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Viral Hepatitis in Solid Organ Transplant Recipients

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1. Introduction

Hepatotropic viral infections are frequent in allograft recipients and may be caused by a number of different viruses. Of these, the most important infectious agents are hepatitis B virus (HBV) and hepatitis C virus (HCV), which can cause both acute and chronic hepatitis. In addition, Hepatitis E virus (HEV), thought previously to only cause acute hepatitis in the developing world, is emerging as an increasing cause of chronic hepatitis and even cirrhosis in solid organ transplant recipients in industrialized countries(Gerolami, Moal et al. 2008; Kamar, Mansuy et al. 2008; Gerolami, Moal et al. 2009; Haagsma, Niesters et al. 2009). Hepatitis D virus (HDV) additionally plays an important role in both coinfection and superinfection of HBV in solid organ transplant recipients. In addition to the primary viral hepatitis infections, a variety of other systemic viral infections, such as the herpesviruses, cytomegalovirus (CMV), Ebstein Barr Virus (EBV), and varicella zoster virus (VZV) can have toxic effects on the liver in the posttransplant recipient. This chapter will focus primarily on the epidemiology, transmission, clinical presentation and management of the primary hepatitis viruses: HBV, HCV, HDV and HEV, following solid organ transplantation. General concepts in the prevention of post-transplant hepatotropic infections and recent advances and challenges will also be discussed.

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 posttransplantation. These include the first month; the second through sixth months, and the late posttransplant period (beyond the sixth month) (Fishman 2007). 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 in the early posttransplant period.

2.1 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 some type of screening for common types of infections in order to reduce transmission from the donor to the recipient. 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 in solid-organ transplant recipients.

2.1.1 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, however active donor infection (e.g. viremia) may also cause viral hepatitis in solid organ transplant recipients. HBV, HCV and CMV are the most commonly reported hepatotropic viruses transmitted during solid organ transplant though the incidence of transmission 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(Haagsma, Niesters et al. 2009).

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 CMV, HBV (hepatitis B surface antigen (HBsAg), antibodies against hepatitis B surface antigen (anti-HBs)), HCV, EBV, and VZV. In certain situations (e.g. history of intravenous drug use or known exposure to a hepatotrophic 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(Humar, Morris et al. 2010). For example, NAT for HBV can detect infections 21.8-36 days earlier when compared to standard serologic assays(Singer, Kucirka et al. 2008). 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(Humar, Morris et al. 2010). A 2008 survey of the 58 U.S. organ procurement organizations (OPOs) documented that 47% performed NAT on all potential donors(Orlowski, Alexander et al. 2009). 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

state 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)(Humar, Morris et al. 2010).
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 or who were previously infected with HBV, provided there is prophylaxis with anti-HBV antiviral agents(Fabrega, Garcia-Suarez et al. 2003; Seehofer and Berg 2005; Prakoso, Strasser et al. 2006). The use of organs infected with HCV can generally be used in other HCV-infected recipients, although this practice remains somewhat controversial(Peek and Reddy 2007).

2.1.2 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, since immunosuppression will exacerbate the infectious process. Prior to the era of antiviral prophylaxis (late 1980s), 80% of patients experienced HBV reinfection after liver transplantation(O'Grady, Smith et al. 1992). 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 (Buti, Mas et al. 2007; Coffin and Terrault 2007). In contrast, the course of HCV infection after liver transplantation remains discouraging. Since effective antiviral therapies are lacking, recipients are uniformly reinfected by HCV, with outcomes determined by the viral strain, the presence or absence of previous immunity, and the response to antiviral therapy(Lake 2006; Gurusamy, Tsochatzis et al. 2010).
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 epidemiologic risk factors and recent exposures is performed (e.g. HBV or HCV viral load).

2.1.3 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 (Zou, Dorsey et al. 2010). The transmission of HCV via transfusion currently stands at about a rate of 1 in 2 million units(Dwyre, Holland et al. 2008).
In the hemodialysis setting, 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(Edey, Barraclough et al. 2010). The incidence and prevalence of HCV infection among hemodialysis patients remain higher than the corresponding general population.

2.2 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 (Acott, Crocker et al. 2004). In addition, alemtuzumab (Campath-1H, anti-CD52 monoclonal antibody) induction has been associated with rapidly progressive HCV recurrence in addition to an increased risk of viral infections posttransplant compared to controls (Marcos, Eghtesad et al. 2004; Levitsky, Thudi et al. 2011). On the other hand, the IL-2 receptor antagonists have been shown to result in lower rates of CMV infection, especially in kidney transplant recipients (Webster, Ruster et al. 2010). 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) which is commonly an EBV-related lymphoma(Opelz and Dohler 2004).

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

The issues related to viral hepatitis in organ transplant recipients are complex, and the approach to management is highly dependent on the organ transplanted. The approach to liver transplant patients is significantly different from that of nonhepatic organ transplant recipients of viral hepatitis and thus the discussion will be presented based on the type of organ (liver versus non-liver) transplanted.

3.1 Hepatitis B

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)(Dienstag 2008).

Chronic HBV infection can be divided into several phases(Lok 2002). 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, the immune tolerance phase evolves to an immune clearance phase 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(Lok 2002). HBV replication correlates with the presence of hepatitis B e antigen (HBeAg). Prolonged HBeAg sero-positivity or high HBV viral load is associated with prolonged liver injuries and a higher risk of HCC(Yang, Lu et al. 2002). The immune responses during HBV infection are responsible to the injuries in the liver (Bertoletti and Gehring 2007).

3.1.1 HBV in the Liver Transplant recipient

3.1.1.1 Epidemiology & specific risk factors

Fulminant hepatitis and cirrhosis caused by HBV are important indications for LT accounting for ~10% of all LT in the United States. Vaccination against HBV has dramatically reduced the prevalence of HBV infection in candidates for LT, but it remains elevated in patients from developing countries(Chen 2009).

Prior to the era of antiviral prophylaxis, 80% of patients experienced HBV reinfection after LT, resulting in a 50% two-year posttransplant mortality(Todo, Demetris et al. 1991). Although the major source of viral replication (the liver) is removed, circulating virions in extrahepatic sites, such as peripheral blood mononuclear cells, can reinfect the newly transplanted liver soon after liver transplant(Feray, Zignego et al. 1990). In the mid 1990s, Lamivudine (LAM), the first oral antiviral agent for HBV, in addition to hepatitis B immunoglobulin (HBIG) revolutionized the treatment of HBV. Long-term high-dose HBIG combined with LAM can reduce HBV recurrence to less than 10%(Chen, Yi et al. 2010).

However, combined treatment with HBIG and LAM is sometimes unable to control recurrent HBV infection. Recurrent graft infection may lead to rapid disease progression and even death within the first year after LT(Kennedy and Alexopoulos 2010). While uncommon, viral resistance to antiviral therapy and HBIG may cause HBV-related graft dysfunction(Cooreman, Leroux-Roels et al. 2001). Additional risk factors for recurrence include high viral load (> 2 X 10^4 IU/mL [10^5 copies/mL]) at the time of LT, high levels of immunosuppression, HBeAg positivity and prophylaxis noncompliance. Recurrence is less common in patients undergoing LT for fulminant HBV or those with concurrent hepatitis delta virus (HDV) infection as such patients typically have lower viral loads(Marzano, Gaia et al. 2005). The aggressive clinical course is probably due to stimulation of viral replication and direct cytotoxicity of HBV under immunosuppressive therapy(Jiang and Yan 2010). Therefore, suppression of HBV replication is paramount to prevent disease progression in the transplanted liver.

3.1.1.2 Diagnosis

HBV recurrence is typically defined as the reappearance of HBsAg after LT. This is generally associated with detectable HBV DNA in the blood, although viremia may also occur in the absence of HBs-antigenemia. HBV DNA has been detected in the serum, liver and peripheral blood mononuclear cells of HBsAg-negative patients on long-term prophylaxis using sensitive polymerase chain reaction (PCR)-based techniques(Roche, Feray et al. 2003). The clinical significance of these observations remain uncertain but is likely because of persistent occult HBV infection which may be sensitive to changes in HBV prophylaxis or modulation of immunosuppression.

Once activation of virus replication takes place, aggressive hepatitis and subsequent rapid development of liver failure may develop (a syndrome described as fibrosing cholestatic hepatitis, or FCH). FCH is defined as a rapidly progressive liver disease with cholestasis, jaundice, hepatic fibrosis, and liver failure, often complicated by sudden and severe multiorgan dysfunction(Angus, Locarnini et al. 1995). With appropriate post-LT prophylaxis, FCH is an extremely rare condition and should not be seen unless there is patient nonadherence. Retransplantation has been performed in patients with FCH, but those who have rapid liver failure shortly after OLT have poor survival (Kim, Wiesner et al. 1999).

Monitoring protocols for HBV recurrence after LT vary among transplant centers. HBsAg and DNA should be performed at least every 3 months even with HBIG and oral antiviral therapy. Although newer, more potent antiviral agents or combination therapy are associated with a lower potential for drug resistance, currently there are insufficient data to allow for less frequent monitoring(Levitsky and Doucette 2009). Persistent detection of HBV DNA levels of >3 log copies/mL during prophylaxis therapy indicates HBV recurrence and warrants a change in HBV therapy.

3.1.1.3 Treatment

Pretransplant: Antiviral therapy prior to LT, particularly if HBV DNA can be reduced to undetectable levels (or at least < 2 X 10^4 IU/mL), reduces the risk of HBV recurrence. Seven drugs are licensed in the United States for the treatment of HBV infection: interferon alfa (IFNα), pegylated interferon alfa-2a (Peg-IFNα), lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine, and tenofovir (TDF)(Dienstag 2008). The use of IFN, which requires injections daily or thrice weekly, has been supplanted by long-acting Peg-IFN, which is injected once weekly. A detailed discussion of pre-transplant HBV therapy is beyond the scope of this chapter. In general, therapy should be with a potent nucleos(t)ide analogues or combination therapy and based on published guidelines(Bhattacharya and Thio 2010; Alberti and Caporaso 2011). IFN therapy is not recommended in decompensated cirrhotic patients given the risk of precipitating hepatitis flares and further decompensation(Levitsky and Doucette 2009).

Posttransplant recurrence: HBV infection after LT is usually the result of failed prophylaxis (see *prophylaxis/prevention),* either due to noncompliance or the development of drug- or HBIG-resistant HBV infection. The management strategies are the same regardless of the reason for HBV infection, but the choice of antiviral agents will be dictated by whether the virus is wild-type or mutant.

In the pre-LAM era, IFN-α was a common therapeutic option for patients with recurrent HBV infection after LT. However, with the advent of LAM, it has not been used as a first-line treatment drug. Patients using IFN-α have a lower efficacy and a higher risk of precipitating allograft rejection than those using LAM(Terrault, Holland et al. 1996). LAM has been used in the treatment of recurrent HBV infection, with an excellent safety profile in both compensated and decompensated cirrhotic patients(Perrillo, Rakela et al. 1999). However, the major factor limiting the use of LAM in the treatment of graft HBV infection after LT is the development of mutations in the thyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase gene, which confers resistance to LAM. In non-immunosuppressed patients, the LAM resistance rate is 15%-20%, however LAM resistance is detected in as many as 45% immunosuppressed patients within the first year of treatment (Lai, Dienstag et al. 2003). Thus, although LAM therapy results in a loss of viral replication markers in serum, an improved hepatic biochemical profile and improvement or stabilization in liver histology, LAM resistance and its possible accompanying clinical deterioration have limited its long-term use in the treatment of recurrent HBV infection after LT(McCaughan, Spencer et al. 1999).

Adefovir dipivoxil (ADV), a nucleotide analog that selectively inhibits viral polymerases and reverse transcriptase, is effective against HBeAg-negative and positive cases and has an excellent activity against wild-type as well as LAM-resistant HBV strains(Perrillo, Schiff et al. 2000; Hadziyannis, Tassopoulos et al. 2003). Additionally, ADV plus LAM can achieve favorable outcomes of HBsAg seroconversion and undetectable HBV DNA in patients with *de novo* graft HBV infection and LAM resistance(Toniutto, Fumo et al. 2004). Mildly elevated serum creatinine level may occur after treatment with ADV, especially in combination with calcineurin inhibitors, but only a small number of patients require dose adjustment, and even discontinuance(Jiang and Yan 2010). However, renal function should be regularly monitored, with dose adjustments based on renal function, as necessary.

Entecavir (ETV), a very potent anti-HBV selective guanosine analogue, approved by the United States FDA in 2005, can also be used in the treatment of chronic HBV infection.

Unfortunately, few reports are available on ETV in treatment of recurrent HBV infection. Most data concerning its efficacy and safety are obtained from patients without LT. ETV is superior to LAM or ADV in rendering HBV-DNA undetectable and has a very good resistance profile, with <2% cumulative 5-year resistance rate in nucleos(t)ide-naïve chronic HBV patients(Papatheodoridis, Manolakopoulos et al. 2008). In addition, it lacks the nephrotoxicity that can be seen with ADV, making it an attractive option. However, the high probability of resistance with long-term ETV documented in non-transplant patients with LAM resistance suggests this ETV is not a good option for LAM-resistant cases post-transplant(Tenney, Rose et al. 2007). In cases without LAM resistance, ETV could be used due to its great potency, high genetic barrier and absence of nephrotoxicity.

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue has excellent antiviral activity against both wild-type and LAM-resistant HBV both *in vitro* and *in vivo*(Ying, De Clercq et al. 2000; Kuo, Dienstag et al. 2004; Lada, Benhamou et al. 2004; Marcellin, Heathcote et al. 2008). Furthermore, TDF shows a stronger antiviral effect than ADV on LAM-resistant HBV(van Bommel, Zollner et al. 2006). In addition, TDF plus LAM can safely and markedly suppress HBV replication in patients with resistance to or non-response to ADV(Choe, Kwon et al. 2008). Finally, in pretransplant chronic HBV patients with resistance to both LAM and ADV, TDF retains significant activity against HBV although this appears diminished in comparison with studies of naïve patients(Patterson, George et al. 2011). Only two studies are available on the application of TDF in the treatment of recurrent HBV infection after LT(Neff, Nery et al. 2004). An additional pilot study suggests that combination therapy with ETV-TDF may be more effective than monotherapy for HBV recurrence following LT(Jimenez-Perez, Saez-Gomez et al. 2010). Finally, TDF has significant renal tubular toxicity, and in more severe cases, patients can develop Fanconi syndrome (which is characterized by tubular proteinuria, amino aciduria, phosphaturia, glycosuria, and bicarbonate wasting [leading to metabolic acidosis] or acute kidney injury. Renal toxicity is especially prevalent after liver transplant in the setting of immunosuppressant medications that also effect renal function. Although TDF can significantly decrease LAM-resistant HBV variant replication after LT, further studies are needed to determine its efficacy and safety profile with a long follow-up time and a large cohort of patients.

3.1.1.4 Prevention/prophylaxis

Advances in antiviral prophylaxis have dramatically improved the outcome of transplantation in HBV-infected recipients. HBIG, a polyvalent immunoglobulin with a high titer of anti-HBs, binds to intracellular and circulating virions to prevent graft infection and quickly became the standard of care at most centers worldwide that provide LT. The high cost of HBIG ($30–50,000/yr), the inconvenience of ongoing IV infusions and the need for continued anti-HBs monitoring have stimulated discussions about alternative prophylaxis therapies(Gish and McCashland 2006). LAM monotherapy improves the rate of recurrence over no prophylaxis, although the development of resistance results in recurrence in 10-50% of patients within 1-3 years after LT(Perrillo, Rakela et al. 1999; Zheng, Chen et al. 2006). In contrast to monotherapy, combination therapy with IV HBIG and LAM is highly efficacious in preventing graft infection (<10%)(Markowitz, Martin et al. 1998; Dumortier, Chevallier et al. 2003; Gane, Angus et al. 2007). Samuel et al. was the first to describe the use of hepatitis B immunoglobulin (HBIG) in a large clinical trial to prevent recurrent liver disease after LT in patients with liver failure due to HBV infection(Samuel, Muller et al. 1993).

One major question to answer has been to discover if and when patients can be discontinued from HBIG therapy and maintained on antiviral therapy alone. Notably, the recurrence rate of HBV infection in the liver graft exceeds 60% with short-term HBIG monotherapy (< 6 months), but is < 10% if HBIG is stopped more than 6 months to 1 year after LT with continuation of a nucleoside such as LAM(Dodson, de Vera et al. 2000). In addition, the use of low-dose intramuscular HBIG is also evolving(Yao, Osorio et al. 1999; Yan, Yan et al. 2006; Gane, Angus et al. 2007). Although it has not yet been defined who can safely discontinue HBIG therapy, the best candidates are probably patients with undetectable HBV DNA before LT who use combination therapy with medications that have low risk of resistance.

In addition to HBIG + LAM prophylaxis, low recurrence rates have also been demonstrated in patients given combination oral antiviral therapy (LAM + ADV) prior to LT and who continued therapy post-LT with or without the use of postoperative HBIG therapy(Schiff, Lai et al. 2003). In addition, cost modeling has demonstrated that LAM + ADV may be much cheaper because of the high cost of HBIG(Dan, Wai et al. 2006). However, there are currently insufficient data to recommend post-LT prophylaxis with nucleos(t)ide analogues alone in the absence of HBIG. Similar to treatment of recurrent HBV, the choice of prophylaxis for HBV should be based on antiviral exposure history, resistance testing and the principles of HBV therapy pre-LT.

Finally, all HBV uninfected, nonimmune LT candidates should be vaccinated for HBV as early as possible pre-LT. The percentage of patients who successfully seroconvert, however is suboptimal (16-62%), even with double dose regimans, and many (37%-73%) lose antibodies to HBsAg within the first year following LT(Levitsky and Doucette 2009).

3.1.1.5 Anti-HBc positive donors

Donors who are anti-HBc positive pose a significant risk (ranging 34–86%) of transmitting HBV infection to liver transplant recipients without prophylaxis(Nery, Nery-Avila et al. 2003). Oral antiviral therapy is effective prophylaxis, with or without HBIG, in recipients of these organs and should be continued indefinitely post-transplant, unless HBV DVA negativity can be confirmed in the serum and liver tissue of the donor(Nery, Nery-Avila et al. 2003).

Rarely, despite prophlyaxis, late HBV infection with antiviral-resistant HBV has been described. The role of HBIG is not defined and should not have any specific benefit because the liver is already infected and there is no benefit to binding circulating virus(Gish and McCashland 2006). Because patients have developed fulminant HBV in this setting, even with the use of LAM, combination therapy or drugs with a high barrier to resistance may be the best option. The role of routine HBsAg and/or HBV DNA monitoring in recipients of anti-HBc-positive grafts is unclear; however unexplained aminotransferase elevation should be investigated with HBsAg and HBV DNA to rule out *de novo* HBV infection(Levitsky and Doucette 2009).

3.1.2 HBV in other solid organ transplants

3.1.2.1 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%(Burdick, Bragg-Gresham et al. 2003). 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%(Covic, Iancu et al. 1999; Vladutiu, Cosa et al. 2000; Carrilho, Moraes et al. 2004; Yakaryilmaz, Gurbuz et al. 2006). 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(Fabrizi, Lunghi et al. 2002). Iatrogenic transmission of HBV has also been reported after transplantation of two stored vessel conduits from hepatitis-seropositive donors into seronegative kidney transplant recipients(MMWR 2011). The prevalence of chronic HBV in other nonhepatic transplant candidates has not been well studied, but likely mirrors the population prevalence(Wedemeyer, Pethig et al. 1998). Interestingly, in cardiac allograft recipients, HBV contamination can occur after transplantation and is 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)(Thompson, Perz et al. 2009).

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(Correa, Rocha et al. 2003). Increased mortality, if it occurs, is usually seen ten years or more following renal transplantation. Contradictory results concerning the long-term outcomes of HBV infection in heart transplant recipients have been reported. Some authors have described a poor outcome, with cirrhosis occurring in more than 55% of patients within the first decade after transplantation, and 17% of patients dying of liver failure(Wedemeyer, Pethig et al. 1998). Others have reported little impact on short- or long-term survival (Lunel, Cadranel et al. 2000). However, more recent studies in renal and cardiac transplantation have demonstrated excellent outcomes in HBsAg-positive patients managed with nucleos(t)ide analogue therapy(Ko, Chou et al. 2001; Park, Yang et al. 2001; Potthoff, Tillmann et al. 2006; Ahn, Kim et al. 2007).

In nonhepatic solid organ transplant (SOT) recipients with markers of past HBV infection (HBsAg-negative; anti-HBc positive), there is a low risk (<5%) of HBV reactivation(Blanpain, Knoop et al. 1998). Although uncommon, when present, reactivation has been associated with rapid progression to cirrhosis and death(Knoll, Pietrzyk et al. 2005).

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-HBc-positive nonhepatic donor is significantly lower (<5%) than that of hepatic donors. Organs from anti-HBc-positive donors can be safely used with informed consent and appropriate strategies to prevent transmission (Levitsky and Doucette 2009).

3.1.2.2 Diagnosis

The diagnosis of HBV in nonhepatic SOT relies on the same serological and nucleic acid assays used in the nontransplant population(Lok 2002). Liver biopsy should be incorporated

in the evaluation of renal transplant candidates with HBsAg because it is difficult, on clinical grounds alone, to estimate the severity of liver disease in uremic patients(Fabrizi, Lunghi et al. 2002). 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).

3.1.2.3 Treatment

Nonhepatic 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(Bhattacharya and Thio 2010; Alberti and Caporaso 2011). 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 nonhepatic 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(Fabrizi, Lunghi et al. 2002).

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 may be appropriate in immunosuppressed individuals following transplant(Dulai, Higa et al. 1999). 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 and associated with a low rate of response in immunocomprised 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 low in treatment-naive patients, it may be as high as 51% 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 three years of treatment(Marcellin, Heathcote et al. 2008; Heathcote, Marcellin et al. 2011). TDF has a much lower renal toxicity than ADF and should be preferred in kidney transplant recipients.

3.1.2.4 Prevention/prophylaxis

As in liver transplantation, HBV uninfected, nonhepatic SOT candidates who are nonimmune should be vaccinated for HBV as early in the course of their disease as possible(Levitsky and Doucette 2009). 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(Keating and Noble 2003). Additionally, seroconversion rates decrease with declining renal function(DaRoza, Loewen et al. 2003). Factors related to a poor vaccine response can be acquired, such as ageing, or genetic, such as gender or the HLA

A1B8DR3 "non-responder" haplotype(Davila, Froeling et al. 2010). When the standard protocol is ineffective, the use of intensified protocols or intradermal injections can reinforce immunogenicity in hemodialyzed patients(Benhamou, Courouce et al. 1984; Nagafuchi, Kashiwagi et al. 1991). Finally, booster vaccinations can play an important role in improving immunogenicity, even in the absence of response to primary immunization: a booster injection in renal transplant recipients, vaccinated while on hemodialysis, has a global efficacy of 84%(Jungers, Devillier et al. 1994). 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% and 53%, respectively(Hayney, Welter et al. 2003; Foster, Murphy et al. 2006).

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(Kasiske, Zeier et al. 2010). 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(Knoll, Pietrzyk et al. 2005). Either antiviral prophylaxis or regular serologic monitoring should be employed to limit the risk associated with HBV reactivation(Levitsky and Doucette 2009). 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 progressively rises.

3.1.2.5 Anti-HBc positive donors

Recipients of an organ from a HBsAg positive donor, regardless of immune status, should receive combined prophylaxis with HBIG and a nucleos(t)ide analogue indefinitely(Chung, Feng et al. 2001). If the HBsAg and HBV DNA remain negative, consideration may be given to discontinuing HBIG 6-12 months posttransplant. 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(Chung, Feng et al. 2001; Levitsky and Doucette 2009). 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 HBIG for at least 3-6 months or LAM 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(Levitsky and Doucette 2009).

3.2 Hepatitis C

Hepatitis C Virus (HCV) affects more than 4 million people in the United States and more than 170 million people globally(Lauer and Walker 2001). 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, and infection with the virus is a leading cause of liver transplantation worldwide.

HCV is an RNA virus that belongs to the flaviviridae family, hepciviridae genius; the most closely related flaviviruses viruses are hepatitis G virus, yellow fever virus, and dengue virus(Robertson, Myers et al. 1998). The natural targets of HCV are hepatocytes and, possibly, B lymphocytes(Zignego, De Carli et al. 1995; Okuda, Hino et al. 1999). 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(Neumann, Lam et al. 1998). 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(Lauer and Walker 2001).

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 virtually never found in these countries but 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(Poynard 2004).

3.2.1 HCV in the Liver Transplant recipient

3.2.1.1 Epidemiology & specific risk factors

End-stage liver disease due to HCV is the most common indication for LT in the United States and Europe(Adam, McMaster et al. 2003). HCV recurrence post-LT is essentially universal. The time course of HCV reinfection is faster than among immunocompetent individuals: histologically proven hepatitis C–related cirrhosis can be documented within a mean of 5 years after transplantation. For this reason, recipients with HCV-related liver disease show worse posttransplantation outcomes and greater mortality rates compared with HCV-negative recipients(Forman, Lewis et al. 2002). Fibrosing cholestatic hepatitis, similar to that seen in the early days of HBV transplantation, fortunately only occurs in a small percentage of patients. Once recurrent HCV cirrhosis occurs, 40% decompensate within 1 year, resulting in a 1- and 4-year patient survival of only 66% and 33%, respectively(Brown 2005). Retransplantation for HCV-induced graft failure is associated with particularly poor outcomes and might not be considered in higher risk recipients with advanced age, renal insufficiency, high MELD, deconditioned status and aggressive early (<1 year) HCV recurrence(Neff, O'Brien et al. 2004).

Risk factors for accelerated HCV recurrence are shown in Table 1. The strongest predictors of recurrence are immunosuppressive therapy for acute rejection, CMV infection, preservation injury and older recipient and donor age. Pulsed intravenous methylprednisolone treatment for acute cellular rejection is associated with transient 1–2 log increases in HCV RNA levels(Gane 2008). In addition to being proviral, treatment of acute cellular rejection with corticosteroids is associated with increased mortality and graft loss in LT recipients with HCV infection (relative risk = 2.7–2.9, p = 0.04)(Charlton, Ruppert et al. 2004). In general, induction therapy with either lymphocyte depleting or nondepleting (IL-2 inhibitors) antibodies does not appear to increase the risk of recurrence. However, the use of lymphocyte depleting antibodies for treatment of steroid-refractory rejection profoundly increases the risk of an aggressive HCV recurrence and FCH. HIV coinfection has recently

emerged as an important predictor of poor survival among liver transplant recipients with HCV infection. One-year patient mortality attributable to HCV in coinfected recipients ranges between 27% and 54%. Factors associated with increased risk of post-LT mortality among HCV–HIV coinfected recipients include African-American recipient ethnicity, pre-LT MELD score of >20, intolerance of HAART therapy and higher pre-LT HCV level of viremia(de Vera, Dvorchik et al. 2006). Reduced response rates to treatment of HCV with IFN and ribavirin further attenuate post-LT outcomes in HIV–HCV coinfected liver transplant recipients.

Definite	Controversial	Not clearly associated
Acute rejection therapy intravenous steroids Lymphodepleting antibody	Corticosteroid therapy Use vs. complete avoidance Rapid vs. slow tapering	Induction therapy IL-2 antibody Lymphodepleting antibody
Donor Age	Viral load (> 1 X 10^6 copies/ml) at transplant	HCV+ donor
Recipient Age	Genotype (1b)	Live donor
Cytomegalovirus infection	Donation after cardiac death	Maintenance immunosuppression
Ischemia/reperfusion injury	HLA mismatch	
Diabetes Mellitus		
HIV coinfection		

Table 1. Risk factors for accelerated HCV recurrence after liver transplantation
Adapted from Levitsky & Doucette, Am J Transplantation 2009

More controversial and less clearly defined risks for recurrence include pre-LT viral load, HCV genotype (1b), donor/recipient HLA differences and the use of donors after cardiac death. The effects of different maintenance immunosuppressive agents and steroid tapering regimens are also quite controversisal. Although steroid sparing regimens appear to be safe, a large (n = 312) randomized controlled study, that included a steroid free arm of immunosuppression, has, to date, found no difference in the rate of recurrence of HCV nor in patient or graft survival between steroid free and steroid utilizing arms (Klintmalm, Washburn et al. 2007). Currently, there is no compelling basis for avoiding corticosteroids in the early postoperative period. Recent data also support a slow tapering schedule of steroids in HCV+ recipients to avoid precipitating a more aggressive early recurrence seen with rapid steroid withdrawal(Berenguer, Aguilera et al. 2006). The effect of calcineurin inhibitors on HCV recurrence post-LT has also been a topic of debate. In a prospective randomized controlled study of 495 recipients with HCV infection, no difference was seen in the histological recurrence rate of hepatitis C at 12 months post-LT between patients receiving cyclosporine versus tacrolimus (Levy, Grazi et al. 2006). However, a meta-analysis of studies comparing the two calcineurin inhibitors found a patient and graft survival benefit associated with tacrolimus as maintenance immunosuppression (graft loss: hazards ratio (HR) = 0.73, 95% CI = 0.61–0.86) (McAlister, Haddad et al. 2006). Interestingly, cyclosporine has well-recognized *in vitro* anti-HCV effects and may also have antiviral *in vivo* effects (Martin, Busuttil et al. 2004). In one small uncontrolled study of 8 liver transplant recipients with recurrence of HCV, conversion from tacrolimus to cyclosporine while receiving treatment with Peg-IFNα and ribavirin resulted in 5 patients becoming HCV RNA negative (Sugawara, Kaneko et al. 2006). This finding needs to be confirmed in a controlled fashion and currently data do not support a significant difference in recurrence rates with

the use of cyclosporine versus tacrolimus. Other adjunctive agents, such as mycophenolate mofetil, rapamycin and azathioprine, have not been shown to definitively impact the risk of recurrence (Zekry, Gleeson et al. 2004; Bahra, Neumann et al. 2005; Wiesner, Shorr et al. 2005).

Finally, the effect of living donor liver transplant (LDLT) and HCV+ donors on recurrence has recently been elucidated. While early reports suggested a higher rate of recurrence following LDLT, subsequent data have dispelled these concerns(Garcia-Retortillo, Forns et al. 2004; Terrault, Shiffman et al. 2007). The use of HCV+ donors (without fibrosis) for HCV+ recipients also does not appear to impact recurrence rates (Arenas, Vargas et al. 2003; Peek and Reddy 2007). The use of genotype 1 HCV+ donors into nongenotype 1 recipients is, however, not recommended.

3.2.1.2 Diagnosis

HCV infection of the allograft occurs at the time of transplantation, with negative-strand HCV RNA detectable in the first postoperative week. There are three phases in the physiology of a transplant (resection or 'pre-anhepatic' phase, anhepatic phase and post-reperfusion phase). HCV RNA is cleared rapidly from serum during the anhepatic phase. Following reperfusion, the rate of decrease in HCV RNA accelerates, almost certainly reflecting HCV binding to its obligatory hepatic receptors(Watt, Veldt et al. 2009). HCV RNA levels typically increase rapidly from week 2 post-LT, peaking by the fourth postoperative month. At the end of the first postoperative year, HCV RNA levels are, on an average, 10–20-fold greater than pre-LT levels. Histological features of hepatitis develop in approximately 75% of recipients in the first 6 months following LT(Neumann, Berg et al. 2004). By the fifth postoperative year up to 30% have progressed to cirrhosis(Neumann, Berg et al. 2004). A small proportion of patients (4–7%), develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Early post-LT histology, for example at 1 year, has been consistently predictive of subsequent fibrosis progression.

Liver function test abnormalities are common in HCV+ recipients and do not reliably differentiate HCV recurrence from other etiologies (i.e. rejection). The "gold standard" for diagnosis of HCV recurrence is liver biopsy, which still may not be accurate in differentiating other causes of early graft dysfunction from HCV recurrence and may also inaccurately stage the degree of fibrosis (Skripenova, Trainer et al. 2007). While supportive evidence is not available, most centers perform protocol liver biopsies every 1-2 years post-LT to monitor for evidence of histological recurrence. Therapy is usually reserved for patients who develop biopsy-proven recurrence (grade 3 or stage 1-2 by METAVIR) (Wiesner, Sorrell et al. 2003).

The hepatic venous pressure gradient (HVPG), noninvasive blood tests or imaging are additional available supportive tests for evaluation of the development of fibrosis, which is a marker of disease severity, following liver transplant. While a direct correlation between HVPG measurements and fibrosis may not be present in LT recipients, an elevated HVPG by itself has been shown to predict progression to more advance disease and the development of portal hypertension, and declines with successful anti-HCV therapy(Blasco, Forns et al. 2006; Forns and Costa 2006). Liver stiffness measurement with transient elastography offers a higher sensitivity and positive predictive value for advanced fibrosis in HCV+ recipients in comparison to other clinical markers(Carrion, Navasa et al. 2006; Benlloch, Heredia et al. 2009). In addition, serum markers of fibrosis, such as hyaluronic

acid, have been shown to have reasonable predictive value(Carrion, Fernandez-Varo et al. 2010). Overall, none of these tests appear to individually provide an accurate assessment of disease progression, supporting the need for further investigation into combined modalities or surrogate markers.

3.2.1.3 Treatment

Pretransplant: Patients with higher pre-LT HCV RNA titers experience greater mortality and graft loss rates than recipients with lower pre-LT HCV RNA titers(Charlton 2007). Pre-LT therapy in patients with advanced liver disease is limited by reduced patient tolerability and efficacy(Crippin, McCashland et al. 2002). While IFN based therapy is generally safe in compensated cirrhotic patients, it is poorly tolerated and often risky in decompensated patients with advanced liver disease (MELD>20, Child Turcotte Pugh (CTP) class C). Given the high frequency of serious adverse events (33%), among patients with more severe liver disease (CTP class B or C), the International Liver Transplant Society (ILTS) consensus panel concluded that treatment should be limited to cirrhotic patients with CTP score ≤ 7 or MELD score < 18, and is contraindicated when the CTP score is >11 or MELD score is >25.

In 2010, the phase III results of the first generation HCV nonstructural protein 3/4A protease inhibitors (PIs: boceprevir, telaprevir) were presented(Jacobson, McHutchison et al. 2010; Poordad, McCone et al. 2011). After a decade in which Peg-IFNα–ribavirin therapy was the only available option, triple therapy with HCV PIs in combination with Peg-IFNα–ribavirin is becoming the new standard of care. However, since IFN is still used, this therapy also cannot be given in decompensated cirrhosis.

Posttransplant: Two approaches to post-LT HCV recurrence have been identified: early, pre-emptive, treatment, to be started within weeks after liver transplantation (see *prevention/prophylaxis* below); and treatment of established recurrent HCV infection. The treatment of histologically proven HCV reinfection with pegylated (PEG)-IFN and ribavirin is, at present, the standard of care at most LT centers.

Treatment of histological recurrence is only successful in 20-30% of recipients and is associated with high rates (30-50%) of discontinuation due to intolerability(Beckebaum, Cicinnati et al. 2004; Kornberg, Kupper et al. 2007). A major limiting factor in achieving an acceptable SVR rate is the inability to reach target ribavirin doses due to the high prevalence of renal insufficiency in HCV+ LT recipients(Chalasani, Manzarbeitia et al. 2005). Although earlier studies reported high rates (21-35%) of IFN-induced allograft rejection, a recent randomized study of early post-LT prophylaxis and therapy did not demonstrate an increase in the risk of acute rejection(Chalasani, Manzarbeitia et al. 2005). Finally, although triple therapy (addition of a PI to Peg-IFNα–ribavirin) is becoming the new standard of care for pretransplant HCV, this treatment regimen is not approved in solid organ transplant recipients and has significant potential for drug interaction with immunosuppressive therapy. Recently, genetic variation in the region of the IL28B gene on chromosome 19, coding for IFN-λ3, has been demonstrated to be strongly associated with SVR in patients with genotype 1 chronic HCV infection who are treated with pegIFN plus RBV in the nontransplant setting(Ge, Fellay et al. 2009). Charlton et al. recently also confirmed this finding in a transplant population(Charlton, Thompson et al. 2011). Donor and recipient IL28B genotype were independently associated with SVR and IL28B recipient genotype was predictive of fibrosis stage, with TT genotype being associated with more rapid fibrosis.

3.2.1.4 Prevention/prophylaxis

On a theoretical basis, an early antiviral approach should warrant better results. However, it is currently not recommended for at least 3 reasons: (1) in the immediate postoperative period, the exposure of human leukocyte antigen (HLA) of the major histocompatibility complex (MHC) is maximized, thus increasing the risk of acute rejection episodes in cases of use of immunomodulatory agents; (2) the recipient is usually still recovering from a major surgical procedure; and (3) this policy would cause unnecessary therapy for a significant number of recipients (maybe up to 50%) who will never develop overt liver disease(Castedal, Felldin et al. 2005). PHOENIX was a large, randomized study designed to compare the efficacy, tolerability, and safety of prophylactic initiation (before significant histological recurrence) of Peg-IFN2α plus ribavirin within 26 weeks after LT versus initiation only upon HCV recurrence. SVR was achieved in 22% of treated patients, however on an intent-to-treat basis, significant HCV recurrence at 120 weeks was similar in the prophylaxis (61.8%) and observation arms (65.0%, $P = 0.725$). The most common adverse event was anemia leading to dose reduction in 70% of the patients. The authors concluded that because of the safety profile of Peg-IFN2α/ribavirin and the lack of a clear benefit in terms of HCV recurrence and patient or graft survival, routine use of prophylactic antiviral therapy is not warranted(Bzowej, Nelson et al. 2011). Similar findings have been demonstrated in smaller, randomized controlled trials(Chalasani, Manzarbeitia et al. 2005). Finally, Hepatitis C immunoglobulin (Civacir®, Nabi Biopharmaceuticals, Rockville, MD) has been shown to lower HCV RNA but does not eliminate HCV viremia or the risk of recurrence(Davis, Nelson et al. 2005). There is currently no vaccine available for primary HCV prevention.

3.2.2 HCV in other solid organ transplants

3.2.2.1 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(Aroldi, Lampertico et al. 2005). 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(Elamin and Abu-Aisha 2011). 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(Fissell, Bragg-Gresham et al. 2004; Jadoul, Poignet et al. 2004). Isolation of HCV-infected patients or the use of dedicated dialysis machines are not recommended(KDIGO 2008). 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 (Lunel, Cadranel et al. 2000).

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 (Zylberberg, Nalpas et al. 2002). HCV infection decreases both patient and graft survival post renal transplant, with the greatest impact occurring 5 or more years following transplant (Mathurin, Mouquet et al. 1999). 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(Kamar, Boulestin et al. 2005). HCV+ recipients of a renal allograft also have an increased risk of posttransplant diabetes, graft dysfunction and proteinuria(Meyers, Seeff et al. 2003).

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 affected by HCV status(Lunel, Cadranel et al. 2000; Cano, Almenar et al. 2007; Sahi, Zein et al. 2007). 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.

3.2.2.2 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. Recent studies suggest that the proportion of the liver biopsy specimen occupied by collagen (a marker of liver fibrosis) is correlated with the HVPG in liver transplant recipients with HCV infection, with or without cirrhosis, and represents a predictor of clinical decompensation(Blasco, Forns et al. 2006). 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(Doucette, Weinkauf et al. 2007).

3.2.2.3 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(Cruzado, Casanovas-Taltavull et al. 2003; Casanovas-Taltavull, Baliellas et al. 2007). Furthermore, IFN therapy after transplantation is associated with reduced treatment response rates, a greater incidence of organ rejection, and impairment of renal function(Rostaing, Izopet et al. 1995). Thus, it is best if treatment can be undertaken before embarking on the solid organ transplant.

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(Fabrizi, Bunnapradist et al. 2005). Patients with bridging fibrosis or compensated cirrhosis should undergo IFN-based therapy and may 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 standard interferon that is dose-adjusted for a GFR of <15 ml/min per 1.73 m^2(KDIGO2008). 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(Mousa, Abdalla et al. 2004; van Leusen, Adang et al. 2008).

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, one small series has shown that selected lung transplant candidates can safely and effectively be treated for HCV prior to transplant(Doucette, Weinkauf et al. 2007).

Posttransplant: Generally, posttransplantation IFN therapy is contraindicated in recipients of SOT, other than liver allografts due to a high risk of precipitation of organ rejection from IFN therapy(Shu, Lan et al. 2004; Kamar, Ribes et al. 2006). There is well-documented evidence to support the theory that the liver allograft provides some level of immunologic protection to the kidney allograft(Calne, Davis et al. 1971; Rasmussen, Davies et al. 1995). As such, recent reports have demonstrated successful HCV treatment with Peg-IFN and ribavirin in SLK recipients without development of renal rejection on therapy, although data are limited to small numbers of patients(Montalbano, Pasulo et al. 2007; Mukherjee and Ariyarantha 2007; Van Wagner, Baker et al. 2009).

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 postrenal transplant and may be considered on a case-by-case basis in those with severe disease following careful review of the potential risks and benefits.

3.2.2.4 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 and active viral replication. Those with decompensated cirrhosis should be considered for SLK transplant.

There is 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(Steinman, Becker et al. 2001). 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(Orens, Estenne et al. 2006).

3.3 Hepatitis D

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(Pascarella and Negro 2011). The distribution pattern of this virus, investigated by seroprevalence studies of anti-HDV in HBsAg-positive patients, is worldwide but not uniform(Rizzetto, Ponzetto et al. 1991). 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(Farci 2003).

Like HBV, HDV is transmitted via the parenteral route through exposure to infected blood or body fluids, and tests in chimpanzees have shown that only a very small inoculum is sufficient to transmit infection(Ponzetto, Hoyer et al. 1987). Thus, transmission rates remain high in intravenous drug users and those with high risk sexual activities. Perinatal transmission of HDV is uncommon. Because of screening of blood products, new infections in hemophiliacs, blood transfusion recipients, and patients receiving 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 the presence of anti-HDV IgM antibodies, it is now confirmed by the detection of serum HDV RNA with a commercially available sensitive real-time PCR assay(Mederacke, Bremer et al. 2010).

A third minor pattern of infection, the so-called helper-independent latent infection, has been reported in the liver transplant setting and is discussed briefly below(Ottobrelli, Marzano et al. 1991). Patients who undergo LT with HDV infection are interesting from the perspective that they often have low or very low serum levels of HBV (low replication) and have an overall high survival rate (>80%) after LT as a result of the "antiviral" effect of HDV on HBV replication(Samuel, Zignego et al. 1995). Suppression of HBV replication by HDV has historically led to better posttransplantation survival in coinfected patients(Lerut, Donataccio et al. 1999). As discussed previously, HBV infection of the grafted liver is usually prevented by administration of hepatitis B immunoglobulins and thus, hepatocytes may thus be infected with HDV alone. HDAg can be detected in the liver by immunohistochemistry before HBV recurrence, as the helper virus is only necessary for particle formation and not for viral replication(Kuo, Chao et al. 1989). HDV viremia (as determined by molecular hybridization) is only observed several months later, when

residual HBV evades neutralization, thus allowing for HDV rescue and cell-to-cell spread(Ottobrelli, Marzano et al. 1991). This third pattern of infection has been revisited with the advent of more sensitive, reverse transcription (RT)-PCR-based techniques for detecting HDV RNA(Pascarella and Negro 2011).

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(Farci, Roskams et al. 2004). 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(Niro, Ciancio et al. 2006). 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(Yurdaydin, Bozkaya et al. 2002; Niro, Ciancio et al. 2005; Hynicka, Yunker et al. 2010; Wedemeyer, Yurdaydin et al. 2011). Ribavirin has been shown to inhibit HDV replication *in vitro* but is ineffective *in vivo,* even if associated with Peg-IFNα(Rasshofer, Choi et al. 1991; Garripoli, Di Marco et al. 1994; Niro, Ciancio et al. 2006). 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. There are currently no published reports of HDV recurrence following solid organ transplant.

3.4 Hepatitis E

3.4.1 Epidemiology & specific risk factors

Hepatitis E, caused by hepatitis E virus (HEV), was unknown as a disease entity until 1980 during an outbreak of acute viral hepatitis in the Kashmir Valley, India, with 275 clinical cases in small villages with a common water source(Khuroo 1980). In the initial years after its discovery, it was believed to be a common cause of sporadic and epidemic waterborne acute hepatitis in, and limited to, developing countries, primarily in Asia and Africa. However, in recent years, the host range, geographical distribution and modes of transmission of this virus, and clinical presentations of this infection have been shown to be much broader than were previously believed(Purcell and Emerson 2008; Aggarwal 2011).

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(Lu, Li et al. 2006). The disease is characterized by a particularly severe course and high mortality among pregnant women(Navaneethan, Al Mohajer et al. 2008). 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. In non-endemic regions, chronic infection with genotype 3 HEV, which may progress to liver cirrhosis, has been reported among immunosuppressed hosts—including heart, kidney, kidney-pancreas and liver transplant recipients(Kamar, Mansuy et al. 2008; Haagsma, Niesters et al. 2009). There are no published reports of HEV in lung or small bowel transplant recipients.

Anti-HEV IgG antibodies are present in 16.6% of blood donors in France and in 6–16% of renal transplant recipients(Mansuy, Abravanel et al. 2009)(Kamar, Mansuy et al. 2008;

Mansuy, Abravanel et al. 2009). Approximately 60% of SOT patients infected with HEV will develop chronic hepatitis, and up to 15% will develop cirrhosis(Kamar, Garrouste et al. 2011). The use of tacrolimus rather than cyclosporine A and low platelet count have been reported as the main independent factors associated with chronic HEV infection after SOT(Kamar, Garrouste et al. 2011). Factors determining the severity of illness caused by HEV infection are not fully understood. These could include host factors or viral factors. Of these, host factors, in particular pregnancy, age and pre-existing liver disease clearly appear to be important(Aggarwal 2011). In addition, host immune response may also play a role. In a report from Japan, patients with genotype 4 HEV infection were found to have more severe illness than those who had infection with genotype 3 virus(Ohnishi, Kang et al. 2006). 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.

3.4.2 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(Drobeniuc, Meng et al. 2010). Serologic testing for anti-HEV antibodies has a significant false-negative rate in immunosuppressed patients, so negative results should be treated with caution(Kamar, Garrouste et al. 2011). 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(CDC 2010).

3.4.3 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(Kamar, Rostaing et al. 2010). Reduction of immunosuppression may be helpful. In one study nearly one-third of patients who were chronically infected with HEV achieved viral clearance after dose reduction of immunosuppressive therapy, and this was mainly due to the reduction of T cell therapy(Kamar, Garrouste et al. 2011). Small studies have reported that ribavirin has promising efficacy in immunocompromised patients with chronic HEV infection, including kidney and heart recipients(Kamar, Rostaing et al. 2010; Mallet, Nicand et al. 2010; Chaillon, Sirinelli et al. 2011) .

3.4.4 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(Shrestha, Scott et al. 2007; Zhu, Zhang et al. 2010). 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 immunuity against zoonotic HEV genotype 3 infection, which currently represents the main

clinical challenge to immunocompromised patients in Europe and the USA(Wedemeyer and Pischke 2011).
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, as for hepatitis A virus(Franco, Giambi et al. 2003). Of note, following successful clearance of HEV, no reactivation has been observed following SOT(Legrand-Abravanel, Kamar et al. 2011).

4. Challenges and new advancements in the management of hepatotropic infections

Basic research, as well as the development of drugs and vaccines targeting human hepatotropic pathogens, has been handicapped by the lack of robust in vitro and in vivo platforms that mimic human liver biology and disease susceptibility. For example, despite prolonged viremia in mice models, none of the commonly observed sequelae associated with HBV or HCV infections in humans, namely fibrosis or HCC, have been observed in mouse models. However, the recent development of human liver–chimeric mice is evolving and appears promising(de Jong, Rice et al. 2010). Trials are ongoing to optimize the efficacy of available treatment options, for example, the use of protease inhibitors in combined therapy for HCV. In general, therapy for hepatotropic viruses is limited by the use of a few drugs that cause significant toxicities often resulting in dose adjustments and thus less efficacious regimens. Continuous efforts to improve treatment options available for viral hepatitis following solid organ transplant are urgently needed as viral hepatitis is a largely underestimated disease with an enormous impact on post-transplantation outcomes.
Finally, emerging concepts of individualized immunosuppression may result in a decreased incidence of overall infection following solid organ transplant.(Sarwal, Benjamin et al. 2011). The transplant community is putting significant effort into finding/solving the “Holy Grail” of transplantation: true, donor-specific tolerance (free of chemical immunosuppressive agents). One of the main questioned topics related to immunologic tolerance is whether the most realistic achievable ultimate goal is “true tolerance,” with no maintenance immunosuppressive agents whatsoever or to achieve the status of “prope/almost tolerance,” with minimal or non-toxic maintenance drug therapy (Scherer, Banas et al. 2007). In order to achieve either of these goals, an effective clinical-tolerance monitoring assay to identify and predict possibly tolerant transplant recipients who could possible be weaned off immunosuppressive agents is yet to be found.

5. Conclusions

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 hepatropic viruses. Future studies to address prevention and improved treatment modalities both pre- and post-SOT are needed.

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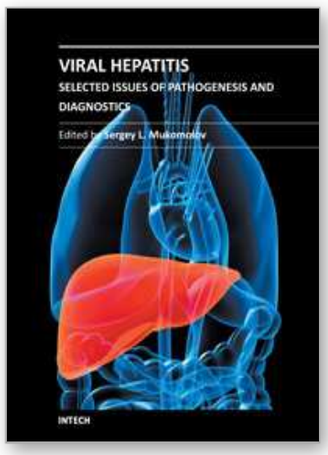
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There are a lot of important issues related to viral hepatitis studies: molecular biology of viruses, laboratory diagnostics, epidemiology, treatment etc. However, there is a number of special textbooks and monographs on the subject. Considering this fact and rather fast progress in our understanding of the problem this book focuses on the important sections of the problem immune pathogenesis of parenterally transmitted viral hepatitis and some aspects of hepatitis diagnostics. Seven chapters were prepared by several groups of researchers to share information and results of studies with specialists working in the field and persons who are interested to learn about the viral hepatitis issue. The Nobel Prize Committee (the field of physiology and medicine, 2011) awarded Bruce A. Beutler and Jules A. Hoffmann for their discoveries concerning the activation of innate immunity whilst Ralph M. Steinman was awarded for his discovery of the dendritic cell and its role in adaptive immunity. We are proud to say that our book is in line with these discoveries, because 3 chapters cover the problems of innate and adaptive immune response in case of viral hepatitis.

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