Hepatitis A, B, and C

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Practice Gap

Because hepatitis A, B, and C viruses are responsible for substantial morbidity and mortality, clinicians must learn to recognize, treat and prevent infections caused by these viruses.

Objectives

After completing this article, readers should be able to:

1. Describe the epidemiology of hepatitis A, B, and C virus infections.
2. Recognize the clinical features of hepatitis A infection.
3. Appropriately administer vaccines for the prevention of hepatitis A and B infection.
4. Recognize the various antiviral regimens used for the treatment of hepatitis B and C liver disease.
5. Order the most appropriate tests for the diagnosis of hepatitis virus infections.

INTRODUCTION

During the past 30 years, the understanding of hepatitis viruses has greatly expanded. Knowledge of hepatitis has progressed from merely describing the various clinical syndromes to a greater understanding of the pathogenesis of disease caused by these viruses and the development of chronic infection that eventually leads to cirrhosis or hepatocellular carcinoma. Expanded understanding also has led to the development of effective vaccines against hepatitis A virus (HAV) and hepatitis B virus (HBV) and antiviral therapies against hepatitis C virus (HCV). The introduction of routine vaccination against HAV and HBV starting in early childhood in the United States has resulted in a substantial decrease in both of these infections in children and the subsequent complications of HBV-related chronic liver disease. Effective screening of mothers during pregnancy and the administration of HBV vaccine soon after birth, along with administration of hepatitis B immune globulin (HBIG) to infants born to women who have HBV infection, has led to near eradication of perinatally acquired HBV disease in the United States and other countries with effective screening programs. The introduction and routine administration of HAV vaccine in the United States in the 1990s led to near complete elimination of HAV outbreaks among children.

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Now, antiviral therapies are available for the treatment of chronic HBV and HCV infections. Newer agents are more effective, especially against most genotypes, and cures are frequently observed. In the following review, we summarize the clinical manifestations of these viral infections, the various diagnostic assays that clinicians must know how to order and interpret, therapeutic regimens for HBV and HCV infection, and the various measures used to prevent disease. Table 1 provides a quick review of the important clinical aspects for each virus.

HEPATITIS A

Epidemiology

HAV is a *Hepatovirus* within the *Picornaviridae* family. It is a nonenveloped, single-stranded RNA virus. HAV is transmitted via the fecal-oral route. Person-to-person transmission is observed in most cases, but transmission through the consumption of contaminated food or water and even transfusions has been documented. Following ingestion, the virus replicates within the gastrointestinal tract, gaining entry into the liver via the portal venous system. Although the virus appears to be noncytopathic to hepatocytes, inflammation ensues, although chronic liver disease does not occur. Following the incubation period, a large amount of virus is shed in the stool.

The burden of disease throughout the world is greatly influenced by the availability of safe drinking water and uncontaminated food. This is, in large part, dependent on the quality of the sanitary infrastructure. As a result, resource-poor countries and regions often have a higher burden of infection. The improvement of infrastructure and implementation of vaccine programs are 2 key factors that have substantially reduced the burden of HAV infection in many countries. In 2005, the World Health Organization estimated that 126 million cases of HAV infection occurred worldwide, resulting in the death of 35,245 persons. (1) Most infections occur in the community, but hospital-acquired

TABLE 1. **Clinical Comparison of Hepatitis Viruses**

CATEGORY	HEPATITIS A	HEPATITIS B	HEPATITIS C
Incubation period, mean	28 days (range, 15-50 days)	90 days (range, 45-160 days)	6-7 weeks (range, 2 weeks-6 months)
Modes of transmission	Fecal-oral	Transfusion, IVDA, sexual activity, maternal-fetal	Transfusion, IVDA, sexual activity, maternal-fetal
Clinical features	Asymptomatic disease is common in young children (<6 years) Self-limited illness Symptomatic disease: fever, jaundice, anorexia, malaise, nausea, fatigue	Symptomatic disease is more common in children >5 years old Chronic infection is more likely if infected perinatally and <1 year old Nonspecific symptoms: fever, jaundice, anorexia, malaise, nausea, fatigue	Most infections are asymptomatic Nonspecific symptoms are common: fever, jaundice (<20% of patients), anorexia, malaise, nausea, fatigue Chronic infection is common
Chronic infection?	No	Yes	Yes
Diagnostic tests	Serology (HAV-specific IgM and IgG antibodies)	Serology (HBsAg, HBsAb, HBcAb IgM), PCR	Serology (HCV IgG antibody), PCR
Treatment	Supportive	Supportive Antiviral therapy for chronic liver disease	Supportive Antiviral therapy for chronic liver disease
Prevention	Vaccination Immune globulin	Screening Vaccination	Screening
Isolation, hospitalized patients	Contact + standard precautions for diapered and incontinent patients for at least 1 week after onset of symptoms	Standard precautions	Standard precautions

HAV=hepatitis A virus, HBsAb=hepatitis B surface antibody, HBcAb IgM=hepatitis B core IgM antibody, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, IgG=immunoglobulin G, IgM=immunoglobulin M, IVDA=intravenous drug abuse, PCR=polymerase chain reaction.

cases of HAV infection have been reported. In many instances, infected infants may remain asymptomatic or mildly ill but spread the virus to adults who are known to become much sicker. (2)(3) Outbreaks of HAV infection have been reported in child care centers (4) as well as nursery and primary schools. (5) Food-borne outbreaks of HAV infection were often seen in the United States before implementation of the vaccination program that initially was administered in regions with high disease burden and now is part of the routine childhood immunization schedule. (6)(7) Before the widespread use of HAV vaccination, a disproportionate number of cases occurred among Native American populations. The rate of infection in this group was at least 20 times higher than that in the non-Hispanic white population. At that time, 11 western states were responsible for more than 50% of the cases reported in the United States.

Currently, the incidence of HAV infection in the United States is at its lowest. Population-based surveillance collected between 2005 and 2007 estimated an annual incidence rate of 1.3 cases per 100,000 population (range, 0.7-2.3). (8) Before implementation of vaccination programs, the rate of infection was 14 per 100,000 population. More than 90% of affected persons resided in urban areas. Although nearly 50% of all cases occurred in persons ages 15 to 39 years, ~20% of cases were among those younger than age 15 years. Increased disease susceptibility has now shifted to older age groups in whom morbidity and mortality rates are greater. (8)

Travel remains a key risk factor for the acquisition of HAV infection. International travel was found to be a risk factor in 45% of reported cases. Contact with a case was a risk factor in ~15% of cases. Of interest, 24% of reported cases had been in contact with a traveler but had not travelled themselves. To minimize this source, vaccination of susceptible individuals prior to travel is imperative. (9)

Although there is a single HAV serotype, various genotypes and subgenotypes have been identified. Subtyping has been found to be useful in outbreak investigations because various HAV genotypes circulate throughout the world. Genotype 1A is responsible for most infections within the United States and most of Latin America, whereas 1B is almost exclusively observed in Brazil.

Clinical Features

HAV infection is a self-limited infection of the liver. The average incubation period is ~30 days (range, 15-50 days). Most infections in children (>70%) are asymptomatic or of mild severity. Asymptomatic infection was observed in 13.6% of children, and subclinical disease was observed in 18.6% of children. Approximately 15% of children with HAV infection have atypical manifestations of the disease.

Fever, abdominal pain, nausea, fatigue, loss of appetite, and jaundice are common features in the symptomatic child. Symptomatic HAV infection is rarely observed among infants and children younger than age 6 years, with fewer than 10% having jaundice. (10) In those younger than age 3 years, anicteric infection is 17 times more common than icteric infection. In a cohort of 118 children whose mean age was 8.6 years, jaundice was observed in only 48.3%. (11) Cholestasis, acute liver failure, relapsing hepatitis, ascites, and hematologic problems (autoimmune hemolytic anemia, aplastic anemia, and pure red cell aplasia) are described. In addition, pleural and pericardial effusion, acute kidney injury (AKI), pancreatitis, and acute reactive arthritis are reported in children and adults. (12) Approximately 80% of adults infected with HAV may develop severe hepatitis. (12)

HAV does not usually cause chronic disease. However, some children with protracted jaundice have liver histology suggestive of chronic liver disease. (13) Fulminant hepatitis is rare, with a reported incidence of less than 1%. In a study from Pakistan, 56% of children with fulminant hepatic failure had HAV infection compared with 18% who had HBV infection. (14) Young age, encephalopathy, severe coagulopathy, and low transaminases are markers of severe disease and poor outcomes. In a study of patients with HAV infection, ~8% developed concomitant AKI. (15) In another study, 7% of patients had AKI. (16) Fulminant hepatitis, leukocytosis, and elevated C-reactive protein were independent markers for risk. A fatal case of encephalitis has been described in an 11-year-old girl presenting with seizures, coma, and anicteric hepatitis. (15)(17)

Diagnostic Testing

Detection of HAV-specific antibodies (anti-HAV immunoglobulin [Ig]G and IgM) is the most common method for diagnosing HAV infections (Table 2). Anti-HAV IgM antibodies appear within 5 to 10 days after symptom onset and may persist for up to 4 months. Anti-HAV IgG titers tend to rise later but persist for a longer duration. Most patients with HAV infections develop anti-HAV IgM antibodies at the end of the incubation period (~4 weeks) and with the onset of symptoms. However, ~11% of patients in 1 study had a negative IgM at the time of presentation. Although HAV IgM is the diagnostic test for acute HAV infection, clinicians must keep in mind potential negative results when evaluating children in the early phases of the disease. (19)

Treatment

There is no available antiviral treatment for HAV. Management is largely supportive.

TABLE 2. **Interpretation of Diagnostic Test Results for Hepatitis Viruses**

TEST	RESULT	INTERPRETATION
Hepatitis A		
Anti-HAV IgM antibody assay[a]	Positive	Acute or recent infection Postvaccination (18)
Anti-HAV IgG antibody assay	Positive	Immunity from past infection or vaccination
Anti-HAV IgM + IgG	Negative	No HAV infection
Anti-HAV IgM + IgG	Positive	Acute, recent infection or past infection Will require a separate IgM assay
Hepatitis B[b]		
HBV surface antigen (HBsAg)	Negative	No chronic infection
HBV surface antigen (HBsAg)[c]	Positive	Acute infection Chronic infection Postvaccination
HBV surface antibody (HBsAb)	Positive	Past infection, past vaccination, immunity to HBV; rarely positive with chronic infection
IgG antibody to HBV core (HBcAb IgG)[d]	Positive	Acute, resolved, or chronic infection Not detected after hepatitis B immunization
HBcAb IgG + HBsAb	Positive	Resolved infection
IgM antibody to HBV core (HBcAb IgM)	Positive	Acute infection, recent infection Useful for diagnosis during "window" period
HBV e antigen (HBeAg)	Positive	High level of infectivity
Antibody to HBeAg	Positive	Infectivity is unlikely
Hepatitis C		
Anti-HCV antibody assay	Positive[e]	Acute, recent, or resolved infection
HCV polymerase chain reaction (NAAT)[f]	Positive	Acute, chronic infection

[a]*Can be detected following hepatitis A vaccination.*
[b]*American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds.* Red Book: 2015 Report of the Committee on Infectious Diseases. *30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400-423.*
[c]*Transient antigenemia can be detected following hepatitis B vaccination.*
[d]*Should not be present following vaccination.*
[e]*False-negative test results are common early in the infection.*
[f]*Frequently used to detect viremia early in the infection (window period when antibody assay is negative), to determine infection in a young infant (in the presence of maternal antibodies), and to monitor response to antiviral therapy.*
HAV=hepatitis A virus, HBV=hepatitis B virus, HCV=hepatitis C virus, IgG=immunoglobulin G, IgM=immunoglobulin M, NAAT=nucleic acid amplification test.

Prevention

HAV vaccine is routinely administered to children in the United States as a 2-dose series starting at age 1 year (Table 3). HAV vaccine is also recommended for all susceptible travelers to countries that have a high prevalence of HAV infection. (20) Some adolescents may require pretravel vaccination if they have not been vaccinated against HAV. In spite of this recommendation and because of lack of awareness among some older travelers, HAV vaccine is often not received before travel to high-risk areas. Sub-Saharan Africa and south Asia have high endemicity levels and almost no susceptible adolescents and adults because most infections occur early in life. (21) Vaccination rates in adolescents remain low because catch-up vaccination has not been completely implemented.

HAV vaccination programs in Native American communities in the United States led to a 20-fold decrease in the number of HAV cases. (22) In Israel, a substantial effect of vaccination was observed in children younger than age 5 years, with a reduction from 239.4 cases per 100,000 in

TABLE 3. **Hepatitis A and B Vaccines for Infants, Children, Adolescents, and Adults**

VACCINE/TYPE OF PATIENT	DOSE (mL)	NUMBER OF DOSES	SCHEDULE
Hepatitis A vaccines			
1-18 years of age			
Havrix® (GSK Biologicals), 720 ELU	0.5	2	0, 6-12 months later
Vaqta® (Merck & Co), 25 U	0.5	2	0, 6-18 months later
>19 years of age			
Havrix® (GSK Biologicals), 1,440 ELU	1.0	2	0, 6-12 months later
Vaqta® (Merck & Co), 50 U	1.0	2	0, 6-18 months later
Hepatitis B vaccines			
Infants of HBsAg-negative mothers	0.5[a]	3-4	3-dose schedule recommended; 4 doses may be administered if birth dose and combination vaccine is used
Children and adolescents <20 years of age	0.5[c]	3-4	3-dose schedule recommended; 4 doses may be administered if birth dose and combination vaccine is used
Infants of HBsAg-positive mothers[b]	0.5	3-4	Give within 12 hours of birth; HBIG is also recommended
Adolescents 11-15 years of age, unvaccinated	1.0[c]	2	0, 4-6 months later
Adults >20 years of age	1.0[d]	3	0, 1, and 6 months
Adults on dialysis and other immunocompromised conditions	1.0[e] or 2.0[f]	4	0, 1, 2, and 6 months
Hepatitis A and B vaccine			
Adults >18 years of age			
Twinrix® (GSK Biologicals)[g]	1.0	3-4[h]	0, 1, and 6 months or 0, 7, 21-30 days + 12 months later

[a]Recombivax HB® (Merck & Co), 5 μg or Engerix B® (GSK Biologicals), 10 μg
[b]First dose is given in combination with hepatitis B immune globulin
[c]Adult formulation of Recombivax HB®
[d]Recombivax HB®, 10 μg or Engerix B®, 20 μg
[e]Special formulation of Recombivax HB®
[f]Two 1.0-mL doses of Engerix B®
[g]Combination vaccine: hepatitis B (Engerix-B®, 20 μg) + hepatitis A (Havrix®, 720 ELU)
[h]Accelerated schedule: useful in previously unvaccinated adults planning international travel and/or international adoption; requires 4 doses; immunogenicity after 3 doses is ≥99.9%
ELU=enzyme-linked immunosorbent assay units, HBIG=hepatitis B immune globulin, HBsAg=hepatitis B surface antigen, U=antigen units (each unit equivalent to 1 μg of viral protein).

1998 to 2.2 cases per 100,000 in 2007. (23) HAV infection may lead to decompensation in individuals affected by HBV- or HCV-related liver disease, sometimes resulting in death. (24) HAV vaccine is recommended for all individuals with chronic liver disease. With the introduction of this vaccine, HAV-related mortality rates in persons with chronic liver disease have decreased dramatically. (20)

Individuals at an increased risk of HAV infection include contacts of international adoptees. (25)(26) Nontraveling contacts at home should be vaccinated before the arrival of the adopted child. Even when asymptomatic, infected infants and young children can be contagious and transmit virus to susceptible adults. (26)(27) Some experts recommend screening of all international adoptees for HAV. (27)(28)

Screening for HAV performed at an international adoption center determined that 29% of children had evidence of infection. (29) One percent of children were found to have acute infection (positive IgM). Children born in Africa had the highest prevalence of infection (72%) and children adopted from the Asia/Pacific Rim had the lowest prevalence (17%). In a systematic review of published studies, the protective effects of HAV vaccine was observed for up to 15 years after vaccination, (30) and a more recent analysis demonstrated a high level of seroprotection for at least 20 to 30 years. (31) Although vaccines are highly effective in preventing HAV infection, the most recent National Immunization Survey in 2013 demonstrated that only ~50% of children ages 19 to 35 months have received 2 doses of HAV vaccine. (32)

Immunocompromised persons should also receive HAV vaccination. Approximately 75% subsequently develop antibodies, but the robustness of this response is influenced by the degree and type of immunosuppression. Tumor necrosis factor-α blocker recipients appear to respond better than other individuals, with 92% developing good serologic response. Only 69% of persons receiving regimens consisting of methotrexate and azathioprine with or without corticosteroids responded to the vaccine. (33) Because of the variability of immune responses, obtaining an antibody titer after completion of the vaccine series appears reasonable.

Before the licensing of HAV vaccines, protection for susceptible individuals (pre- and postexposure) was achieved through intramuscular administration of human immune globulin (Table 4). Unfortunately, protection was short-lived and only partially protective in some individuals. Travelers expecting prolonged stays in high-risk regions or individuals expecting prolonged or frequent exposures require readministration every 3 to 5 months.

Studies have demonstrated that HAV is immunogenic in infants younger than age 1 year who are born to seronegative mothers. (34)(35)(36) Maternal antibodies appear to blunt the immune response to the vaccine. Although still greater than concentrations considered to be protective, postvaccination antibody values in infants born to seropositive mothers were lower than those in infants born to seronegative mothers. (37) HAV vaccine has not been approved by the Food and Drug Administration (FDA) for use in children younger than age 1 year. Unimmunized and susceptible individuals exposed to HAV and at risk for infection benefit from postexposure HAV vaccination or immune globulin. (38) However, finding immune globulin in the United States has become difficult.

HEPATITIS B

Epidemiology

HBV is a pro-oncogenic, noncytotoxic, enveloped circular DNA hepadnavirus infrequently responsible for chronic infection in developed countries. (39) The prevalence of chronic HBV infection has decreased in several regions of the world, especially in central sub-Saharan Africa, tropical and central Latin America, southeast Africa, and central Europe. (40) The routine use of HBV vaccination at birth and in early childhood in Native American communities resulted in a substantial decrease in acute symptomatic

TABLE 4. **Use of Immune Globulin Preparations to Prevent Hepatitis A and B Infection**

CLINICAL SCENARIO	DOSE*	NUMBER OF DOSES	COMMENTS
Hepatitis A			
Preexposure, <12 months of age**	0.02 mL/kg	1	IG is administered deep into large muscle mass Protects up to 3 months
	0.06 mL/kg	1	For travel of ≥3 months' duration Repeat every 5 months if exposure to hepatitis A continues
Postexposure**	0.02 mL/kg	1	To be given within 2 weeks of exposure
Hepatitis B			
Infants of HBsAg-positive mothers	0.5 mL	1	HBIG should be administered within 12 hours of birth

**Not more than 5 mL at 1 site (adults), 3 mL in infants and small children*
***For children ≥1 year of age: if unvaccinated, use hepatitis A vaccine (see Table 1)*
HBsAg=hepatitis B surface antigen, HBIG=hepatitis B immune globulin, IG=immune globulin.

HBV infections from 200 per 100,000 persons in 1981 to less than 5 per 100,000 in 1996. (22) Among those with chronic hepatitis B disease (CHB) in developed countries, as many as 2% were infected as a consequence of being unimmunized and via a behavioral exposure outside of the pediatric age range. Globally, more than 350 million people are infected with HBV, the vast majority of whom acquired the infection in the perinatal period and during early childhood.

Mother-to-child transmission is responsible for at least one-third of all CHB disease worldwide. (41) The risk of perinatal infection is greatest (90%) when a mother becomes acutely infected during the third trimester and demonstrates antigenemia with both HBV surface antigen (HBsAg) and HBV envelope antigen (HBeAg), with HBeAg being a marker for higher infectivity. Approximately 65% of children born to HBeAg-positive mothers develop chronic infection compared to only ~28% of those born to HBeAg-negative mothers. (42) Not surprisingly, the risk of infection is related to the magnitude of endemicity. In addition, not surprisingly, mothers with high HBV DNA values and who deliver vaginally are more likely to infect their infants at birth. (43) Progress to CHB is related to the timing of acute infection, with the greatest risk (90%) conferred on those infected before their first birthdays. The risk of CHB declines substantially with age, peaking at 50% of those infected between ages 1 and 5 years and 1 in 10 of those infected thereafter. According to a recent study, perinatally acquired HBV infection was documented in 1% of infants for whom HBsAg test results were available. Nearly 95% of these infants had received HBV vaccine and HBIG within 12 hours of birth. (44) Younger maternal age, HBeAg positivity, high maternal viral load (≥2,000 IU/mL), and infant receipt of fewer than 3 HBV vaccines were associated with increased risk of infection. Children infected perinatally are infectious for years, but despite often profound viremia, they do not exhibit clinical disease, having only mildly elevated alanine aminotransferase values and living as immune-tolerant patients as they transition to states of immune-active/clearance or inactive carrier. Persons who are HBsAg-positive are at risk of HBV reactivation if they receive any type of immunosuppressive therapy. Forty percent of persons receiving immunosuppressive therapy reactivate HBV, with liver failure developing in 13% and a case-fatality of 16%. (45)

Clinical Features

Acute HBV infections can be asymptomatic or symptomatic. Older children, adolescents, and adults are more likely to have symptomatic disease, with 30% to 50% of children older than age 5 years exhibiting symptoms. Nonspecific symptoms such as nausea, malaise, fever, and fatigue may be present. Acute disease, characterized by jaundice, decreased appetite, and emesis, presents after viremia and HBsAg antigenemia have peaked. Fulminant hepatitis can also be observed. Extrahepatic manifestations of HBV infection, such as exanthems, arthralgias-arthritis, cryoglobulinemia, thrombocytopenia, glomerulonephritis, and Gianotti-Crosti syndrome, may also be present with acute infection. Some 95% of mother-to-child transmissions occur during the intrapartum period, with the remainder occurring in utero. Most infected infants lack symptoms. Between 15% and 40% of children who have CHB infection develop cirrhosis and/or hepatic carcinoma, and 25% of those children die from these complications. (41) Viral replication, inflammation, regeneration, and fibrosis associated with cirrhosis are virologic and histopathologic features of chronic infection. Although the precise mechanism by which HBV causes hepatocellular carcinoma is not completely known, a direct oncogenic effect by the virus is suspected. (46)

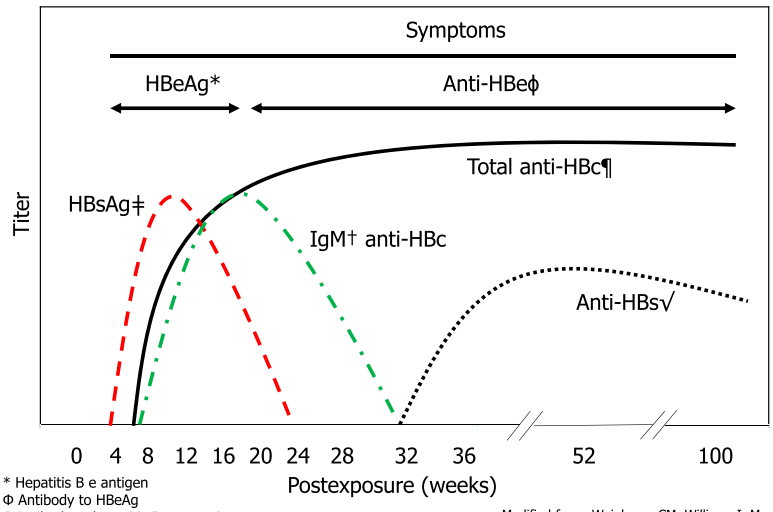
Diagnostic Testing

The interpretation of diagnostic tests for HBV infection can be challenging. The usual diagnostic serology should include IgG antibody against hepatitis B surface antigen (HBsAb), IgM antibody against hepatitis B core antigen (HBcAb), and HBsAg. Based on these results, clinicians can determine if the child is immune to HBV, has active HBV infection, is in the "window period" for HBV infection, or is immune following vaccination (Table 2, Figs 1 and 2). The "window period" is defined as the time from the onset of infection to the development of serologic evidence of infection. The diagnosis of HBV infection is made by serum detection of HBsAg. Antigenemia persists in carriers, but integrated viral genome can reactivate in certain circumstances. Hepatitis B surface antibodies result from infection and vaccination, but hepatitis B core IgG antibody can only result from infection and not vaccination because the vaccine lacks the core antigen. (47) Among those who clear the infection, HBsAg is no longer detectable after 6 months. It is important to remember that vaccination may lead to the detection of antigenemia. (48)(49)(50) The antibody against HBsAg is neutralizing and confers lifelong immunity. The presence of IgG antibodies against hepatitis B core antigen is indicative of a current or past infection. Vaccination does not lead to a positive HBcAb.

Treatment

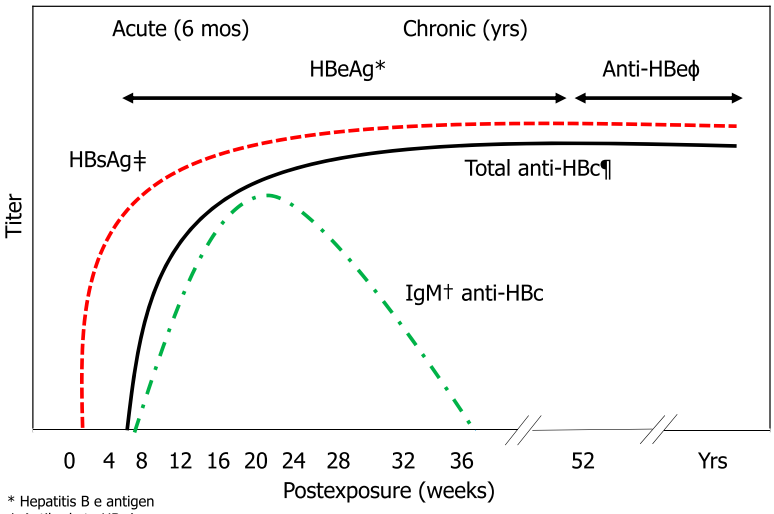
Acute infections can be managed supportively. Treatment of CHB is reserved for the subset of patients in immune-active

Figure 1. Serologic course of acute hepatitis B virus infection with recovery. From Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57(RR-8):1-20.



states. Antiviral therapy is not indicated for the person in the immune-tolerant or inactive phase of the disease. (51) Therapy is complicated by the potential for resistance. Therefore, combination therapy should be used. Patients with CHB may develop cirrhosis and a minority may develop cancer. Consequently, these patients should undergo annual ultrasonography and α-fetoprotein screening to monitor for the development of hepatocellular carcinoma (HCC). Therapy is rarely indicated during childhood, but there is controversy about such treatment. (52) Only an estimated 3% to 5% of chronic carriers develop cirrhosis and 0.01% to 0.03% develop HCC before adulthood. (51) Interferon and nucleoside analogs (such as tenofovir, lamivudine, entecavir, and telbivudine) have been used in persons who meet criteria for initiation of therapy. (53) Chronically infected children who acquired their infection perinatally rarely (10%) clear HBV infection with interferon-α. Newer therapies using drugs derived from human immunodeficiency virus (HIV) care, such as lamivudine, emtricitabine, tenofovir, and adefovir, some of which are administered in combination, are used in treatment of CHB. Infected patients should be screened for coinfection with HCV and hepatitis D virus as well as HIV.

Figure 2. Serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection. From Weinbaum CM, Williams I, Mast EE et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57(RR-8):1-20.



The use of antiviral agents in late pregnancy has been shown to reduce mother-to-child transmission. (54)

Prevention

Screening all pregnant women at the first prenatal visit captures nearly all infected mothers. However, supplemental testing during the third trimester or at the time of delivery is warranted in some women. This is especially important if mothers report additional risk factors, such as injection drug use, having been incarcerated, being a household or sexual contact of a person known to have HBV infection, being from a country with greater than 2% endemicity, or having parents from a country with greater than 8% endemicity. Neonates born to HbsAg-positive mothers should be given both passive and active immunization within 12 hours of birth using HBIG and HBV vaccine (Tables 3 and 4). This combination mitigates against vertical transmission for 85% to 95% of infants who are appropriately treated. (55) The course of routine active vaccination against HBV is not altered among these newborns, who should receive 3 doses by age 6 months, with the second dose provided at age 2 months. All other newborns should receive the first dose of the HBV vaccine series before hospital discharge. Screening of exposed infants is best undertaken after age 18 months, once maternal antibodies and immunoglobulin have cleared. (56)

Although virus is detectable in the milk of lactating mothers, breastfeeding is not contraindicated as long as the child has received appropriate prophylaxis.

All children, but especially those with CHB, should be vaccinated against HAV (Table 3).

HEPATITIS C

Epidemiology

Like HBV, HCV is enveloped, pro-oncogenic, and noncytotoxic and is most commonly transmitted via exposure to contaminated blood. As a flavivirus, HCV has a genome composed of a single-stranded positive-sense RNA molecule. HCV has 6 distinct genotypes, and mutations generate quasispecies, both of which influence overall response to specific therapy as well as the patient's clinical presentation. Genotype 3 infection is most likely to progress to fibrosis. Unlike HBV, mother-to-child transmission of HCV is extremely uncommon, approaching 5% among the singly infected and reaching ~10% among mothers coinfected with HIV. In developed countries, 1% to 2% of mothers are infected with HCV. Globally, however, some 150 million individuals are infected. Among those infected perinatally with HCV, nearly 80% progress to chronic infection, although most are asymptomatic. (39) For patients infected with either HBV or HCV, progression to liver disease is greatly accelerated by the consumption of alcohol. Accordingly, abstinence is most appropriate. Risk factors for acquiring these viruses are similar. Specifically, patients requiring hemodialysis, those who have received a tattoo from an unregulated venue, those who have received an intravenous blood product before July 1992, recreational intravenous and/or nasal drug users, and men who have sex with men are at increased risk for acquiring HCV (Table 1).

Diagnostic Testing

The detection of anti-HCV IgG antibodies is the primary diagnostic method for acute and past HCV infection (Table 2). As for many other infections that can be potentially acquired during pregnancy, the presence of IgG antibodies in young infants born to mothers known to have HCV is not diagnostic because of the presence of transplacentally acquired antibodies. In HCV-exposed infants, clinicians must wait at least until age 18 months before the assay can be useful as a diagnostic test. In young infants in whom it is important to determine the presence of infection, a nucleic acid amplification test (NAAT) such as polymerase chain reaction assay is necessary. No antiviral therapy is indicated pending confirmation of infection.

Rapid diagnostic antibody tests are highly accurate, with high sensitivity and specificity. (57)(58) Although newer antibody detection assays have greater sensitivity and specificity, a large number of HCV-infected persons may experience a window period in which antibody assay results may be false-negative. Within 3 months of exposure, most infected persons have a positive antibody test. NAAT is used to detect the presence of viremia, to help predict clinical outcomes and need for antiviral therapy, and to determine response to therapy.

Infants born to mothers with HCV infection should be evaluated at age 18 months via both antibody and RNA screening. RNA screening could be undertaken as early as age 2 months, but some who have positive results still clear the infection spontaneously. As with HBV, those infected with HCV in whom therapy is deferred should receive annual serial screening with α-fetoprotein and ultrasonography to monitor progression of fibrosis and development of HCC. Patients who have HCV infection must have immunity against HAV and HBV confirmed and should receive active immunization if not previously vaccinated (Table 3).

Treatment

The development of effective antiviral regimens for the treatment of chronic HCV infection (CHC) has been a

major advance in the fields of hepatology and infectious diseases. Although data on their use in young children are limited, ongoing studies in adolescents and young adults should yield information on which regimens are safer and more effective for use in children with CHC. Perhaps in the near future, therapy can be initiated earlier in the infection before advanced liver disease develops. Historically, use of pegylated interferon-α and ribavirin therapy was limited both by sustained virologic response and adverse effect profile. (56) This combination was only ~50% effective in children and adolescents with HCV genotype 1 infection, the most common genotype in the United States. The regimen was more effective in persons with genotype 2 and 3 infections. However, treatment was usually initiated once the person had developed advanced disease. Adverse effects with interferon were not uncommon. Influenzalike symptoms, leukopenia, and anemia could limit completion of treatment regimens.

Costly new direct-acting antivirals (DAAs), such as sofosfubir, telaprevir, and dasabuvir, are used in combination. DAAs target viral protease, polymerase, and NS5A protein necessary for replication and assembly of new viruses. In studies performed in adults, cure was achieved in nearly all patients, whether they had treatment-naïve or refractory CHC, in as few as 12 weeks of therapy based on genotype distinctions. (59) Cure rates of greater than 90% can now be achieved with interferon-free combinations. Various combinations are undergoing clinical trials in children ages 3 to 17 years. The combination of ombitasvir, paritaprevir/ritonavir, and ribavirin is undergoing trials against genotype 4 HCV, while this combination plus dasabuvir is being studied against genotype 1 disease. (56)

Infection is more difficult to manage among those coinfected with different HCV genotypes or with HBV or HIV. Therapy should be directed by hepatology and infectious diseases specialists because patients should be considered for ongoing trials of these newer agents given the adult outcomes to date. New antiviral treatments for HCV consisting of protease inhibitors, sofosbuvir, and ribavirin have demonstrated increased quality-adjusted life-years and reduced deaths in adults. Although cost-effectiveness per person treated is noticeable, the demand for these newer therapies may pose a major financial burden to the health care system as these agents become available. (60)

The availability of safe, effective, and less expensive antiviral regimens has the potential to reduce the incidence, morbidity, mortality, and health care expenditures associated with HCV. Such availability also may serve to trigger routine prenatal screening to identify infected mothers and potentially lead to early treatment of mother and infant to prevent CHC. (56) In addition, these agents could be used following an occupational exposure as a strategy to prevent infection.

Prevention

Recognition and prompt treatment of infected individuals (especially mothers) can prevent the transmission of HCV to young infants. Recently, the Centers for Disease Control and Prevention advocated screening all individuals born between 1945 and 1965, regardless of the absence of risk factors. (61) Patients with ongoing risk should be screened annually with an antibody test (anti-HCV) and if positive, with confirmatory testing with a quantitative RNA viral load. When HCV is detected, genotype screening is important because therapy can be optimized, if indicated. At this time there is no vaccine against HCV. Furthermore, because perinatal interventions such as elective cesarean section or abstaining from breastfeeding do not appear to diminish vertical transmission and because vertical transmission is most likely to occur in the presence of maternal viremia, infection appears to occur in utero. Nevertheless, mothers should be advised to forgo breastfeeding if their nipples are cracked or bleeding. (59)

OTHER HEPATITIS VIRUSES

HAV, HBV, and HCV have been recognized as pathogens of great importance in the United States and throughout the world. In recent years, other viruses have gained recognition as causes of acute hepatitis and jaundice. Without going into great detail, hepatitis E and D viruses deserve special mention.

Hepatitis E virus (HEV), transmitted by the fecal-oral route, is recognized as a major cause of morbidity and mortality, especially in pregnant women and immunocompromised hosts. In some regions of the world, HEV may the most common cause of acute hepatitis. (62) HEV is a small, nonenveloped RNA virus within the newly formed Herpesviridae family. Four genotypes have been identified, and genotypes 1 and 2 have been associated with epidemic hepatitis outbreaks after contact with contaminated water. Genotypes 3 and 4 are mostly zoonotic and emerge after contact with domestic and wild pigs. Humans are usually infected after close contact with swine. Infections with HEV are still uncommon in the United States. However, travel to endemic areas poses a risk for acquisition. (63) Clinical features of the disease are similar to those of HAV infection. Chronic infection is usually not the norm in the previously healthy person, but severe disease and death is well described in infected pregnant women and older adults.

Chronic disease has been described in immunocompromised individuals. Antiviral therapy consisting of pegylated interferon-α and ribavirin or ribavirin monotherapy has been used to treat persons with chronic infection. (64)(65) The precise efficacy of this regimen is still unknown, with most of the data resulting from case reports and small studies. An effective HEV vaccine has been produced in China. (66)

Hepatitis D virus (HDV) causes infection in persons infected with HBV. HDV requires HBV for replication and cannot produce infection in its absence. HDV is distributed worldwide. It can infect the person acutely as a coinfection with acute HBV or in someone who has a chronic HBV infection. The clinical presentation of infection resembles that of HBV, but it may contribute to a more severe presentation aggravated by fulminant hepatitis. Transmission is similar to that for HBV, with most infections resulting from exposure to contaminated body fluids such as blood or blood products, through intravenous drug use, or via sexual contact. The prevention of HBV through vaccination prevents HDV infection.

Summary

- On the basis of strong epidemiologic evidence, hepatitis viruses are responsible for significant morbidity and mortality in young infants and children throughout the world. (1)(22)(33)
- On the basis of research evidence, hepatitis A and B vaccines are effective in preventing disease. Furthermore, data strongly demonstrate that hepatitis A and B vaccines are safe in young infants and children. (23)(24)(26)(34)
- On the basis of strong evidence, pregnant mothers should be screened and concomitant active and passive immunization against hepatitis B should be provided to newborns as a strategy to prevent chronic hepatitis B in children. (44)(47)
- On the basis of new research, the use of antiviral agents is beneficial in the treatment of and potential clearance of chronic infections caused by hepatitis B and C viruses. (54)(55)(57)(58)

References and CME quiz for this article are at http://pedsinreview.aappublications.org/content/37/10/426.

Parent Resources from the AAP at HealthyChildren.org

- **Hepatitis A:** https://www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/Hepatitis-A.aspx.
- **Hepatitis A Vaccine: What You Need to Know (VIS):** https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Hepatitis-A-Vaccine-What-You-Need-to-Know.aspx.
- **Hepatitis B:** https://www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/Hepatitis-B.aspx.
- **Hepatitis B Vaccine: What You Need to Know (VIS):** https://www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/Hepatitis-B.aspx.
- **Hepatitis C:** https://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Hepatitis-C.aspx.

PIR Quiz

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1. A previously healthy 10-year-old boy has a 3-day history of jaundice, fever, malaise, loss of appetite, and vomiting. He is unvaccinated against hepatitis A. Which of the following statements is most accurate about this child's clinical diagnosis?
    A. All patients require hospitalization.
    B. Antiviral therapy is useful when administered early in the disease.
    C. Polymerase chain reaction is the preferred diagnostic test.
    D. Hepatitis A may be the cause of his illness.
    E. Vaccination against hepatitis A is indicated at this stage.
2. Antiviral therapies have been found to be effective in hepatitis B and C infections. Which of the following statements best describes the new antiviral regimens that are emerging?
    A. Regimens for hepatitis B infection are indicated for patients in the immune-tolerant or inactive phase of the disease.
    B. Their use in late pregnancy has been shown to reduce mother-to-child hepatitis B virus transmission.
    C. Therapy for hepatitis C virus infection is generally recommended for younger children with evidence of acute infection.
    D. They are inexpensive.
    E. They are safe and have no reported adverse effects.
3. A previously healthy 6-year-old boy presents with fever and jaundice. He has no history of vomiting or diarrhea. There is no change in appetite. He has successfully completed hepatitis A and B immunizations in the past. Physical examination is significant for scleral icterus and hepatomegaly. There is no splenomegaly, exudative tonsillitis, or cervical adenopathy. There is evidence of right lower quadrant tenderness. Preliminary studies show elevated serum transaminases and bilirubin. His immunizations are up to date. In addition to abdominal ultrasonography, which of the following is the most appropriate next step in making a diagnosis in this patient?
    A. Anti-hepatitic C virus immunoglobulin G antibody titers.
    B. Epstein-Barr virus titers.
    C. Hepatobiliary (HIDA) scan.
    D. No further testing is needed.
    E. Percutaneous liver biopsy.
4. The mother of a healthy 5-month-old girl is found to be hepatitis C virus-positive. She has a past history of intravenous drug abuse. She is known to be human immunodeficiency virus-negative. The mother would like to know if her infant is at risk of hepatitis C infection. Which of the following is the most accurate statement regarding testing for hepatitis C?
    A. All infants who test positive at 2 months of age with an RNA screening will remain infected when tested at 18 months of age.
    B. Antibody to hepatitis C virus assay can be performed now for the confirmation of infection.
    C. A polymerase chain reaction assay is always required for the confirmation of infection.
    D. A polymerase chain reaction can be performed now if a diagnosis is desired before 18 months of age.
    E. Because the infant is healthy and unlikely to be infected, no testing is needed.
5. The parents of a 2-year-old child come to you for advice on the prevention of infections due to hepatitis viruses. In counseling these parents, which of the following statements best describes the vaccine strategy that would be most protective of a young child 2 years of age from infection with hepatitis viruses?

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This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

A. Hepatitis A and B vaccines are indicated for all infants and children.
B. Hepatitis B vaccination is only needed if the mother is a chronic carrier.
C. In patients who received the hepatitis A vaccine as recommended, serum immune globulin is indicated if exposed to hepatitis A.
D. Because vaccines are highly effective, screening of mothers for hepatitis B is no longer needed.
E. Vaccination against hepatitis C is routinely completed in the first postnatal year.

Hepatitis A, B, and C

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