be considered in certain situations with careful monitoring: (1) donor serum, if available, is HBV DNA negative; (2) recipient is vaccinated or exposed pre-LT and maintains anti-HBs positivity post-LT and (3) recipient is vaccinated post-LT (∼12 months) and maintains anti-HBs positivity (81,83–88). Rarely, HBV infection despite LAM or ADV has been reported in recipients of anti-HBc positive organs (82), although there are insufficient data to recommend newer agents as primary prophylaxis compared to rescue therapy for breakthrough (89). Routine HBsAg and/or HBV DNA monitoring in prophylaxed recipients of anti-HBc positive grafts may not be necessary, although transaminase elevations should prompt these investigations to exclude HBV infection.

Recommendations:

- Recipients of anti-HBc positive donors should generally receive indefinite prophylaxis with antiviral therapy ± HBIG (II-2).
- Discontinuation of prophylaxis is not standard of care but might be considered in closely monitored patients who maintain anti-HBs positivity and/or receive a donor with undetectable HBV DNA (III).
- Routine antiviral prophylaxis is not recommended for anti-HBc positive "alone" recipients (donor negative, recipient sAg and DNA negative) but may be considered in those felt to be at increased risk of reactivation (e.g. lymphodepletion therapy) (III).

Infection control issues: All HBV noninfected, nonimmune patients with cirrhosis should be vaccinated, as *de novo* HBV infection can lead to decompensated liver failure. Even with double dose regimens, the percentage who successfully seroconvert is suboptimal (16–62%), and many (37–73%) lose anti-HBs within the first year after LT (90–96). Thus, repeat or booster vaccination should be attempted at ∼12 months post-LT with the goal of seroconversion. All household and sexual contacts of HBV-infected recipients should be vaccinated. HBV-infected recipients should not share with others personal items that may be contaminated with blood, such as toothbrushes, razor blades, nail clippers, etc.

Recommendation:

- All HBV noninfected, nonimmune patients with cirrhosis and transplant recipients should receive the HBV vaccine with seroconversion documented (II-2).

HBV: Nonhepatic Transplantation

Epidemiology and risk factors: The prevalence of chronic HBV infection and markers of prior HBV in nonhepatic solid organ transplant (SOT) candidates and recipients vary widely by population and geographic region (97). In Western countries, the strict institution of infection control practices and HBV vaccination in patients on dialysis has led to a decline in the prevalence of chronic HBV, which now ranges between 0% and 6.6% (97). In contrast, a registry study of dialysis patients in Asia-Pacific countries found a prevalence of HBsAg positivity ranging between 1.3% and 14.6% (98). Although incident cases of HBV acquired on dialysis are considered uncommon, particularly in the U.S. and Europe, transmissions and outbreaks are still reported and reflect a need for ongoing education, case identification and management (99,100). There are no data with regards to the prevalence of chronic HBV in thoracic organ transplant candidates/recipients. It is likely that the prevalence and risk factors for HBV mirrors that of the general background population, with mother-to-child transmission and early childhood horizontal acquisition being the major risk factors in those in or born in highly endemic regions. Parenteral and sexual transmission are the dominant modes of transmission in areas of low endemicity (101).

The risk of reactivation of HBV in HBsAg positive renal transplant recipients, in the absence of antiviral prophylaxis, ranges from 50% to 94% (102–104). Historically, before the era of effective antiviral therapy, nonhepatic SOT in recipients with chronic HBV infection was associated with substantial reductions in patient and graft survival due to rapidly progressive liver disease (105–108). Several recent studies in both renal and cardiac transplantation have showen excellent outcomes in HBsAg positive patients managed with antiviral therapy (109–114).

The prevalence of markers of prior HBV infection (HBsAg negative but anti-HBc positive, with or without positive anti-HBs) is significantly higher than the prevalence of chronic HBV in any given population. In the U.S. population, the estimated prevalence of HBsAg is 0.27%, whereas that of positive ant-HBc is 4.7% (115). In nonhepatic SOT recipients with markers of past HBV infection there is a risk of reactivation, although this is low and estimated to be at most 5% (116,117). The natural history of reactivation in this setting seems to be a loss of the protective anti-HBs (if present at baseline) followed by a rise in HBV DNA and then seroreversion to a positive HBsAg state. It generally occurs early, within the first year, after transplant. Although the overall risk of reactivation in this setting is low, when it does occur, rapid progression and death due to liver disease have been described in the absence of antiviral therapy (117).

Diagnosis: The diagnosis of HBV relies on the same serologic and virologic assays used in the nontransplant

population (39,45,118). As in all patients with chronic HBV, there is an increased risk of hepatocellular carcinoma (HCC). Nonhepatic SOT who are HBsAg positive should undergo HCC surveillance based on published guidelines (118,119).

Recommendations:

- Initial screening for HBV should be done at the time transplant candidate assessment and include HBsAg, anti-HBs and anti-HBc (III).
- Nonhepatic SOT candidates identified as HBsAg positive should undergo additional testing, including HBeAg, anti-HBe, quantitative HBV DNA, liver enzymes, alfa-fetoprotein and abdominal ultrasound (III).
- HBsAg positive nonhepatic SOT candidates and recipients should undergo risk based surveillance for HCC, in concordance with published guidelines in the nontransplant population, with an abdominal ultrasound and alpha-fetoprotein every 6 months (III).

Treatment: A nonhepatic SOT candidate identified to be HBsAg positive during assessment should be evaluated for the need for therapy before transplant. The management of HBV is complex and requires lifelong monitoring and follow-up whether or not antiviral therapy is initiated, and thus referral to a specialist with expertise in the management of HBV is recommended. Therapy should be based on guidelines published for the management of HBV in the general population (39,45,118). In those with indications for therapy before SOT, LAM is no longer recommended as first line therapy due to the high risk of resistance, unless more potent agents are unavailable. Treatment with a potent nucleos(t)ide analogue, such as ETV or TDF adjusted for renal function as needed, should be used given the need for long-term therapy and to limit the risk of future resistance. It has been suggested that ETV may be preferred over TDF in the renal transplant population due to the lack of nephrotoxicity (45). Interferon or peginterferon is not recommended due to poor tolerability, bone marrow suppression and a low rate of response in immunocompromised hosts.

The risk of HBV reactivation persists as long as patients remain on immunosuppressive therapy. Thus, once treatment is initiated pretransplant, it should be continued up to the time of transplant and indefinitely posttransplant as long as the patient remains on immunosuppressive therapy. If the recipient comes off immunosuppression (e.g. return to dialysis due to failed renal graft), the need for ongoing HBV therapy should be reviewed and any consideration of discontinuation of antiviral therapy should follow national guidelines (45).

As in the general population, nonhepatic SOT candidates initiated on therapy for chronic HBV should undergo regular follow-up and monitoring for response to antiviral therapy and continue HCC surveillance (39,45,118).

Recommendations:

- Nonhepatic SOT candidates with chronic HBV should be evaluated for the need for therapy by a specialist with expertise in HBV management before transplantation (III).
- If therapy for HBV is indicated, TDF or ETV are preferred due to their potency and high barriers to resistance (III).
- All nonhepatic SOT candidates or recipients with chronic HBV on nucleos(t)ide analogue therapy should undergo liver enzyme and HBV DNA monitoring every 3–6 months (III).
- Once therapy is started it should be continued indefinitely in the setting of immunosuppression (III).

Prevention/Prophylaxis: Nonimmune nonhepatic SOT candidates/recipients are at risk for acquisition of HBV through the usual risk factors, but also importantly via transmission from an organ donor. In many circumstances, vaccination with documented seroconversion can protect against donor-transmitted HBV (see below). Although the proportion of those with end-stage renal disease who will seroconvert, even to double dose HBV vaccine, is suboptimal, 55–67% will respond (120). Response rates are higher in those with lesser degrees of renal dysfunction and certainly better pre- than posttransplant (121). Amongst thoracic organ transplant candidates, response rates to HBV vaccine seem similarly suboptimal (45–53%) but still worthwhile (101,122).

If HBV vaccine was not given before transplant, consideration should be given to vaccination posttransplant. The rate of seroconversion to a protective titre of positive anti-HBs in the renal transplant population has been found to be 17–36% (123,124).

Recommendations:

- All HBV uninfected, nonimmune, nonhepatic SOT candidates should be vaccinated for HBV as early in the course of their disease as possible (III).
- In those not vaccinated before transplant, HBV vaccine should be considered posttransplant, once immunosuppression is at maintenance doses (generally 12 months) (III).

As described previously, the risk of reactivation of HBV in HBsAg positive renal transplant recipients, in the absence of antiviral prophylaxis, ranges from 50% to 94% (102–104). In the era before effective HBV antiviral therapy, this resulted frequently in rapidly progressive liver disease and an increased risk of graft loss and death (105–108). As LAM was the first available oral antiviral for HBV, this is the agent that has been used in most studies (110,125).

Although LAM has been shown to significantly improve patient survival after renal transplant (83% vs. 34% at 20 years), its use and impact is limited by a high (60–70%) risk of resistance over 4–5 years (125). As such, despite the improvement in overall survival, there remains an increased risk of liver-related mortality in HBsAg positive renal transplant recipients managed with LAM (125). In light of these data (126), ETV or TDF are recommended to limit the potential for resistance, with LAM or ADV reserved for those without other options (45). Interferon-based therapy is contraindicated posttransplant due to the risk of rejection.

Recommendations:

- Because of the high risk of reactivation, nonhepatic SOT recipients with chronic HBV who are not on antiviral therapy before transplant should be initiated on nucleos(t)ide analogue therapy at the time of transplant (II-2).
- Antiviral therapy should be continued indefinitely posttransplant (II-2).
- ETV or TDF is recommended as first line therapy, with LAM or ADV reserved for those without these options (III).
- Follow-up monitoring should include liver enzymes and HBV DNA every 3–6 months (III).

In those with markers of past HBV infection (HBsAg negative, anti-HBc positive ± anti-HBs positive), there is a low (∼5%) risk of HBV reactivation (116,117). Data are lacking regarding the optimal approach in this situation. Given the absence of data and the low overall risk, routine antiviral prophylaxis in this group cannot be recommended. Some centers use prophylaxis in patients felt to be at increased risk (e.g. anti-HBc alone, intense immunosuppression). Alternatively, some have advocated monitoring of HBV DNA and institution of pre-emptive antiviral therapy if the DNA progressively rises (45). The challenge with this strategy is that there are no data regarding the optimal frequency of monitoring or the HBV DNA threshold at which antiviral therapy should be initiated. Given the natural history of reactivation, in those who are both anti-HBc and anti-HBs positive, some centers monitor only anti-HBs over the first 12 posttransplant months because as long as this remains above protective titres, there is a negligible risk of reactivation.

Recommendations:

- In those with markers of past HBV infection (HBsAg negative, anti-HBc positive ± anti-HBs positive), routine antiviral prophylaxis is not recommended, but may be considered in those felt to be at increased risk of reactivation (e.g. anti-HBc+ alone or intense immunosuppression) (III).
- Alternatively, HBV DNA and HBsAg should be monitored, with antiviral therapy initiated if HBsAg becomes positive or if HBV DNA progressively rises (III). With this strategy, given that antiviral therapy will be started at higher levels of HBV DNA, TDF or ETV are recommended (III).

The HBsAg or anti-HBc positive donor: Hepatitis B uninfected, nonimmune patients undergoing nonhepatic SOT may acquire donor derived HBV. The HBsAg positive donor carries a high risk of transmission to recipients although satisfactory outcomes have been described generally with the use of combined HBIG and antiviral prophylaxis (127–130). The duration of prophylaxis required is unknown, although lifelong nucleos(t)ide analogue therapy has been suggested (127). If the HBsAg and HBV DNA remain negative, consideration may be given to discontinuing HBIG 6–12 months posttransplant.

The risk of HBV transmission from an anti-HBc positive nonhepatic donor is significantly lower than that of hepatic donors, ranging from 0% to 5.2% in different studies (131,132). Renal and thoracic organs from anti-HBc positive donors have been safely used with strategies to minimize the risk of transmission (127,133,134). In recipients of a nonhepatic organ from an anti-HBc positive donor, the risk of transmission is negligible if the recipient is immune (127,133), thus highlighting the importance of pretransplant immunization. In HBV nonimmune recipients of an anti-HBc positive organ, the risk of transmission is presumed to be related to the presence of HBV DNA present in the plasma or PBMC of the organ donor. As such, assessment of HBV DNA in the donor may guide the need for prophylaxis (127). Although the optimal duration of prophylaxis is unknown, the risk period is thought to be restricted to the early posttransplant period until elimination of donor PBMC.

Recommendations:

- Consideration may be given to using organs from HBsAg positive donors, particularly for a lifesaving (i.e. nonrenal) transplant, and with HBIG/antiviral prophylaxis and informed consent (II-3).
- In HBV immune (anti-HBs positive) recipients of an anti-HBc positive nonhepatic organ, no prophylaxis is needed (II-2).
- For HBV nonimmune recipients of an anti-HBc positive nonhepatic organ:
  - If the donor is HBV DNA negative, no antiviral prophylaxis is needed.
  - If the donor HBV DNA is positive or unknown, prophylaxis with either antiviral therapy or HBIG is suggested for at minimum 6–12 months (II-2).
- Recipients of organs from HBsAg or anti-HBc positive donors should undergo monitoring with liver enzymes, HBsAg and HBV DNA:
  - Every 3 months for at least 12 months posttransplant (II-3) (127).
  - Beyond 12 months, every 6 months indefinitely, particularly in recipients of an HBsAg positive organ (III).

Infection control issues: HBsAg positive SOT recipients should not share personal items that may be contaminated with even small amounts of blood. All close contacts should be screened for HBV, vaccinated if nonimmune and have documentation of anti-HBs seroconversion.

Hepatitis C Virus

Hepatic transplantation

Epidemiology and risk factors: HCV is an RNA flavivirus closely related to hepatitis G, yellow fever and dengue viruses (135). Replication is dependent on cellular proteases and an error-prone RNA polymerase resulting in a diverse array of quasispecies that challenge immunological clearance (136). It is the cause of >4 million and >170 million cases of chronic hepatitis in the United States and world, respectively (137). Blood-screening measures have nearly eliminated the risk of transfusion-associated hepatitis in Western countries, but new cases continue to occur related to injection-drug use, repeated mucous-membrane exposures (commercial sex workers; men who have sex with men), accidental percutaneous exposures and occasionally iatrogenic transmissions (53). In the Western world, genotypes 1a and 1b are the most common, followed by genotypes 2 and 3. The other genotypes are primarily seen in the Middle East (genotype 4), southern Africa (genotype 5) and Southeast Asia (genotype 6).

Worldwide, hepatitis C is a leading indication for LT. The number of patients requiring LT for HCV is expected to peak in the next 10–15 years followed by a decline due to advances in treatment and fewer new infections (138). Recurrence after LT is universal and histological injury is accelerated in the new graft compared to the rate pretransplantation (139,140). For this reason, recipients with HCV-recurrence (HCV-R) have worse 5-year patient (65%) and graft survival (60%) compared with HCV-negative recipients (75% and 70%), both with primary or repeat transplantation (141). Early FCH due to HCV only occurs in <5% and is associated with poor outcomes (Figure 2). Fibrosis progression is best predicted by performing early (6–12 months post-OLT) liver biopsies (142,143). Once recurrent HCV cirrhosis occurs, ~50% decompensate within 1 year (140,144). Retransplantation is controversial and is often not considered in those with advanced age, deconditioning, renal failure, MELD > 25 and early (<1–2 years) aggressive recurrence (145–154).

The strongest risk factors for recurrence are high dose immunosuppressive therapy for acute rejection, concurrent HIV or CMV infection, older donor/recipient age, HCV viral load and severe preservation injury or steatosis. In contrast to HCV-negative recipients, treatment of acute rejection is associated with increased mortality and graft loss in recipients with HCV (relative risk = 2.7–2.9, p = 0.04; Ref. 155).

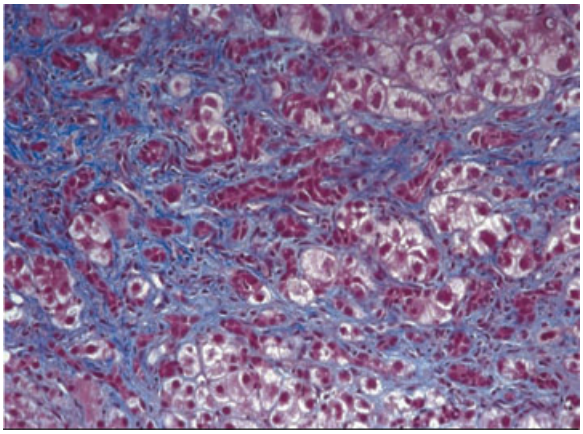

Figure 2: Fibrosing cholestatic hepatitis C.

It is not, however, conclusive that lymphocyte depleting or nondepleting antibodies increase the risk of recurrence when used primarily as induction therapy (156–159). There has been significant recent interest in donor/recipient IL-28b gene polymorphisms (either favorable C or unfavorable T alleles) being predictive of progressive HCV-R and response to IFN therapy post-LT (160–174).

Inconclusive risk factors for recurrence include genotype 1 versus non-1, HLA mismatches, the use of donors after cardiac death or live donors and the choice of maintenance IS therapy (155,157,162,168,175–204). Recent data have supported a slower steroid tapering schedule or no steroids to avoid precipitating early recurrence, although this is not universally practiced. There has been some interest in the antifibrotic properties of mTOR inhibitors in minimizing fibrosis progression in HCV+ recipients, although conflicting data suggest a higher risk of mortality in this setting (205,206). The use of nonfibrotic HCV-positive donors for HCV-positive recipients results in outcomes similar to the use of an HCV-negative donor (207,208). However, the use of genotype 1 donors for genotype 2/3 or any HCV positive donor into nonviremic recipients should be avoided. Recent studies also suggests that outcomes are inferior if HCV-positive donors over age 45 are used compared to younger HCV-positive donors (209) or if HCV-positive donors are used for HIV–HCV co-infected recipients (210).

Recommendations:

- Avoidance of older donors, acute rejection and other forms of liver injury and infectious complications may limit the progression of HCV recurrence after LT (II-2).
- Genotype 1 donors should not be allocated to recipients who are genotype 2 or 3 (III).
- No HCV positive donors should be allocated to HCV positive recipients who have had a sustained virological response (i.e. nonviremic).

Diagnosis: During the anhepatic phase of the LT procedure, HCV RNA rapidly decreases from the serum. The rate of HCV RNA decline accelerates further after reperfusion, likely due to HCV binding to its hepatocellular receptors (211). HCV RNA levels then increase rapidly after the first few weeks and, at 1 year, can reach >10–20 fold higher levels than pre-LT. In the first 6 months, acute hepatitis of varying severity occurs in approximately 75% of recipients, with <10% developing severe cholestatic forms. Fibrosis occurs in >50% at 1–2 years after LT and up to 30% progress to advanced fibrosis or cirrhosis by year 5 (212). Thus, the gold standard for diagnosis is liver biopsy, with the caveat that it may not distinguish other causes (rejection, biliary obstruction) from HCV-R early after LT and may underestimate fibrosis stage (213). Most centers routinely perform protocol liver biopsies at defined time points (i.e. yearly) to monitor for recurrence indicating the need for treatment (grade 3 or stage 1–2; Ref.214). Other adjunctive measures that are less routinely used include hepatic venous pressure gradients (HVPG), and blood tests and imaging for fibrosis. An elevated HVPG regardless of fibrosis stage has been shown to predict the development of progressive HCV-R and portal hypertension and declines with successful antiviral therapy (215–218). Noninvasive liver stiffness assessments with transient or magnetic resonance elastography can detect fibrosis and may be appropriate for fibrosis monitoring, although neither are widely available in the United States (219–221).

Recommendations:

- The current gold standard for diagnosing HCV recurrence is liver biopsy (II-2).
- Other adjunctive measures to assist in determining the progression of HCV recurrence include HVPGs and elastography (III).

Treatment:

Pretransplant: Achieving a sustained virologic response (SVR) with pre-LT antiviral therapy may delay the need for OLT and eliminate the risk of HCV-R. However, this comes at a price due to poor patient tolerability and efficacy, depending on the degree of hepatic decompensation and the genotype (222–224). A low accelerated dose regimen (LADR) approach of slowly advancing Peg-IFNα and RBV doses to target levels may improve tolerability and achieve an SVR that is usually maintained after OLT, assuming >8–12 weeks of pre-LT viral negativity is achieved (223). However, this approach is most effective in nongenotype 1 cirrhotic patients and is associated with a high risk of infectious complications with little benefit (<10% SVR) in genotype 1 patients. Thus, treatment should be limited to decompensated cirrhotic patients with CTP score ≤7, physiological MELD score <20, and primarily genotype 2 and 3 infection. In 2011, two first generation NS3/4A protease inhibitors (PIs: boceprevir, telaprevir) became available for use in combination with Peg-IFNα and ribavirin (RBV) for the treatment of genotype 1 HCV, even in compensated cirrhosis (225,226). Although there are no current published data in decompensated patients, a number of centers are starting to initiate this triple therapy regimen with the goal of viral eradication before LT. It is not currently known if the overall benefit will ultimately exceed the added risks, and it is likely that combinations of oral antiviral agents without IFN or RBV will eventually be more desirable in this high-risk population.

Posttransplant (Pre-emptive vs. Wait for Recurrence)

Preemptive HCV therapy instituted immediately or within a few weeks after OLT has not been shown to delay the onset of recurrence (227). The largest, randomized study compared the safety, tolerability and efficacy of preemptive initiation of Peg-IFNα-2a plus RBV within 26 weeks after LT versus initiation only upon established recurrence. On an intent-to-treat basis, recurrence at 120 weeks was similar in the prophylaxis (61.8%) and observation arms (65.0%, $p = 0.725$). Similar results were shown with PEG alone and other smaller trials (228–230). Given the toxicity and lack of virologic benefit, preemptive therapy is not currently advisable in clinical practice.

Most centers wait until the development of histological recurrence, typically detected by protocol or for-cause liver biopsies. Post-LT treatment of histological recurrence with PEG + RBV is only successful in 20–30% of recipients and is associated with high rates (30–50%) of discontinuation due to intolerability (228,231–245). A major limiting factor in achieving an acceptable SVR rate is the inability to reach target RBV doses due to renal insufficiency and anemia (228,237,246). Although some reports have not shown an increase in the risk of acute rejection with IFN (228), a recent multicenter case-control study reported a 7.2% rate of PEG-related immunological graft dysfunction that was associated with poor patient and graft survival regardless of SVR (247). Evidence of alloimmune injury on pretreatment biopsy, such as plasma cell hepatitis, was the main risk factor for the development of this worrisome complication. Thus, careful review of pretreatment liver biopsies for alternative diagnoses other than pure HCV-R may suggest the need to avoid IFN therapy and instead augment IS therapy in this situation.

Finally, a number of abstracts at recent meetings have revealed preliminary data of the use of triple antiviral therapy (PEG + RBV + PI) for post-LT HCV-R. These early data are inconclusive and show the potential for benefit (higher SVR than non-PI approaches) and risk (severe anemia, infection) with this approach. In addition, both telaprevir and boceprevir strongly inhibit CYP3A4 enzymes and drug (CNI therapy) metabolism and may result in CNI toxicity or graft rejection upon drug discontinuation (248,249). Therefore, no conclusive recommendations can be made at this point

and further clinical trials, particularly with IFN-free regimens, are of great need in this population.

Recommendation:

- HCV treatment should be considered at the time of histological recurrence with PEG + RBV (II-2). It is not clear if the addition of a PI to this regimen in either decompensated pre-LT candidates or post-LT recipients is safe or more effective (III).

Prevention/prophylaxis: There have been multiple failed attempts to prevent HCV reinfection in the new graft. Agents such as hepatitis C immunoglobulin and IFN do not fully eliminate blood virions, even when given in the anhepatic or immediate postoperative phase (250). Thus, no current agents are available to prevent HCV-R.

Infection control issues: HCV-infected recipients should avoid sharing potentially contaminated items with other contacts. Sexual transmission is primarily seen in HIV+ individuals engaging in high-risk behavior (251–253). Thus, the use of contraception to prevent HCV transmission in longstanding monogamous relationships is unnecessary (251). The risk of vertical transmission is low (<5%) although higher in women with HIV or high HCV RNA levels.

HCV: Nonhepatic Transplantation

Epidemiology and risk factors

The prevalence of HCV infection in candidates for nonhepatic SOT varies by organ group and geography. The prevalence of HCV in dialysis patients has declined largely due to blood product screening implemented in the early 1990s and adherence to infection control practices. In 2002, the seroprevalence of HCV in US hemodialysis units was 7.8% (254). Substantial variability in HCV prevalence however exists by country and amongst different dialysis centers within a single country (254,255). HCV infection is an independent risk factor for mortality in hemodialysis patients (267,268). The prevalence of HCV infection in thoracic organ transplant candidates has been less rigorously assessed but seems to approximate the population prevalence (256,257).

The impact of HCV on the outcomes of nonhepatic SOT has been studied most extensively in renal transplant recipients. Several studies have looked at the rate of fibrosis progression using paired liver biopsies. Some have found the rate of HCV-related fibrosis progression is accelerated (258) whereas other have documented stable or improved findings on liver biopsy postrenal transplant (259–261). With long-term follow-up, it is clear that there is an adverse impact of HCV infection on overall patient and graft survival (106,262) with the 10-year survival being approximately 15% lower in HCV-positive compared to HCV negative renal transplant recipients. In addition, there is an increased risk of posttransplant diabetes, the potential for de novo or recurrent HCV-related renal disease, and an increased risk of severe infectious complications (263–265).

On an individual basis, however, the risk of accelerated progression of fibrosis and progression to end-stage liver disease and its complications seem to be limited largely to those with advanced fibrosis or cirrhosis at the time of transplant (106,259,261). Renal transplant patients with moderate (METAVIR stage 2) or less liver disease at baseline have a low risk of progression of liver disease (106,260,266).

There are no long-term studies regarding the impact of HCV on outcomes of heart or small bowel or pancreas recipients. Studies in these populations have suggested no difference in patient and graft survival (269–271), likely due to short-term follow-up and/or the relatively small numbers studied. In lung transplant recipients, a recent analysis of the OPTN/UNOS database showed similar 5-year survival amongst HCV-seropositive and seronegative recipients (272). In a study of 14 HCV-RNA lung transplant recipients, the 5-year survival was similar to HCV negative recipients (273). Based on extrapolation from the renal transplant literature, however, there may be an increased risk of HCV-related death beyond 5 years in other nonhepatic SOT recipients. Further studies are needed to clarify the impact of HCV on the outcomes of nonrenal nonhepatic SOT.

Diagnosis

The diagnosis of hepatitis C infection relies on the same serologic and virologic investigations used in the nontransplant population. Initial screening for antibody to HCV should be done at the time of transplant assessment. In those with positive HCV serology, qualitative HCV RNA should be used to confirm current infection. In any patient considered a potential candidate for HCV therapy, HCV genotype should be determined.

In chronic HCV infection, the liver biopsy remains the "gold standard" for assessing the degree of hepatic inflammation and fibrosis and thus the prognosis of the disease. Liver biopsy results are used to guide antiviral treatment decisions, identify those who may be considered for combined (with liver) transplant and those who may be ineligible for nonhepatic SOT due to advanced liver disease (274,275). Noninvasive methods to assess hepatic fibrosis, such as FibroScan, FibroTest, transient and magnetic resonance elastography, are increasingly used but need to be validated in this population. In a small study of six renal transplant candidates, measurement of HVPG assessing for portal hypertension was shown to alter management when added to the diagnostic assessment (276).

Recommendations:

- Initial screening for antibody to HCV should be done at the time of transplant candidacy assessment, with HCV RNA used to confirm current infection (II-1).
- Liver biopsy is recommended in the assessment of all nonhepatic SOT candidates with chronic HCV to guide further management ((II-2).
- Although not recommended as routine, HVPG measurements may guide therapy and selection of candidates who may be more appropriate for combined liver-kidney transplant (III).

Treatment: The current standard of care for treatment of HCV infection in the general population is combination therapy with pegylated interferon and RBV in those with genotype 2 or 3 and peginterferon, RBV and an HCV NS3 protease inhibitor in those with genotype 1. However, treatment of HCV in nonhepatic SOT recipients is generally contraindicated due to a significant risk of acute allograft rejection. Amongst renal transplant recipients, this may occur in up to a third of patients, and is not uncommonly steroid resistant (277,278). IFN-based therapy is not recommended in life-sustaining (e.g. heart, lung) transplants (279). Clinical cure of HCV postrenal transplant has however been reported and in those with progressive HCV-related liver or renal disease, therapy may be considered (280–282). Ribavirin however is key to successful HCV therapy, but contraindicated in those with GFR <50 mL/min. There are no data on the use of HCV protease inhibitors in this population and thus they cannot be recommended. There are important interactions between telaprevir/boceprevir and calcineurin inhibitors. All of these factors severely limit the applicability of current HCV therapies to the posttransplant population. This highlights the importance of treating HCV before transplant whenever possible (see Prevention/Prophylaxis below)

Recommendations:

- In recipients of life-sustaining (e.g. heart, lung) transplants, HCV treatment with IFN-based therapy should be avoided (III).
- In renal transplant recipients, HCV therapy may be considered on a case-by-case basis in those with significant HCV-related disease and after careful review of the potential risks and benefits (II-3).

Prevention/Prophylaxis: Given the risks associated with posttransplant therapy, treatment of HCV should be considered at the time of candidacy assessment in all patients. Although this has been best studied in renal transplantation, similar principles are applied to other nonhepatic SOT patients with a few caveats noted below.

Liver biopsy is key to the management and selection of patients for HCV therapy and listing (179,282,283). Those with minimal liver disease (METAVIR stage F0-F1) have an excellent posttransplant outcome with low risk of progression of liver disease and do not generally need to undergo HCV therapy before listing (106,260,266). Those with moderate (F2) fibrosis also generally have reasonable outcomes posttransplant, although an attempt at HCV therapy is recommended but not considered necessary before listing. There are a number of factors that should be considered in those with mild to moderate fibrosis that may lead to a decision to treat on an individual basis (Table 2).

Table 2: Factors to consider in assessment for HCV treatment in nonhepatic SOT candidates with mild to moderate fibrosis

Factor	Implication
HCV genotype	Higher rates of cure for genotype 2/3 vs. 1 Greater complexity of therapy for genotype 1 (3 drugs vs. 2; more adverse effects; more drug-drug interactions)
Degree of fibrosis	Stronger consideration of therapy in F2 vs. F0/F1 fibrosis
Age	Older patients with milder disease unlikely to have significant progression
Estimated duration of infection	If estimated duration of infection is short, those with mild-moderate disease may have more rapid progression than those with similar degrees of fibrosis but longer estimated duration of infection
Comorbidities	Renal dysfunction, cardiac disease and anemia severely limit the treatment of HCV
Estimated posttransplant survival	Factoring in age, comorbidities, type of transplant to estimate survival may guide therapy as the negative impact of HCV generally not seen until 5–10 years posttransplant

Those with bridging fibrosis (F3) or compensated cirrhosis (F4) should be strongly considered for HCV therapy due to the increased risk of progressive fibrosis, cirrhosis and liver related mortality. If therapy is not otherwise contraindicated and SVR is achieved, they may then be listed for nonhepatic transplant alone. If therapy is unsuccessful, the options include nonhepatic transplant with a full discussion of the increased risk of poor outcomes, combined liver-nonliver transplant, or decline/defer nonhepatic transplant. Those with decompensated cirrhosis are not appropriate candidates for isolated renal transplant but should be considered for combined liver-kidney transplant (179,282,283). Some centers use HVPG to identify those with portal hypertension who may be particularly poor candidates for isolated renal transplant and better served by combined.

Regimens studied for the treatment of HCV in dialysis and prekidney transplant patients include IFN or peg-IFN with or without RBV (284,285). Most show response rates significantly lower than that in the general population. Standard IFN and Peg-IFN monotherapy results in SVR rates of 13–75% (179). Most studies are small and many do not report response by genotype. Prerenal transplant HCV therapy is also hampered by a higher rate of adverse events and discontinuation compared to the general population. Several small case series have documented safe use of RBV in combination with IFN in patients with chronic HCV and poor renal function, generally with measurement of plasma RBV levels (286–291). Given the limited data however, RBV remains contraindicated in patients with a GFR $<$50 mL/min (292). For patients with genotype 1 HCV, triple therapy with peg-IFN, RBV and PI (boceprevir or telaprevir) is the standard of care (293,294). Although the PIs are not contraindicated in renal failure there are no data on the use of triple therapy in this population.

Data regarding the management of heart and lung transplant candidates with chronic HCV are limited. Until further data are available, the principles and data from the renal transplant population may be used to guide management. A liver biopsy, or noninvasive assessment of fibrosis, should be done as part of the assessment in those infected with HCV. 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) (295,296). Those with mild to moderate disease (METAVIR stage F0–F2) may be listed for transplant, whereas those with advanced HCV-related fibrosis or cirrhosis are often not considered candidates for cardiac transplantation (297). There are limited data on the outcome of lung transplantation in HCV-positive recipients (272,273). According to international guidelines, HCV infection is a contraindication to lung transplantation (298). However, some centers do consider listing HCV-positive lung transplant candidates, using the liver biopsy to guide the decision for listing and/or consideration of therapy pretransplant (257,272,273,275). One small series has shown that selected lung transplant candidates can safely and effectively be treated for HCV before transplantation (275).

Recommendations:

- Nonhepatic HCV-infected transplant candidates should be evaluated for eligibility for HCV therapy before transplant (II-2).
- A suggested approach to the assessment and management of HCV infected nonhepatic transplant candidates is as follows (III):
  - Those with mild to moderate liver disease (METAVIR stage F0-F2) do not need to undergo HCV therapy before listing; treatment may be considered in kidney or lung transplant candidates weighing factors outlined in Table 1.
  - Kidney or possibly lung transplant candidates with bridging fibrosis (F3) or compensated cirrhosis (F4) should undergo HCV therapy; if an SVR is achieved they may then be listed for transplant. If therapy is otherwise contraindicated or unsuccessful, options include nonhepatic transplant, assessment for combined liver-nonliver transplant, or decline/defer nonhepatic transplant.
  - In heart transplant candidates, HCV therapy is contraindicated, thus those found to have bridging fibrosis (F3) or compensated cirrhosis (F4), the options include assessment for combined liver-heart transplant or decline/defer heart transplant.
  - Those with decompensated cirrhosis are not considered candidates for isolated nonhepatic transplant but may be considered for combined liver-nonhepatic transplant.

The HCV-positive donor

Transplantation of an HCV-positive organ into an HCV-negative recipient results in near universal transmission (299) and frequently an aggressive course with a high risk of death (300,301). Hence it is not recommended to transplant an HCV positive organ into an HCV negative recipient.

In those already infected with HCV, some groups have found no difference in patient and graft survival when using HCV positive kidneys into HCV positive recipients (302,303). Several other recent large studies however have shown a significant increased risk of death in HCV-positive recipients receiving an HCV-positive kidney or heart transplant (256,302,304,305). Despite this, there remains an overall survival advantage to receiving an HCV-positive kidney transplant over remaining on dialysis (306). The waiting time on the renal transplant list is also reduced significantly in the United States, by approximately 1 year. Despite the overall benefit, HCV-positive kidneys continue to be underutilized (307).

There are no data with regard to the impact of donor and recipient HCV genotype on nonhepatic transplant outcomes. Although it is desirable to avoid transplanting an organ from a genotype 1 donor into a recipient with genotype 2 or 3, data on donor genotype are rarely available at the time of transplant. The HCV genotype of the donor, whether known or unknown, should not routinely impact the decision to accept the organ for an HCV-infected recipient given the documented survival advantage and lack of data showing any negative impact of donor—recipient genotype.

Recommendations:

- Given the current era of organ shortage and risk of death on the waitlist, an HCV-positive organ should be considered for transplantation, with informed consent, into an HCV-positive recipient (II-2).
- The use of HCV-positive organs into HCV-negative recipients should be avoided due to poor outcomes;

however this may be considered with strict informed consent in critically ill patients awaiting a life-sustaining transplant (III).

Infection control issues: Nonhepatic SOT patients with HCV should not share personal items that may be contaminated with even small amounts of blood. The risk of sexual transmission in long-term heterosexual couples is minimal and routine use of barrier protection is not necessary to prevent transmission.

Hepatitis D Virus (Delta Virus)

HDV is a small, defective RNA virus that can only replicate in the presence of HBV surface antigen, either by co-infection or superinfection (308). Nearly 20 million people are infected worldwide with HDV, although the prevalence varies by location (309). Co-infection is common in the Pacific Islands, whereas other parts of the world (Japan, Europe, United States) have <10% co-infection rates. As in HBV, HDV is transmitted parentally and only requires a small inoculum. This results in the high potential for transmission in intravenous drug users and those with high-risk sexual behavior. Because of blood product screening, new infections in patients receiving blood transfusions and hemodialysis are rare. All HBsAg+ patients from endemic regions, with high- risk activities, or with unexplained elevated liver enzymes in the setting of low or undetectable HBV DNA, should be tested for HDV via sensitive real-time PCR assays or anti-HDV (IgG or IgM) antibodies (310,311).

In the transplant setting, patients with HDV infection typically have low or undetectable HBV DNA, ultimately leading to reasonable survival rates even without antiviral prophylaxis (312–314). The goal of treatment is to eradicate HDV together with HBV, although definitive resolution can only be obtained with HBsAg clearance that inhibits the potential for HDV replication. Standard treatment pretransplant is usually with interferon and has been shown to improve long-term clinical outcomes, albeit only 20–30% successful in achieving HDV RNA negativity (206,315). Oral antiviral agents for HBV have no direct efficacy against HDV (316–319). Most transplant centers use a posttransplant protocol that includes the use of HBIG and a nucleos(t)ide analogue to minimize the risk of HBV reactivation, although this will have little impact on HDV replication other than HBsAg clearance. There have been few published reports of HDV recurrence and successful IFN therapy after hepatic or nonhepatic SOT (320–322).

Hepatitis E Virus

First reported in 1980 in India, hepatitis E virus (HEV) is now a common cause of water/food-borne acute hepatitis in the developing world (323). Genotypes 1 and 2 only infect humans by fecal–oral routes, whereas genotypes 3 and 4 primarily infect other mammals (324). The typical disease is characterized by severe acute hepatitis and high mortality in pregnant women, the elderly and patients with preexisting chronic liver disease (325). However, in nonendemic regions, genotype 3 HEV via consumption of infected animal meat is now recognized as an uncommon etiology of chronic liver disease among immunosuppressed hosts and transplant recipients (326–330). Over half of SOT recipients infected with HEV will develop chronic hepatitis and ∼15% will develop cirrhosis (327). The use of tacrolimus-based immunosuppression and the presence of thrombocytopenia have been associated with chronic HEV infection in such recipients (327,329). HEV IgG antibodies are present in ∼ 16% of blood donors and in renal transplant recipients, although this does not specifically distinguish chronic infection versus prior exposure (326,329,331).

The diagnosis and treatment of chronic HEV infection in transplant recipients can be challenging. Most patients are asymptomatic and have a mild to moderate degree of aminotransferase elevations (ALT 100–300 IU/L) that can be elusive particularly in liver recipients with other potential causes of chronic injury. It has also been reported to cause neurological symptoms and glomerulonephritis (329,332). The diagnosis is limited by the lack of commercial assays for HEV RNA and reliance on anti-HEV immunoglobulin M (IgM) antibody testing that may be insensitive (331). It is therefore advisable to send both serological and PCR-based assays if the diagnosis is considered (i.e. unexplained hepatitis). Other than reducing immunosuppression, there is no standard antiviral therapy for chronic HEV infection. Peg-IFN may have some efficacy but carries a risk of graft rejection (328,333). There have been a few reports of successful HEV treatment with RBV in kidney and heart recipients and this can be considered in patients who remain infected despite reduction in immunosuppression. Fortunately, reactivation after clearance of HEV has not been observed to date.

Given limited treatment options, prevention is key, e.g. avoidance of uncooked meats (genotype 3 and 4) and infected water or contacts (genotype 1 and 2). There is no systematic screening for HEV infection in blood banks, as blood-borne transmission is still extremely rare. Two recombinant vaccine candidates, the rHEV vaccine and the HEV 239 vaccine, have been successfully evaluated in Phase II/III trials, although only for genotype 1 infection (334,335).

Recommendations:

- SOT recipients with unexplained chronic hepatitis should be tested for hepatitis D (if HBV+) and hepatitis E viruses, despite the lack of effective treatments in this population (III).
- Although no definitive treatment exists for HEV, reduction in immunosuppressive therapy doses or agents may be advisable (III).

- Recipients should avoid consumption of uncooked meats and potentially contaminated water, as well as contact with HEV-infected individuals (III).

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