Liver transplantation in adults: Hepatitis D virus reinfection in liver transplant recipients

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INTRODUCTION

Hepatitis D virus (HDV) infection is caused by a defective virus. Individuals with clinical manifestations of HDV are dually infected with hepatitis B virus (HBV) infection. Although HDV can replicate autonomously, the simultaneous presence of HBV is required for complete virion assembly and secretion.

Despite the availability of antiviral therapy for patients with HBV, some patients with HBV/HDV coinfection develop progressive liver disease and require liver transplantation. HDV reinfection in liver transplant recipients is rare because post-transplant prophylaxis with a nucleos(t)ide analog alone or in combination with hepatitis B immune globulin (HBIG) is an effective strategy for preventing HBV reinfection.

For most patients with acute HBV and acute HDV coinfection, the clinical course is characterized by a self-limited acute hepatitis and overall good prognosis. However, some patients may develop acute liver failure or progression to chronic hepatitis and cirrhosis. In contrast to HBV infection alone, chronic HBV/HDV coinfection has been associated with more rapid progression to cirrhosis and increased risk of hepatocellular carcinoma [1]. In addition, patients with HBV/HDV coinfection may develop decompensated cirrhosis and need liver transplantation at a younger age than patients with HBV infection alone [2-4].

This topic will review HDV reinfection following liver transplantation. Issues related to liver transplantation in patients with HBV infection alone is discussed separately. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

The pathogenesis, clinical manifestations, prevention, and treatment of HDV infection are discussed separately. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection" and "Treatment and prevention of hepatitis D virus infection".)

Prevention and management of other infections following liver transplantation are discussed separately. (See "Infectious complications in liver transplantation".)

PATHOGENESIS

HDV is a defective virus that is dependent upon hepatitis B virus (HBV) for envelopment, virion assembly, and secretion. In general, HDV infection occurs only in the presence of HBV infection [5]. Thus, reinfection with HDV alone following liver transplantation is usually short-lived and is not associated with recurrent liver disease unless HBV reinfection occurs subsequently. Observational studies on the clinical course of HDV reinfection have provided important insights into the biology of HDV replication and the pathogenesis of HDV-related liver disease. (See 'Clinical course' below and "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Pathogenesis'.)

In vitro experiments using cell cultures have shown that HDV can replicate in the absence of HBV but that the virions cannot be released from the cells [6-8]. In addition, studies in woodchucks demonstrated that HDV infection of the liver can be achieved by inoculating woodchucks with sera containing a high ratio of HDV to woodchuck hepatitis virus (WHV) particles. However, productive infection occurred only when the animals were subsequently administered a highly infectious dose of WHV [9]. In addition, humanized animal models suggested that latent HDV infection was rescued by superinfecting animals with HBV, leading to the appearance of high titers of HDV RNA in serum and an increasing number of hepatocytes expressing HDV antigen (HDAg) [10]. In addition, the newly produced HDV virions were infectious in naive chimeric mice.

It is possible that for liver transplant recipients who have HDV reinfection alone, HBV was present but went undetected because of masking of hepatitis B surface antigen (HBsAg) by hepatitis B immunoglobulin (HBIG) [11]. Although early studies found that HBV DNA was undetectable both in sera and in liver tissues [12], one study demonstrated the presence of HBV DNA by polymerase chain reaction, indicating that small amounts of HBV are present at the time

of HDV reinfection [11]. Another study showed rapid early decline in HDV RNA in parallel with HBsAg during the first few days post-transplant, but HDAg stained positive in transplanted livers in 6 of 26 patients in the absence of HBV DNA in the liver and HBsAg and HDV RNA in the serum for up to 19 months after transplant [13]. These data support the concept that latent HDV reinfection can occur in patients with no evidence of HBV reinfection. However, traces of HBV are likely present in these situations and HDV reinfection can become overt if prevention or suppression of HBV reinfection fails.

With the availability of nucleos(t)ide analogues with low rates of resistance (ie, entecavir or tenofovir), many transplant centers no longer routinely use HBIG to prevent HBV reinfection in patients transplanted for HBV infection alone. However, use of HBIG in combination with an antiviral agent may be important for patients transplanted for HBV/HDV coinfection. (See 'Preventive strategies' below.)

Studies performed before the widespread use of antiviral prophylaxis have described long-term outcomes after liver transplantation for HDV-related cirrhosis in the absence of antiviral agents [12,14]. These studies showed that in the absence of antiviral therapy, long-term HBIG alone can decrease the risk of HBV/HDV reinfection.

HEPATITIS D VIRUS (HDV) REINFECTION

Clinical course — Most patients with HDV reinfection alone are asymptomatic. However, those with HDV/hepatitis B virus (HBV) may present with symptoms of recurrent hepatitis.

HDV reinfection alone — In patients with HDV reinfection without markers of HBV reinfection, serum aminotransferase levels usually remain normal and there is no evidence of hepatitis on liver biopsy. In a study including 61 patients who were transplanted for HDV infection and remained hepatitis B surface antigen (HBsAg) negative, 47 patients (77 percent) had normal grafts, seven (12 percent) had acute or chronic rejection, and seven (12 percent) had acute or chronic hepatitis on liver biopsies that were performed at least two years post-transplantation [12]. All patients with biopsy-proven hepatitis were negative for markers of HDV and HBV infection. However, six patients were positive for hepatitis C antibody, suggesting that hepatitis C infection may have been the cause of the hepatitis.

Latent HDV reinfection activated by HBV reinfection — In some patients, HBV reinfection lags behind HDV reinfection by a few months. When HBV reinfection occurs (ie, reappearance of HBsAg), HBV replication reactivates latent HDV [15,16]. Clinical manifestations are similar to

simultaneous coinfection with HBV/HDV and include hepatitis and progression to chronic liver disease.

Simultaneous HDV and HBV reinfection — Simultaneous reinfection with HDV and HBV after transplantation is usually accompanied by recurrent hepatitis and expression of HDV antigen (HDAg) in the liver graft [12,15,17]. In a study of seven patients who were transplanted for HDV infection and developed simultaneous HDV and HBV reinfection, four patients subsequently became HBsAg negative, either spontaneously or after antiviral therapy with adenine arabinoside 5'-monophosphate (ARA-AMP) [12]. Among these four patients, liver biopsy was normal in two patients and showed chronic hepatitis without cirrhosis in two patients. For three patients who remained HBsAg positive, liver biopsy showed chronic active hepatitis without cirrhosis after 51 to 70 months post-transplant.

Another series presented detailed histopathologic evaluation of nine patients with HDV and HBV reinfection [15]. Two types of lesions were observed. Some patients had productive HBV reinfection with hepatic expression of HDAg, HBsAg, and HBcAg and necroinflammatory changes typical of acute viral hepatitis. However, other patients had hepatic expression of HDAg and HBsAg but not HBcAg. The histologic changes at this stage were mainly degenerative: hepatocyte ballooning, micro- and macro-vesicular steatosis, and eosinophilic alterations of the cytoplasm were seen with little evidence of inflammation. The histologic picture in the latter patients became predominantly necroinflammatory when markers of HBV replication appeared. These patients appear to demonstrate a propensity of HDV to suppress HBcAg expression [17].

Monitoring and diagnosis — After transplant, we monitor patients for HBV reinfection by measuring HBsAg and HBV DNA every one to three months during the first year after transplant and every 6 to12 months thereafter. We also check these markers if there is unexplained elevation in aminotransferases. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'Surveillance post-transplant'.)

The diagnosis of HBV/HDV coinfection is made by reappearance of HBsAg and HBV DNA in addition to detecting HDV RNA in serum and/or HDAg in the liver graft [12]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Diagnostic tests'.)

Testing for HDV RNA should only be performed in patients who have evidence of HBV reinfection. Routine monitoring for HDV reinfection is not needed since reinfection with HDV alone is not clinically significant. (See 'HDV reinfection alone' above and "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Diagnostic tests'.)

Management

Pharmacologic therapy — Specific treatment for HDV reinfection has not been evaluated and is generally not necessary because HDV reinfection in the absence of HBV reinfection is usually self-limited and not associated with recurrent hepatitis. In addition, reinfection with both HBV and HDV is rare with the use of long-term antiviral prophylaxis (ie, entecavir or tenofovir) [18-21]. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'Strategies to prevent HBV reinfection'.)

Although pegylated interferon is used for treating HDV infection in the nontransplant setting, data on interferon therapy for HDV reinfection are lacking. In addition, use of interferon may increase the risk of acute T-cell mediated (cellular) rejection. Emerging therapies such as bulevirtide or lonafarnib show promise for treating HDV reinfection in transplant recipients [22,23]. However, preventing HBV reinfection with long-term antiviral prophylaxis is the primary focus.

Management of HDV infection, including data on efficacy and safety of drug therapy, is presented separately. (See "Treatment and prevention of hepatitis D virus infection".)

Retransplantation — Studies on retransplantation for progressive liver disease related to HDV reinfection are lacking. In an observational study including 76 patients with HDV-related cirrhosis who underwent liver transplantation, none of the recipients required retransplantation because of recurrent liver disease related to HBV or HDV reinfection [12].

PREVENTIVE STRATEGIES

Strategies for preventing HDV reinfection in liver transplant recipients include:

- **Preventing HBV reinfection** – The most effective method for preventing HDV reinfection is to prevent hepatitis B virus (HBV) reinfection because HDV reinfection alone is abortive unless it is reactivated by HBV replication [24]. Thus, preventing HDV reinfection relies on the strategies for preventing HBV reinfection. Specific prophylaxis for HDV reinfection is not available.

  We agree with society guidelines that recommend combination of an antiviral agent plus prophylaxis with hepatitis B immunoglobulin (HBIG) to prevent HBV and HDV reinfection because there is no effective treatment for recurrent HDV [25]. In addition, data from observational studies suggested that post-transplant prophylaxis with antiviral agent(s) plus HBIG was associated with negligible rates of HDV reinfection [26,27]. In a study of 128 patients who were transplanted for HBV/HDV coinfection and received prophylaxis with

antiviral agent plus HBIG, there were no cases of HDV recurrence after mean follow up of 30 months [26].

The dosing and administration of pharmacologic prophylaxis including antiviral agents and HBIG for liver transplant recipients is presented in detail separately. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'Strategies to prevent HBV reinfection'.)

Although the combination of HBV antiviral agents and HBIG should be used during the initial post-transplant period, the duration of HBIG is unclear and is usually transplant center specific. Available data suggest that HBIG may be able to be safely withdrawn after liver transplantation as long as nucleos(t)ide analog is continued indefinitely [4,28]. As an example, in an analysis of six studies including 98 patients who were transplanted for HBV/HDV cirrhosis and received long-term prophylaxis with antiviral agent alone after discontinuing HBIG, the rate of HBV/HDV reinfection was 2 percent after median follow up of approximately two to 20 years [4].

- **Other strategies** – For patients with HDV-related cirrhosis, we do not typically use pharmacologic therapy to eradicate HDV infection prior to liver transplantation because of the risk of drug-related toxicity with high-dose interferon therapy in addition to its limited efficacy [29].

  However, studies of emerging therapies such as bulevirtide and lonafarnib have shown promise for decreasing HDV RNA and alanine aminotransferase levels pretransplant. Preliminary data have suggested that bulevirtide was safe, decreased HDV RNA level, and improved liver function in patients with compensated cirrhosis [22,23]. Further studies including randomized trials are needed to evaluate the impact of these therapies on the risk of HDV reinfection post-transplant. (See "Treatment and prevention of hepatitis D virus infection".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Liver transplantation".)

SUMMARY AND RECOMMENDATIONS

- **Background** – In general, hepatitis D virus (HDV) infection occurs only in the presence of hepatitis B virus (HBV) infection. Thus, reinfection with HDV alone following liver transplantation is usually short-lived and is not associated with recurrent liver disease unless HBV reinfection occurs simultaneously or subsequently. (See 'Pathogenesis' above.)

- **Clinical course** – The clinical course of liver transplant recipients with HDV reinfection depends on whether the recipient has HBV coinfection. In patients with HDV reinfection alone, serum aminotransferase levels usually remain normal and there is no evidence of hepatitis on liver biopsy. However, recipients with HBV/HDV coinfection usually have recurrent hepatitis and expression of HDV antigen (HDAg) in the liver graft. (See 'Clinical course' above.)

- **Monitoring and diagnosis** – We monitor for HBV reinfection by measuring HBsAg and HBV DNA every one to three months during the first year after transplant and every 6 to12 months thereafter. We also check these markers if there is unexplained elevation in aminotransferases. (See 'Monitoring and diagnosis' above.)

  The diagnosis of HBV/HDV coinfection is made by reappearance of HBsAg and HBV DNA in addition to detecting HDV RNA in serum and/or HDAg in the liver graft.

  Testing for HDV RNA should only be performed in patients who have evidence of HBV reinfection. Routine monitoring for HDV reinfection is not needed since reinfection with HDV alone is not clinically significant. (See 'HDV reinfection alone' above.)

- **Management** – Specific treatment for HDV reinfection alone is not necessary because HDV reinfection in the absence of HBV reinfection is usually self-limited and not associated with recurrent hepatitis. (See 'Management' above.)

  Management of HBV reinfection in liver transplant recipients is presented separately. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'HBV reinfection'.)

- **Prevention** – For patients with HBV/HDV cirrhosis who undergo liver transplantation, we suggest immunoprophylaxis with hepatitis B immunoglobulin (HBIG) in addition to antiviral prophylaxis with a nucleos(t)ide analog rather than antiviral prophylaxis alone (**Grade 2C**). This approach is effective for preventing HBV reinfection, and without HBV reinfection, HDV reinfection remains latent. (See 'Preventive strategies' above and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'Strategies to prevent HBV reinfection'.)

We continue the antiviral agent lifelong. The optimal duration of HBIG is unclear and is usually guided by transplant center protocol.

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Contributor Disclosures

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