Viral Hepatitis in Children: A Through E

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ABSTRACT

Hepatitis is defined as inflammation of the liver. This inflammation can be acute and self-limited, chronic (leading to cirrhosis and an increased risk for hepatocellular carcinoma), or fulminant (requiring lifesaving liver transplantation). Although there are many causes of hepatitis, this article focuses on the main childhood viral hepatidities: types A, B, C, D, and E. This review discusses the main characteristics of each virus, including salient epidemiology, clinical characteristics, diagnosis, treatment, and prevention strategies. [Pediatr Ann. 2016;45(12):e420-e426.]

Despite significant advances in the molecular diagnosis, treatment, and prevention of viral hepatidities, they remain an important global health problem. These ubiquitous viral infections account for significant worldwide morbidity and mortality. This article reviews the epidemiology, and the clinical and therapeutic-preventive strategies for the hepatitis A, B, C, D, and E viruses, five of the most common causes of infectious hepatitis.

HEPATITIS A

Hepatitis A virus (HAV) is a single-stranded, nonenveloped RNA virus belonging to the Picornaviridae family (Table 1). After ingestion, HAV replicates in the small intestine, migrates to the liver via the portal circulation, and infects hepatocytes through interactions with membrane-bound receptors. Mature HAV virions are then excreted via bile and feces, where viral particles can usually be detected by electron microscopy within 4 weeks after infection. The incubation period of HAV ranges from 15 to 50 days with an average of 28 days, and it is primarily spread via the fecal-oral route.1 Outbreaks typically occur via person-to-person contact or ingestion of contaminated water and foods, including raw or undercooked shellfish (bivalve mollusks such as mussels, oysters, and clams but not shrimp, lobster, or crabs). Thus, those at highest risk of contracting HAV are people who travel to regions of the world with intermediate or high rates of the virus (such as Africa, Asia, and South and Central America); those who have household members, caregivers, or sexual contacts who are infected; and users of illegal intravenous drugs. It is estimated that 1.4 million people worldwide are infected with HAV every year.2 Although several important outbreaks associated with contaminated foods have occurred, the overall incidence of HAV has declined by 95% in the US since the HAV vaccine became available in 1995 (Figure 1).2,3

HAV infection is typically an acute, self-limited illness without chronic sequelae; relapsing or prolonged cholestatic hepatitis and fulminant liver failure rarely occur. Symptoms associated with HAV infection are usually nonspecific and include anorexia, malaise, fatigue, abdominal pain, vomiting, diarrhea, fever, and headache. Liver-specific issues such as hepatosplenomegaly, dark urine, pale stools, and jaundice can also occur. Liver test
abnormalities are evident by the time patients become symptomatic. In general, jaundice associated with HAV is more prevalent with increasing age: it is seen in fewer than 10% of children below the age of 6 years, in 40% of those age 6 to 14 years, and in more than 70% of those older than age 14 years. Most infected patients recover uneventfully within 2 months of exposure. Extrahepatic manifestations of HAV, including vasculitis, arthritis, thrombocytopenia, acute pancreatitis, acute acalculous cholecystitis, aplastic anemia, Guillain-Barré syndrome, acute renal failure, and pericarditis, are rare.

Total anti-HAV (immunoglobulin M [IgM] and immunoglobulin G [IgG]) antibodies remain detectable after infection (and immunization) throughout the person’s lifetime. In 2015, a group from Brazil reported on the utility of detecting IgM anti-HAV antibody in saliva as a noninvasive means of diagnosing HAV infection. If confirmed, this diagnostic tool may facilitate the identification of patients with HAV infection.

In 1995, a two-dose intramuscular injection vaccine containing inactivated HAV became available in the US for certain people who are at risk. In 2006, the Centers for Disease Control and Pre-

### TABLE 1.

**Overview of Viral Hepatitis in Children**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Nucleic Acid</th>
<th>Transmission</th>
<th>Incubation (days)</th>
<th>Chronic Infection</th>
<th>Vaccine Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Picornaviridae</td>
<td>Single-strand RNA</td>
<td>Fecal-oral</td>
<td>15-50</td>
<td>No (rare recurrent cholestatic hepatitis)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonenveloped</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepadnavirus</td>
<td>Double-strand DNA</td>
<td>Parenteral, sex</td>
<td>30-180</td>
<td>&gt;90% infants &lt;10% adults Cirrhosis, increased risk for HCC</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enveloped</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Flaviviridae</td>
<td>Single-strand RNA</td>
<td>Parenteral</td>
<td>14-180</td>
<td>75%-80% Cirrhosis, increased risk for HCC</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enveloped</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Deltavirus</td>
<td>Circular RNA enveloped</td>
<td>Parenteral, sex</td>
<td>42-180</td>
<td>Superinfection: 75% Coinfection: 5% Cirrhosis, increased risk for HCC</td>
<td>No (prevented through HBV vaccines)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Hepeviridae</td>
<td>Single-strand RNA</td>
<td>Fecal-oral</td>
<td>21-56</td>
<td>Only reported in patients postransplant or who are immunosuppressed</td>
<td>Yes (approved only in China)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonenveloped</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
vention (CDC) expanded its use to immunize all children age 12 to 23 months. All susceptible persons traveling to high-incidence HAV areas or exposed to HAV should receive a single dose of single-antigen vaccine before departure or within 2 weeks of exposure, respectively. Hand washing, avoiding the consumption of uncooked foods, heating foods to 185°F (85°C), and using a 1:100 solution of household bleach to clean surfaces are also effective measures to prevent the spread of HAV. As HAV is mostly self-limiting, treatment is supportive.

HEPATITIS B

Hepatitis B virus (HBV) is a double-stranded DNA virus and a member of the Hepadnavirus family (Table 1). This virus has several genotypes whose predominance varies depending on geographic location. It is estimated that 240 million people worldwide are chronically infected with HBV, and more than 780,000 deaths occur yearly due to HBV-related sequelae. A precise global incidence of HBV infection in children is unknown because 85% to 90% of children are asymptomatic. With the advent of universal HBV vaccination, the incidence of new HBV infection in the US has declined by 62% (Figure 2). The incubation period for HBV varies from 30 to 180 days, and this virus is typically spread via skin or mucosal exposure to infected blood and bodily fluids. The development of chronic HBV infection is inversely related to age at exposure, as it occurs in more than 90% of infants born to infected mothers and less than 10% of adults. Acute HBV is confirmed by the detection of the hepatitis B surface antigen (HBsAg) and the IgM antibody to the hepatitis B core antigen (IgM anti-HBc). The acute presentation of HBV infection varies from asymptomatic to fulminant liver failure; however, severe presentations have been less commonly observed since the advent of the HBV vaccine, and they typically occur in adults. Symptoms during the acute phase are similar to those of HAV. Extrahepatic manifestations occur with HBV and include migratory arthritis, angioedema, and papular acrodermatitis of childhood (Gianotti-Crosti syndrome).

Chronic HBV infection occurs when HBsAg remains detectable for longer than 6 months after infection. Most children who are chronically infected are asymptomatic. There are several stages of chronic disease of varying duration (Table 2). Most children are in the immune tolerant phase, which is characterized by normal or minimally elevated serum aminotransferase activity and evidence of active HBV replication with detectable HBsAg, hepatitis B antigen (HBeAg), and HBV DNA. The duration of this phase varies from months to years and precedes the immune active (clearance) stage. In this next phase, results of HBV serology are similar to those seen in the immune tolerant stage with the exception of elevation in serum aminotransferase levels, reflecting hepatic necroinflammation. Patients in the immune active phase are more likely to respond to treatment than those in the immune tolerant phase. HBeAg can become undetectable during this stage, and this typically occurs after puberty. The next phase is the inactive carrier phase (or latent phase), during which serum aminotransferase levels normalize and HBV replication is abrogated. Patients in the latent stage can revert to the immune active phase. Viral infection resolves in a minority of patients heralded by clearance of HBsAg and appearance of anti-HBs antibodies. Approximately 20% to 30% of patients in the latent stage will have HBV reactivation with a rise in viral DNA levels, normal or elevated aminotransferase levels, and undetectable anti-HBeAg. Cirrhosis and hepatocellular carcinoma (HCC) are the dreaded long-term consequences of chronic HBV infection. Although pediatric-specific screening strategies for the detection of HCC are not available, periodic determinations of serum alpha-fetoprotein and serial abdominal sonography, as are recommended for adults, seem reasonable approaches for children with chronic HBV infection.

Patients with immune tolerant HBV infection should undergo periodic clinical evaluation, including assessment of liver disease and serology of HBV.
DNA. There are several ongoing clinical trials assessing nucleos(t)ides in combination with peginterferon in children with immune tolerant HBV (Table 3). Pharmacological treatment of children with HBV infection is generally recommended for those in the immune active phase. In the US, interferon-based and nucleos(t)ide-based therapies are approved for children with chronic HBV (Table 4). HBV vaccination, as is recommended for all in the US, is the most effective way to prevent infection. The use of hepatitis B immunoglobulin is effective in preventing perinatal transmission and postexposure HBV infection in susceptible people.

**HEPATITIS C**

Hepatitis C Virus (HCV) is a single-stranded, enveloped RNA virus belonging to the Flaviviridae family (Table 1). Six HCV genotypes are recognized. In the US, HCV genotype 1 accounts for approximately 80% of chronic infections, whereas HCV genotypes 2 and 3 account for most of the others. HCV genotype 4 occurs in people from North Africa and the Middle East, HCV genotype 5 in those from South Africa and Mozambique, and HCV genotype 6 in those from Southeast Asia. The incubation period of HCV ranges from 2 weeks to 6 months and is primarily spread through exposure to contaminated blood. Perinatal, or vertical transmission from infected mothers to their offspring, is by far the most common source of HCV infection in children in the US. The risk of perinatal transmission averages 5% to 7% for women who have detectable HCV RNA at the time of delivery, and rises 2- to 3-fold for mothers who are coinfected with human immunodeficiency virus. Adolescents with high-risk behaviors, such as intravenous illegal drug use, and those who received blood product transfusions and organ transplantation before 1992 (when effective screening tests became available) are also at risk for HCV infection. There appears to be no increased risk of HCV transmission by breast milk because the rate of viral infection transmission is similar between breast- and formula-fed infants.

HCV affects an estimated 150 to 180 million people worldwide, and approximately 11 million of these people are children younger than age 15 years. In the US alone, approximately 3.6 million people have detectable HCV antibodies, of whom 75% are chronically infected with the virus. The prevalence of childhood HCV varies from 0.05% to 0.36% of the population, and is up to 30 times higher in developing countries. Reported US pediatric HCV prevalence likely underestimates HCV infection because the identification of children infected with HCV is grossly inadequate.

HCV infection in children is a slowly progressive disease, so sequelae such as cirrhosis or HCC are rare during childhood. The degree of hepatic fibrosis correlates with duration of infection. Spontaneous clearance of HCV is seen in 20% to 45% of children infected during infancy, and usually occurs by age 3 years. Most acute HCV infections in children and adults are asymptomatic, although nonspecific symptoms similar to those of HAV and HBV can occur.

HCV infection is suspected in those with detectable anti-HCV antibodies and confirmed by the presence of HCV RNA by nucleic acid test. In infants born to mothers with HCV, testing for anti-HCV antibody should be performed after age 18 months because positive results before this age may represent passively transferred maternal antibodies. Interferon in combination with ribavirin is the only US Food and Drug Administration-approved therapy.

**TABLE 2. Phases of Hepatitis B Virus Infection**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Characteristic Laboratory and Histology Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant</td>
<td>DNA &gt;20,000 IU/mL; ALT normal; HBSAg and HBeAg detectable; Minimal liver inflammation–fibrosis</td>
</tr>
<tr>
<td>Immune active</td>
<td>DNA levels decline; ALT elevated; HBSAg and HBeAg remain detectable; Liver inflammation–fibrosis can develop</td>
</tr>
<tr>
<td>Inactive infection</td>
<td>DNA &lt;2,000 IU/mL or undetectable; ALT normalizes; HBeAg undetectable, anti-HBe present; No liver inflammation, fibrosis may regress</td>
</tr>
<tr>
<td>Reactivation</td>
<td>DNA levels increase; ALT normal or elevated; HBeAg remains undetectable</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; anti-HBe, hepatitis B antibody; HBSAg, hepatitis B antigen; HBeAg, hepatitis B surface antigen.
for children with HCV. However, the need for weekly injections, low virological response rates (50%-60%), and frequent treatment-related toxicities limit their use. The advent of all-oral direct acting antivirals has transformed HCV treatment in adults, with response rates consistently more than 95% after 12 to 24 weeks of therapy. Pediatric trials using these highly effective and well-tolerated regimens are underway (Table 3). Thus, deferring treatment for HCV-infected children unable to enroll in clinical trials is a reasonable option at this time.

There is no effective vaccine to prevent HCV infection; thus, the main strategies to avert viral spread are education and counseling. Once patients are identified with HCV infection, they should avoid sharing razors, toothbrushes, nail clippers, and other objects potentially contaminated with blood, in addition to using standard precautions with blood exposures. High-risk behaviors such as needle sharing and sexual activity with multiple partners should be avoided. Standard immunizations, including the HAV and HBV vaccines, should be obtained, in addition to avoidance of alcohol to minimize progression of liver disease.

**HEPATITIS D**

Hepatitis D virus (HDV), also known as delta virus, is an incomplete RNA virus that is dependent upon the presence of HBsAg for infectivity (Table 1). As with HBV, HDV is mainly spread via the blood-borne route and by exposure to contaminated body fluids, as occurs with sharing of needles among intravenous drug abusers and through sexual intercourse. Vertical transmission of HDV is relatively uncommon. The prevalence of HDV is high in areas of the Middle East and those surrounding the Mediterranean Sea, as well as in Central Asia, West Africa, some Pacific Islands, and the Amazon regions in South America. HDV is considered to be fairly uncommon in the US, although recent reports have shown an increasing prevalence.

HDV infection can occur in one of two forms: simultaneously with that

**TABLE 3.**

Ongoing Clinical Trials in Children with Chronic HBV and HCV Infection

<table>
<thead>
<tr>
<th>Infection</th>
<th>Medication</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV immune tolerant phase</td>
<td>Lamivudine + peginterferon</td>
<td>NCT02263079^2^</td>
</tr>
<tr>
<td>HBV immune tolerant phase</td>
<td>Entecavir + peginterferon</td>
<td>NCT01368497^3^</td>
</tr>
<tr>
<td>HCV genotype 1</td>
<td>Sofosbuvir/ledipasvir</td>
<td>NCT02249182^2^</td>
</tr>
<tr>
<td>HCV genotype 1,4</td>
<td>Ombitasvir + paritaprevir/ritonavir ± dasabuvir ± ribavirin</td>
<td>NCT02486406^5^</td>
</tr>
<tr>
<td>HCV genotype 2,3</td>
<td>Sofosbuvir + ribavirin</td>
<td>NCT02175758^8^</td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

**TABLE 4.**

Currently Approved Treatment for Children with Immune Active Hepatitis B Virus Infection

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Indication</th>
<th>Route of Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-alpha</td>
<td>Age &gt;1 year</td>
<td>Subcutaneous injection</td>
<td>Finite duration of therapy (24 weeks)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Age &gt;2 years</td>
<td>Oral</td>
<td>Low genetic barrier (high frequency of resistance) Little toxicity</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Age &gt;12 years</td>
<td>Oral</td>
<td>Oral Little toxicity</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Age &gt;16 years</td>
<td>Oral</td>
<td>Oral Little toxicity</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Age &gt;2 years</td>
<td>Oral</td>
<td>High genetic barrier (low frequency of resistance) Little toxicity (reduction in bone mineral density gain)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Age &gt;2 years</td>
<td>Oral</td>
<td>High genetic barrier (low frequency of resistance) Little toxicity</td>
</tr>
</tbody>
</table>

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HBsAg, hepatitis B surface antigen; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.
of HBV (coinfection) or superimposed on a person with chronic HBV (superinfection). In those with HBV-HDV coinfection, liver disease is typically acute and self-limited with an incubation period of 3 to 7 weeks. Symptoms are similar to those described for other viral hepatitides already mentioned. By contrast, HDV super-infection results in severe acute disease, with progression to chronic HDV hepatitis in 70% to 90% of affected patients. Up to 70% of those with chronic HDV develop cirrhosis, along with increased risk for the development of HCC.

HDV infection is confirmed by the presence of anti-HDV antibody. The availability of HDV RNA nucleic acid testing is limited in the US; samples must be sent to the CDC or other specialized HDV research laboratories for analysis. Treatment for HDV consists of interferon-alpha, although this antiviral agent is only modestly effective. Although there are no HDV-specific vaccines to avert infection, this is effectively accomplished through preventing HBV infection with HBV immunization.

HEPATITIS E

Hepatitis E virus (HEV) is a non-enveloped RNA virus belonging to the Hepeviridae family (Table 1). HEV is typically spread via the fecal-oral route; ingestion of contaminated water; consumption of raw or undercooked pork, deer, or wild boar meat; or consumption of raw shellfish. Vertical HEV transmission from mother to newborn also occurs. HEV is thought to be responsible for upwards of 3,000 stillbirths each year in developing countries, as well as preterm deliveries with poor survival rates.

Worldwide, an estimated 20 million HEV infections occur each year. HEV is highly endemic in regions of Asia, Africa, the Middle East, and Central America. The incubation period of the virus ranges between 3 and 8 weeks, and symptomatic infection typically occurs in people older than age 15 years. Although infection in children younger than this age is quite common, many are asymptomatic or develop only a mild disease. Symptoms of HEV are typical of the other viral hepatitides, as previously described.

In general, HEV is an acute self-limiting illness. It can occasionally lead to fulminant disease, particularly among pregnant women, resulting in mortality rates as high as 20%. Chronic HEV infection may also occur in the setting of solid organ transplantation or immunosuppression. HEV is diagnosed by the identification of the virus in serum or stool by polymerase chain reaction (PCR) or by detecting IgM antibodies to HEV. HEV PCR testing is considered the gold standard to confirm infection, as anti-HEV antibodies may be negative in acute infection. HEV nucleic amplification assays are not commercially available in the US; however, testing can be done through the CDC. Treatment is supportive, as HEV disease is generally a self-limited illness. The use of ribavirin may be considered but its potent teratogenicity limits its use in pregnant women. HEV vaccines are approved for use in China.

CONCLUSION

There is regional variation in the prevalence of infectious hepatitides but they remain an important cause of liver disease worldwide. Because they share common clinical presentations, a high index of suspicion along with meticulous history taking and appropriate serological evaluation are critical to their timely diagnosis. HAV and HEV are acquired via the fecal-oral route and typically result in an acute, self-limited disease that is managed with supportive care. In contrast, HBV, HCV, and HDV are usually acquired parenterally, and infection with them can lead to chronic liver disease with increased risk for hepatocellular carcinoma. Curative therapies are available for adults with HCV and are actively being studied in children. Antiviral treatments of varying effectiveness are also available for chronic HBV and HDV infection. Vaccines that effectively prevent infection are widely available for HAV and HBV and in limited scope for HEV but not for HCV. Developing new identification, treatment, and prevention strategies, as well as expanding the use of currently available ones, will be necessary to ensure the eradication of these infections.

REFERENCES

6. Advisory Committee on Immunization Practices Centers for Disease Centers for Disease Control and Prevention (CDC). Updated: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advi-