Hepatitis B and C

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KEYWORDS

• Viral • Hepatitis • Children • Monitoring • Treatment

KEY POINTS

- The epidemiology, natural history, and risk of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are different in children.
- Children are rarely very symptomatic, hence a detailed family history and risk assessment is essential.
- Current and future therapies for HBV and HCV have rapidly evolved and will reduce social stigma, mortality/morbidity, and future health care costs.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections represent a major global public health and economic burden, with an estimated 257 million and 71 million people, respectively, having chronic infection worldwide.[1,2] The natural history of HBV and HCV in children depends on age at time of infection, mode of acquisition, ethnicity, and genotype. Most children infected perinatally or vertically remain asymptomatic but are at uniquely higher risk of developing chronic viral hepatitis, progressing to liver cirrhosis and hepatocellular carcinoma (HCC), hence classifying HBV and HCV as oncoviruses.[3] This article discusses the epidemiology, virology, immunobiology, prevention, clinical manifestations, evaluation, and the advances in treatment of hepatitis B and C in children.

HEPATITIS B

Epidemiology

In the United States, approximately 2 million people are chronically infected with HBV with a higher prevalence of chronic hepatitis B among immigrants from highly endemic areas such as Asia, Africa, and western Pacific regions.[2,4] Most individuals with chronic HBV infection acquired the virus through vertical transmission, highlighting the importance of active and passive immunization for HBV. Since implementation of universal infant vaccination for hepatitis B in 1991, there has been a drastic

Disclosure: The authors have no conflicts of interest to disclose as described by the *Clinics in Liver Disease*.

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Clin Liver Dis ■ (2018) ■–■
https://doi.org/10.1016/j.cld.2018.06.002 liver.theclinics.com

reduction in both acute and chronic HBV rates among children in the United States, which is offset by immigration of patients with chronic HBV from other countries.[5] The incidence of acute hepatitis B in US children (<19 years of age) has decreased from approximately 13.8 cases per 100,000 population (10–19 years of age) in the 1980s to 0.34 cases per 100,000 population in 2002.[6] Even though the prevalence has significantly reduced, children with chronic HBV remain at risk for HCC, with a 100-fold greater incidence compared with the HBV-negative population.[7] Although there is racial disparity in prevalence of HBV in adults in the United States, rates among US-born children showed no racial differences.[8]

Virology and Genotyping: Impact on Prognosis and Treatment

HBV is a DNA virus in the family Hepadnaviridae. It is primarily a hepatotropic, enveloped, coated, double-stranded DNA virus that causes both acute and chronic hepatitis. Important components of the viral particle include hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). The virion is 42 nm in diameter and contains the nucleocapsid that encloses the viral DNA. The outer shell is a lipoprotein envelope derived from host cells and contain hepatitis B surface proteins. The nucleocapsid is an icosahedral structure consisting of 240 core protein subunits and is detected as HBcAg. Within the nucleocapsid is both the viral genome and polymerase. HBeAg is a soluble antigen produced from the same open reading frame as HBcAg and is a marker of active viral replication. HBV replicates via DNA polymerase through reverse transcription of an RNA intermediate; the lack of proofreading in this process leads to a high frequency of mutations, which is a barrier to successful treatment of HBV.[9]

Ten HBV genotypes, A through J, have been characterized and multiple subgenotypes have been identified using molecular techniques. Some genotypes have discrete HBV geographic distributions, but identifying HBV genotype is important because it has implications on mutation patterns and, importantly, on clinical outcomes, such as likelihood of seroconversion or viral suppression.[10–13] Mixed genotype infections and intergenotypic recombination create challenges for effective treatment in HBV. For example, genotypes A (western hemisphere) and C (Asian-Pacific) have a high tendency toward recombination of viral strains, as does genotype B in certain areas of southeast Asia.[10,14,15] Further, mutations of the S gene (the gene that codes for HBsAg) in genotype B/C regions have led to breakthrough HBV infection in previously vaccinated children, highlighting the importance of genotyping and evolution of the virus through mutations.[16] About 77% of US-born patients with HBV are infected with genotype A, but other genotype infections are frequently seen in immigrants from different countries.[17] Overall, genotypes C, D, and F are higher risk for disease progression and HCC; patients with genotypes C and D have delayed seroconversion of HBeAg, higher histologic activity, and poor response to interferon (IFN) and nucleoside therapy (**Table 1**).[10,18–20]

Immune Mechanisms in Hepatitis B Virus

The host immune system plays a key role in viral clearance and hepatocellular damage in chronic HBV because the virus is not directly cytopathic. Children have differences in immune tolerance and rate of progression of liver disease compared with adults. Ninety percent of infants infected with HBV develop chronic infection, whereas only 5% of infected adults develop chronic HBV. Even among children, groups less than 5 years of age have vastly different seroconversion rates, rates of chronicity, and response to treatment compared with their adolescent counterparts. Several mechanisms have been proposed that lead to the persistence of HBV with progression to HCC.