Hepatitis Viruses in Kidney Transplantation

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Summary: Hepatitis viruses are named for their primary clinical illness, inflammation of the liver. Currently, six types of viruses are designated hepatitis viruses (A, B, C, D, E, and G), although only five of these cause hepatitis. Hepatitis viruses are composed of RNA and DNA viruses from different families and with different virologic properties, some of which typically cause acute hepatitis while others cause acute and chronic hepatitis. In addition to their role in liver disease, members of this group of viruses may cause a variety of pathologic changes in the kidney and other organs, and chronic infection may lead to cirrhosis in addition to raising a variety of important issues in the management of kidney transplant recipients. In this brief report, we review the virologic and clinical properties of each of the hepatitis viruses, and highlight the role of each virus in renal disease and kidney transplantation.

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Hepatitis A virus (HAV) is an RNA virus in the family *Picornaviridae*. It was considered a nonenveloped virus until recently, when studies found that viral proteins and genomic RNA can be released from cells within microvesicles similar to exosomes.[1] These enveloped HAV particles are infectious and may cause disease. HAV is highly resistant to heat, acid, drying, and ether, and is transmitted primarily by the fecal-oral route, although transfusion-associated HAV infection is well documented. There is approximately 4 weeks of clinical latency after infection; however, viremia and fecal shedding occur in the days to week before the development of clinical illness (reviewed by Stapleton et al[2]) (summarized in Table 1). Hepatocyte destruction resulting in self-limited illness is mediated by cytolytic T-cell killing of infected cells, and viral infectivity decreases precipitously in immune-competent individuals once symptoms begin. Although viral RNA can be detected in feces for months after illness by highly sensitive nucleic acid amplification techniques,[3] transmission is rare in this setting.

In contrast, immune-compromised individuals may shed HAV in feces for months after infection, and this may increase the risk for outbreaks.[4] The severity of HAV-induced hepatitis is highly age-dependent, with less than 30% of HAV-infected children younger than the age of 14 developing clinical illness whereas more than 70% of infected adults develop clinical illness and jaundice.[2]

Clinical signs and symptoms of hepatitis A generally are indistinguishable from acute hepatitis caused by other etiologies (reviewed by Stapleton et al[2]). Before physical findings specific for hepatitis, a pre-icteric or prodromal phase may occur. The infected person may experience anorexia, nausea, vomiting, altered taste including aversion to cigarette smoking, fatigue, fever, urticaria, and pruritis. After this prodromal phase, the icteric phase may occur and findings such as scleral icterus, dark urine, clay-colored stools, right upper-quadrant pain, and frank jaundice may be detected. During the icteric phase, liver enzyme levels frequently are increased 10 to 100 times higher than the upper limits of normal, and in general the alanine aminotransferase level is greater than the aspartate transaminase. HAV also may lead to a vasculitis including glomerular disease, arthralgia, skin rash, and meningoencephalitis (reviewed by Stapleton et al[2]).

In individuals with acute HAV infection, fulminant hepatitis occurs in less than 0.2% of infections.[5] Nevertheless, HAV is responsible for more than 3% of all cases of acute fulminant hepatitis in one study, and half of these individuals were listed for liver transplantation. Fortunately, the incidence of fulminant hepatitis A appears to be decreasing, although it still accounts for 80 to 100 deaths annually in the United States.[5] Risk factors for severe fulminate hepatitis A include advanced age and pre-existing liver disease including hepatitis C virus (HCV) and hepatitis B virus (HBV) infection.

Renal failure may accompany fulminant HAV on the basis of hepatorenal syndrome,[6] and individuals receiving kidney transplantation for this have lower

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bilirubin levels and similar post-transplant patient and graft survival rates compared with non–HAV-related hepatorenal-related transplant recipients.[7] Post-transplantation renal outcomes appear better in the hepatitis A group. In addition to hepatorenal syndrome, vasculitis has been documented to accompany acute hepatitis A associated with dermatologic, neurologic, and renal abnormalities including glomerulonephritis.[2]

HAV is diagnosed serologically (reviewed by Stapleton et al[2]). Detection of anti-HAV antibodies indicates active or prior infection or vaccination, whereas detection of IgM–anti-HAV antibodies strongly supports a diagnosis of acute hepatitis A. IgG anti-HAV antibodies are protective against re-infection. Groups with increased risk of developing hepatitis A include travelers, men who have sex with men, users of injection and noninjection drugs, people with clotting factor disorders, and people who work with nonhuman primates.[2] In addition, HAV outbreaks occur in food-service establishments, child care centers, schools, among sewage workers, and in institutions for persons with developmental disabilities.

There is no antiviral therapy for HAV. Consequently, vaccination and good hygiene measures are the mainstay of prevention. A formalin-inactivated virus vaccine is available and recommended for pre-exposure vaccination of children in states with historically consistently increased rates of HAV. This recommendation began in 1999.[8] In addition, HAV vaccine is recommended for all pediatric solid-organ candidates, particularly patients age 12 months and older undergoing liver transplantation. Adult kidney transplant candidates and recipients should be vaccinated if they have a high risk of exposure. After vaccination, seroconversion (detection of anti-HAV antibodies) is indicative of protection. Seroconversion rates are high in people with chronic HCV or HBV (94%-98%); however, in one study none of the eight liver transplant recipients vaccinated post-transplantation seroconverted after two doses 2 months apart.[9] Thus, vaccination before transplantation is preferred. In addition, the HAV vaccine can be administered with the hepatitis B virus vaccine in renal transplant recipients. The durability of antibodies after vaccination before solid-organ transplantation is not well characterized, but in one study 29% of those with naturally acquired HAV became seronegative 2 years after transplantation.[10] This raises the possibility that vaccine efficacy may be limited; however, an amnestic response is likely and further studies are required before routine vaccine boosting is recommended. A combination of passive immunization with immune serum globulin and vaccination is recommended for postexposure prophylaxis in nonimmune subjects with significant exposure to HAV (reviewed by Stapleton et al[2]).

HEPATITIS B VIRUS

HBV is a DNA virus within the family *Hepadnaviridae* that infects approximately 240 million people globally. The highest burden of HBV infection is in East Asia and sub-Saharan Africa, where 5% to 10% of the adult population is infected. HBV accounts for more than 780,000 deaths annually from hepatic complications including cirrhosis and hepatocellular carcinoma (HCC).[11] The prevalence of chronic HBV in developed countries is much lower, for example, in the United States, infection occurs in less than 1% of the population.

The HBV particle is composed of a lipoprotein envelope (hepatitis B surface antigen [HbsAg]) that assembles into 22-nm subviral particles that can form filamentous structures that are released into the bloodstream during infection. The viral capsid comprises the hepatitis B core antigen (HBcAg), which encases HBV DNA. HBcAg may be present in plasma during active infection. Hepatitis e antigen (HBeAg) is another capsid component that, when present in the plasma, correlates with increased viral replication and infectivity.

During acute, self-limited infection, infected hosts may elicit neutralizing antibodies to the HBsAg, termed hepatitis B virus surface antibodies (HBsAb). HBsAb confers natural immunity against re-infection or relapse in the immunocompetent patient. HbsAb also can be elicited via vaccination. In chronic HBV infection, HBsAg persists for more than 6 months and HBsAb is not detected. Antibody directed against the HBcAg (HBcAb) is detected in serum shortly after infection. In the first 3 to 6 months it is composed primarily of the IgM isotype, thus IgM HBcAb is indicative of recent infection. HBcAb may be the only detectable seromarker of HBV infection during the window period in which increasing HBsAb levels are bound to HBsAg with a resultant decrease in HBsAg concentration, thus both may be undetectable during a relatively brief period of time. HBcAb does not neutralize HBV and is not protective against re-infection or relapse. However, it is an indicator of an active or resolved infection. Thus, the presence of HBsAg or HBV DNA in plasma implies active infection. HBcAb may be detected in active or past infection, whereas HBsAb implies natural (from previous exposure) or vaccine-mediated immunity. Table 2 summarizes the interpretation of HBV serology.

HBV is transmitted via percutaneous or mucosal exposure to infected blood products, transplant organs or body fluids, and by vertical (mother-to-child) transmission (Table 1). Vertical transmission plays an important role in endemic areas in East Asia. Similar to HAV, the severity of HBV tends to increase with age, and the development of