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Acute Viral Hepatitis

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BACKGROUND

Acute viral hepatitis is a term that is generally given to the disease condition attributed to a group of viruses that have the propensity to infect the liver and cause necroinflammation. Although these hepatotropic viruses share a common clinical presentation, they belong to different virus families, have different modes of transmission, and differ in their propensity to lead to chronic infection (Table 1.1). Even as acute viral hepatitis remains an important public health problem in the United States, it is noteworthy that there has been and continues to be a decline in the number of new infections of hepatitis A, B, and C (Table 1.2).[1]

It is important to keep in mind that there are a number of conditions that can have a clinical presentation consistent with an acute hepatitis – elevated serum aminotransferases with variable elevations in bilirubin levels. Aside from the hepatotropic viruses, other viruses such as the herpes viruses can also lead to acute hepatitis. The differential diagnoses for acute hepatitis include alcoholic hepatitis, acute Budd-Chiari syndrome, drug-induced liver injury, shock liver, autoimmune hepatitis, biliary obstruction, and Wilson's disease (Table 1.3). A careful history and physical examination can usually point the clinician to the appropriate diagnostic evaluation to arrive at a correct diagnosis. This chapter will review the hepatotropic viruses – hepatitis A to E.

ACUTE HEPATITIS A

In 1973, Feinstone and colleagues first identified the hepatitis A virus (HAV) in the stool samples of normal volunteers who were infected with HAV and had developed acute hepatitis.[2] HAV is a nonenveloped, icosahedral particle that measures 27 nm in diameter and belongs to the hepatovirus genus within the picornavirus family of viruses.[3] It is a positive-sense RNA virus and its genome measures 7.5 kilobases in length. HAV has a single open reading frame that transcribes a polyprotein, which is then cleaved into the structural and nonstructural proteins. Although there have been four genotypes of HAV identified, there is

Table 1.1. Hepatotropic Viruses that Cause Acute Viral Hepatitis

Virus	*Genome*	*Virus Particle*	*Classification*	*Incubation Period*	*Mode of Transmission*	*Chronic Infection*
HAV	7.5 kb single-stranded RNA	27 nm	Picornavirus	15–50 days	Fecal-Oral	None
HBV	3.2 kb partially double-stranded DNA	40–42 nm	Hepadnavirus	28–70 days	Parenteral	Present
HCV	9.4 kb single-stranded RNA	40–60 nm	Flavivirus	14–84 days	Parenteral	Present
HDV	1.7 kb single-stranded RNA	36–43 nm	Deltavirus	Variable	Parenteral	Present
HEV	7.5 kb single-stranded RNA	32–34 nm	Hepevirus	15–60 days	Fecal-Oral	None

HAV – Hepatitis A Virus; HBV – Hepatitis B Virus; HCV – Hepatitis C Virus; HDV – Hepatitis D Virus; HEV – Hepatitis E Virus; kb – kilobases– nm – nanometers

Table 1.2. Estimated Number of New Infections of HAV, HBV, and HCV in the United States

	2004	*2003*	*2002*	*1990–1999**	*1980–1989**
Hepatitis A	56,000	61,000	73,000	310,000	254,000
Hepatitis B	60,000	73,000	79,000	140,000	259,000
Hepatitis C	26,000	28,000	29,000	67,000	232,000

*mean (per year)
Data from the CDC[1]

Table 1.3. Conditions that Can Cause Acute Hepatitis

Condition	*Characteristics*
Infections (e.g., Epstein-Barr virus, Cytomegalovirus, Herpes Simplex virus, Yellow fever, Leptospirosis)	Appropriate serologic tests in the setting of negative serologies for the hepatotropic viruses
Alcoholic Hepatitis	History of alcohol abuse, serum aminotransferases generally less than 10x ULN, ASTALT ratio usually > 2
Acute Budd-Chiari Syndrome	Abdominal pain, ascites, hypercoagulable state (e.g., inherited thrombophilic disorders such as protein C or S deficiency, malignancy)
Drug induced liver injury	Recent history of intake of hepatotoxic drugs such as acetaminophen, isoniazid, or herbal agents such as kava
"Shock" liver	Recent history of hypoperfusion or "shock" or severe right-sided heart failure
Autoimmune hepatitis	Positive antinuclear antibody, anti-smooth muscle antibody, elevated gamma globulin levels
Biliary obstruction	Dilated bile ducts on ultrasound
Wilson's disease	Hemolytic anemia, Kayser-Fleischer ring, low ceruloplasmin levels, low uric acid, low alkaline phosphatase

ULN – upper limits of normal

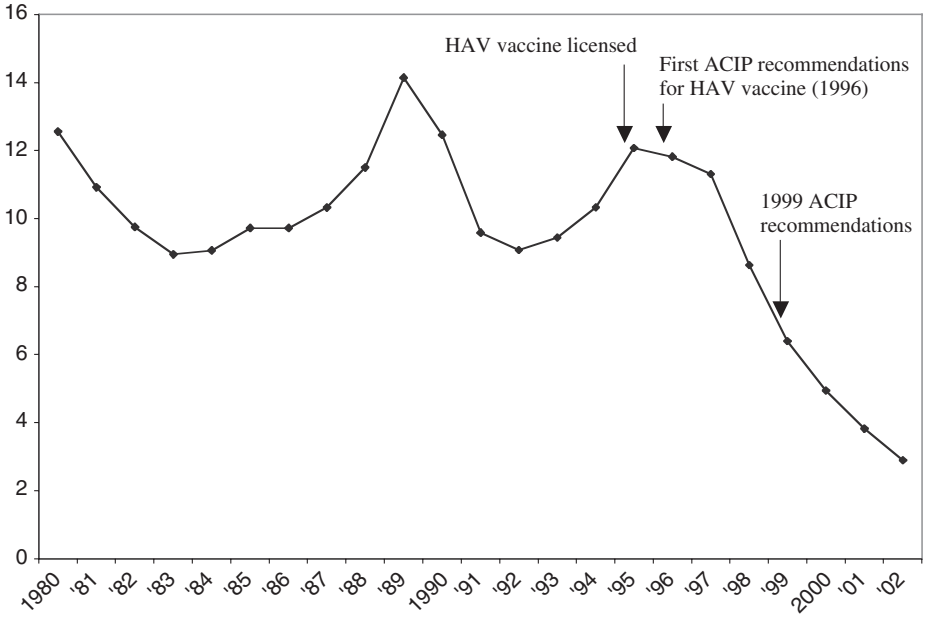

Figure 1.1. HAV Incidence, United States, 1980 to 2002. *Adapted from CDC.[1]

only one serotype and infection with one genotype confers immunity to the other genotypes.[4,5]

Epidemiology

HAV is distributed worldwide and is the most common cause of viral hepatitis. In high-prevalence areas, infection generally occurs in childhood, and immunity to HAV is almost universal in adulthood.[5] These high-prevalence areas include parts of Africa, Asia, South and Central America, and the Middle East.[6] In the United States, the incidence of HAV infection has been declining (Figure 1.1). In 2004, there were 5,683 reported cases of symptomatic HAV infection, the lowest recorded rate in four decades.[7] This corresponds to an estimated 56,000 cases of HAV infection after adjusting for underreporting and asymptomatic infection (Table 1.2). The decline in the incidence has been attributed to the availability and use of HAV vaccination (Figure 1.1).[8]Historically, the incidence of HAV infection was higher among children, men, and certain ethnic groups (e.g., American Indians); however, more recently, the rates have equalized due to the larger declines in incidence rates among children, men, and American Indians.[7]

The principal mode of transmission of HAV is through the fecal-oral route either through person-to-person contact (including sexual activity that involves contact with fecal material) or through the ingestion of contaminated food and water.[5,9] In the past, sexual or household contact with a HAV-infected person was the most frequently reported risk factor.[5,6] However, in 2004, the proportion of cases reporting this risk factor had decreased to 11% from about 20%.[7] The same trend was noted for homosexual activity as a risk factor that decreased from a high of 23% in the early 2000s to a low of 2.5% in 2004.[7] The proportion

Table 1.4. Serologic Diagnosis of Acute Viral Hepatitis

IgM Anti-HAV	*HBsAg*	*IgM Anti-HBc*	*Anti-HCV*	*HCV-RNA*	*Anti-HDV*	*IgM Anti-HEV*	*Diagnosis*
+	−	−	−	−	−	−	Acute HAV
−	+	+	−	−	−	−	Acute HBV
−	−	+	−	−	−	−	Acute HBV ("window period")
−	−	−	+	+	−	−	Acute HCV
−	−	−	−	+	−	−	Acute HCV, early infection
−	+	+	−	−	+	−	Acute HBV/HDV coinfection
−	+	−	−	−	+	−	Acute HDV superinfection on chronic HBV
−	−	−	−	−	−	+	Acute HEV

of cases reporting either international travel or injection drug use as a risk factor was increased in 2004 compared to previous years.[7]

Diagnosis

There are no biochemical test abnormalities that are specific for acute HAV. Significant elevations in serum aminotransferases are not uncommon in acute HAV. The height of the serum aminotransferases have no prognostic significance, however.[10] In those with the cholestatic variant and those with fulminant hepatitis, bilirubin levels are significantly elevated, often higher than 10 mg/dL.[11] Prolongation of the prothrombin time may signify severe hepatic injury and should alert the clinician to watch for signs of fulminant liver failure.

Serologic tests are available to assist in the diagnosis of acute HAV. A positive IgM anti-HAV in a patient with acute hepatitis is consistent with a diagnosis of acute HAV (Table 1.4). The IgM anti-HAV becomes detectable as early as a week after exposure and can remain positive for up to six months. IgG anti-HAV becomes detectable soon after IgM anti-HAV becomes positive. This persists indefinitely and is consistent with lifelong immunity. A positive total anti-HAV with a negative IgM anti-HAV is consistent with immunity to HAV as a result of either prior exposure to HAV or vaccination. Tests for HAV-RNA in serum and stool during HAV infection as well as genotyping of HAV are performed principally for research purposes.

Clinical Presentation

HAV causes acute hepatitis. There is no chronic infection phase in HAV infection. The clinical presentation can range from subclinical infection, where patients present with asymptomatic elevations in serum aminotransferases, to clinically symptomatic hepatitis including fulminant hepatic failure with coagulopathy and hepatic encephalopathy. The severity of clinical presentation depends on the patient's age. Children generally have asymptomatic

or minimally symptomatic hepatitis whereas the majority of adults will present with symptomatic disease.[7,12] Among cases of acute HAV reported to the CDC in 2004, 72% of cases had jaundice with 33% requiring hospitalization. The mortality rate was 0.6%.[7]

In patients with typical symptomatic acute HAV infection, there is an incubation period, a preicteric phase, an icteric phase, and a convalescent phase. The incubation period averages 25 days (range 15–50 days). This is followed by the preicteric phase where patients report fever, malaise, anorexia, diarrhea, nausea and vomiting, and abdominal pain. The icteric phase is characterized by the development of jaundice and the disappearance of the prodromal symptoms. The convalescent phase is marked by the resolution of jaundice and generally occurs within 8–12 weeks of illness onset.[10]

Acute HAV accounted for 4% of 308 cases of acute liver failure in a multicenter NIH-sponsored study in the United States.[13] Among cases with HAV-related acute liver failure, 31% required liver transplantation, and 14% died.[14] A prognostic model incorporating serum ALT, creatinine, intubation, and pressors was found to have better predictive value for either transplantation or death than the King's College Criteria or the Model for Endstage Liver Disease (MELD) score.[14]

Atypical presentations of acute HAV can occur in about 10% of patients. These include an evanescent skin rash, transient arthralgias, and cutaneous vasculitis.[11] Two forms of atypical manifestations of HAV infection are important to mention to avoid diagnostic confusion and unnecessary and potentially invasive procedures. The first is a cholestatic variant of HAV infection, where patients have a prolonged period of jaundice with bilirubin levels reaching 10 mg/dL or higher accompanied by pruritus, fever, diarrhea, and weight loss.[15] In these patients, IgM anti-HAV is positive and serum aminotransferases may have returned to normal levels.[10,15] Complete resolution is the norm in this variant. Corticosteroids have been used in these patients, resulting in relief of pruritus and a more rapid decline in bilirubin levels.[15] Another variant presentation is that of relapsing hepatitis. These patients have often recovered from acute HAV only to redevelop symptoms and liver test abnormalities consistent with acute hepatitis.[16] The disease is often milder during relapse. The IgM anti-HAV is positive during the relapse.[16] Multiple relapses have been observed in some patients. Prognosis is very good, with complete recovery. The role of steroids is unclear in relapsing hepatitis A.

Liver biopsies have very little, if any, additional diagnostic value and are often not done in acute HAV. When they are available, they are usually performed in the process of investigating atypical presentations of acute HAV. In those with cholestatic hepatitis A, marked centrilobular cholestasis with bile thrombi and a periportal inflammatory infiltrate that resembles chronic hepatitis have been observed on their liver biopsy.[15,17]

Pathogenesis

After oral ingestion, the HAV virus is transported across the intestinal epithelium to the liver via the portal circulation.[3] HAV replicates in the cytoplasm of the hepatocyte and newly assembled virus is secreted either into the bloodstream or into bile, subsequently being excreted into the small intestine.

The mechanism of liver injury in acute HAV infection appears to be immune-related as the virus is not directly cytopathic. HLA-restricted, virus-specific, cytotoxic T-cells appear in the liver during acute infection and are likely responsible for both viral clearance and hepatocyte injury.[6,18] These T-cells also release cytokines such as interferon-γ. These cytokines lead to recruitment of other nonspecific, inflammatory cells to the liver, contributing to liver injury. The humoral immune response in acute HAV is robust, and neutralizing antibodies are produced, which also contribute to viral elimination. These antibodies confer lifelong immunity to reinfection.

Management

Patients with acute HAV infection should receive supportive treatment. If the patient shows signs and symptoms indicating fulminant hepatic failure, admission and early referral to a liver transplant center is necessary. There is no specific treatment or antiviral agent for HAV. For patients with prolonged cholestasis, corticosteroids can be considered. This has been shown to lead to improvement in jaundice, pruritus, and fatigue soon after initiating therapy. Forty mg of prednisone daily can be given and tapered over a four-week period.

Effective and safe hepatitis A vaccines have been available since 1995. There are two inactivated hepatitis A vaccines and one combination vaccine with hepatitis A and hepatitis B vaccine components.[19] Both single-antigen vaccines are approved for use in children and adults, whereas the combination vaccine is approved for use in adults only. The vaccines are not approved for children younger than one year of age. The hepatitis A vaccines are highly immunogenic with 94% to 100% of vaccinated persons developing protective antibody levels a month after the first dose. The two single-antigen vaccines are interchangeable, and one can be given as a booster even if it was not the vaccine used for the initial dose. The Advisory Committee on Immunization Practices (ACIP) first came out with its recommendations for prevention of HAV through immunization in 1996.[20] At that time, the target groups were those who were at high risk of acquiring the infection. In 1999, these recommendations were expanded to include children living in states with HAV infection rates that were higher than the national average.[21] In 2006, the ACIP updated its recommendation to include routine vaccination of all children older than one year old and that hepatitis A vaccine be incorporated into the routine childhood immunization schedule.[22] Table 1.5 shows the current recommendations for hepatitis A vaccination. Persons with chronic liver disease do not necessarily have an increased risk for HAV infection; however, it is recommended that they receive routine vaccination because superimposed acute HAV infection has been associated with high morbidity and mortality rates in these patients.[23–25] Prevaccination testing for immunity to HAV might be considered in populations that are expected to have high rates of prior exposure to HAV, such as adults born in or who have lived in countries with intermediate or high endemicity for HAV and adults in certain population groups (e.g., Alaska natives, illicit drug users, persons with chronic liver disease). Prevaccination testing of children is generally not recommended because of the low prevalence of infection in this group.

Once acute HAV is confirmed in a patient, postexposure prophylaxis should be instituted for close contacts who do not have a prior history of hepatitis A

Table 1.5. Recommendations for Hepatitis A Vaccination

Men who have sex with men
Persons traveling to or working in areas that have intermediate or high endemicity of HAV
Users of illicit drugs
Persons who have an occupational risk for HAV infection such as those work with HAV in research settings
Persons with clotting factor disorders
Persons with chronic liver disease
All children at age 1 year (12–23 months). Children not vaccinated at the end of 2 years can be vaccinated at subsequent visits.

From Morbidity and Mortality Weekly Report[22]

vaccination. The CDC recommends HAV immune globulin at a dose 0.02 mL/kg via the intramuscular route.[22] This should be given within two weeks of exposure, as efficacy after two weeks has not been confirmed. Hepatitis A vaccine should be given to those contacts who also have an indication for vaccination.

ACUTE HEPATITIS B

Since the discovery of the Australia antigen in the 1960s, significant advances have been made in the understanding of the molecular virology, pathogenesis of liver disease and natural history, as well as management of hepatitis B virus (HBV) infection. In particular, the last decade has seen the evolution of antiviral therapy for HBV from the use of standard interferon to the development of safe and potent oral antiviral agents.[26]

HBV is an enveloped, DNA virus measuring 40–42 nm in diameter. Its genome is a circular and partially double-stranded DNA that is 3.2 kb long. The genome has four overlapping open reading frames. Unique features of HBV include the use of reverse transcription in its life cycle and the generation of covalently closed circular (ccc) DNA. The cccDNA serves as a template for all viral mRNAs and is responsible for viral persistence in chronic HBV infection.[27,28] There are eight genotypes of HBV – A through H.[29] The genotypes differ from each other by more than 8% of their nucleotide sequence. The genotypes have a varied geographic distribution worldwide. The most common genotypes in the United States are genotypes A and C.[30] There is a strong correlation between genotype and ethnicity, with genotype A being common among white and black patients and genotypes B and C among Asians patients. In chronic HBV, differences in genotypes may affect HBeAg seroconversion rates, severity of liver disease, likelihood of development of liver cancer, as well as treatment response rates.[31] It remains unclear if HBV genotype influences the outcome of acute HBV infection.[29,32,33]

Epidemiology

Hepatitis B is a major public health problem worldwide.[34] Nearly one-third of the world's population, or 2 billion people, have been infected with HBV, with 350 million people having chronic infection.[35] The prevalence of infection varies geographically. The highest prevalence of chronic HBV infection can be found in

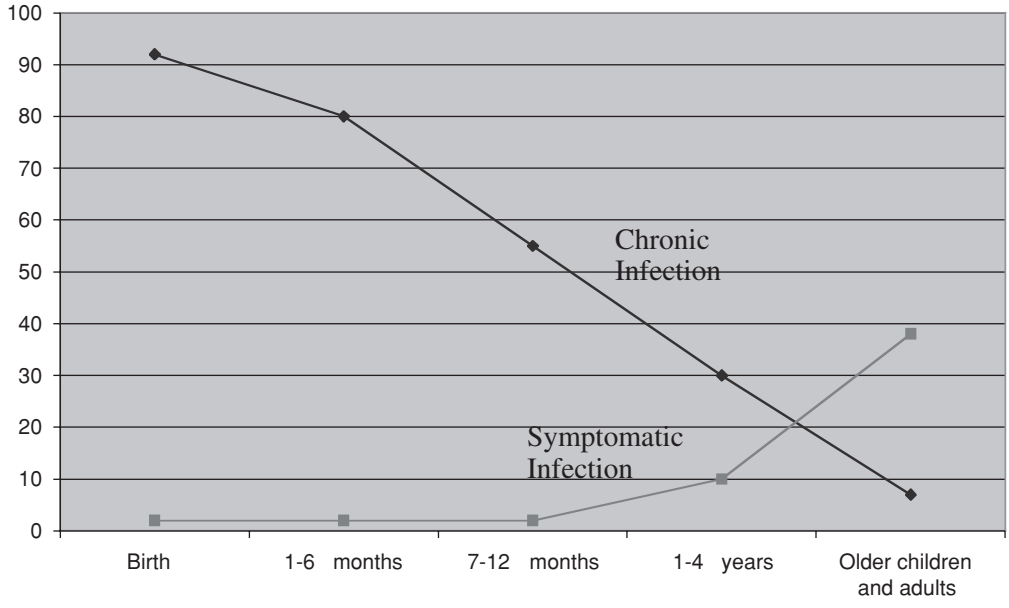

Figure 1.2. Outcome of HBV infection according to the age at infection. *Adapted from CDC.

sub-Saharan Africa, Asia, and the South Pacific region. Areas with intermediate rates of endemicity include North Africa, Southern and Eastern Europe, the Indian subcontinent, and the Amazon basin. Western Europe and the United States are considered low-prevalence regions. In the United States, the prevalence of HBV infection is 0.42%, with an estimated 1.25 million persons who are chronically infected.[1,36] The incidence of HBV infection has been declining in the United States. This has decreased from a peak of 287,000 infections per year in the 1980s to 51,000 in 2005.[1] Acute HBV infection rates are highest among persons 25–44 years old.[7] The rate of acute HBV is higher among men than women and non-Hispanic blacks have the highest rates among all racial and ethnic groups.

HBV is transmitted through contact with infected body fluids. Unlike the situation in endemic countries, where the primary mode of transmission of HBV is perinatal and close household contact, the primary modes of transmission in the United States are sexual transmission and via injecting drug abuse practices.[7,37] An important risk group in the United States is men who have sex with men.[35,37] Up to one-third of infected persons report no risk factors for HBV infection, although half of these persons have high-risk characteristics or behaviors that place them at risk for HBV infection.[37] The age at infection and the mode of transmission of HBV correlate with the likelihood of developing chronic infection. Infection in infancy and childhood, which is usually through perinatal or horizontal transmission, carries a high likelihood of developing chronic infection (60–95%) whereas infection during adulthood, which is usually through sexual transmission or injection drug use, is associated with a significantly lower risk of developing chronic infection (~5%) (Figure 1.2).[38]

The disease burden of HBV infection is significant and is mainly due to the consequences of chronic HBV infection such as liver failure and hepatocellular

carcinoma. The most catastrophic consequence of acute HBV infection is fulminant hepatitis. In the United States, HBV accounts for about 7% of all cases of acute liver failure.[13] Among patients with HBV-related acute liver failure, 41% went on to receive a liver transplant and 32% died.[33] Older age was the only factor associated with a poor outcome. An interesting finding in a large series of HBV-related acute liver failure was the association between genotype D infection and HBV-related acute liver failure. This requires confirmation in other studies.

Diagnosis

The available serologic tests for acute HBV infection include hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), antibody to HBcAg (anti-HBc), and hepatitis B e antigen (HBeAg). The diagnosis of acute HBV infection is based on the results of serologic testing performed in the appropriate clinical scenario. In acute HBV infection, both HBsAg and IgM anti-HBc are positive (Table 1.4). In some patients, HBsAg disappears before the development of anti-HBs as the acute illness resolves. During this so-called window period, the IgM anti-HBc remains positive (Table 1.4). A person with acute HBV can take one of two clinical courses – recovery with viral clearance or persistent infection. With viral clearance, anti-HBs appears as HBsAg disappears. Those who develop persistent infection generally do not develop anti-HBs and have persistently detectable HBsAg. HBeAg in acute HBV infection correlates with ongoing viral replication. HBV-DNA testing is now available and is useful in chronic HBV infection, especially in the monitoring of patients on antiviral therapy. In acute HBV, HBV-DNA testing may be useful in cases with a protracted course of severe acute hepatitis in whom antiviral therapy is being contemplated.

Clinical Presentation

The presentation of acute HBV infection can range from asymptomatic elevations in serum aminotransferases to icteric hepatitis to fulminant hepatitis. Symptomatic infection is less likely among infants and children than in adults (Figure 1.2). The incubation period for acute HBV infection is about 4–10 weeks. HBsAg, the hallmark of HBV infection, becomes positive in the incubation period. HBV-DNA is detectable at this time as well. This is followed by the development of anti-HBc, generally coinciding with the onset of symptoms or biochemical abnormalities with the IgM fraction appearing before IgG anti-HBc. With clinical recovery, HBsAg disappears and anti-HBs becomes positive, conferring immunity. In addition, the IgM anti-HBc becomes undetectable within six months, whereas the IgG anti-HBc persists for life. Among acute HBV cases reported to the CDC in 2004, 76% had jaundice and 39% were hospitalized.[7] Clinical presentation was milder among children than in adults, with fewer children presenting with jaundice and a lower proportion of children requiring hospitalization. The mortality rate for acute HBV was 0.5%.

Pathogenesis

The hepatitis B virus is not directly cytotoxic. The liver injury in HBV infection is believed to be primarily the result of the immune response of the host to the virus.[39] Virus-specific cytotoxic T lymphocytes recognize virally infected

hepatocytes and cause hepatocyte death through direct cell lysis. Other antigen-nonspecific inflammatory responses involving macrophages, NK cells, and neutrophils also contribute to the liver damage seen in acute infection.

In acute, self-limited hepatitis, studies have shown strong, polyclonal, and multispecific CD4+ and CD8+ T-cell responses to multiple epitopes of the HBV core, polymerase, and envelope proteins. On the other hand, the T-cell responses in persons with persistent infection are significantly diminished. These findings highlight the importance of cytotoxic T lymphocytes in viral clearance. Noncytolytic clearance of virus via the antiviral effects of inflammatory cytokines such as tumor necrosis factor and interferon-γ may also be important.

Management

Persons with symptomatic acute HBV infection should be provided supportive care. Prompt referral to a liver transplant center is necessary for those who develop fulminant hepatitis. Liver transplantation can be life-saving in these patients. Prevention of HBV infection is very important to decrease the burden of chronic liver disease, especially in regions of the world where the disease is endemic. Preventive measures include all the traditional activities for a parenterally transmitted agent such as screening of blood and blood products and risk reduction counseling. By far, however, immunization is the single most effective preventive measure for HBV infection. The use of hepatitis B vaccine has resulted in dramatic reductions in HBV infection rates and hepatocellular carcinoma among children in Taiwan, an achievement considered a "milestone in the annals of preventive medicine."[40,41] There are currently two licensed single-antigen hepatitis B vaccines and three licensed combination vaccines. Hepatitis B vaccine efficacy is as high as 95%. Several factors may affect vaccine response rates, including older age, obesity, male gender, smoking, and immunodeficiency.[19] At the present time, the immunization strategy to eliminate transmission of HBV in the United States includes (1) universal vaccination of infants beginning at birth, (2) prevention of perinatal HBV infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to HBsAg-positive women and to women whose HBsAg status is unknown, (3) routine vaccination of previously unvaccinated children and adolescents, and (4) vaccination of previously unvaccinated adults at increased risk for infection.[42] The ACIP recently updated its recommendations for hepatitis B vaccination of adults (Table 1.6).[43]

Immunoprophylaxis for children born to HBsAg-positive mothers should include hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth.[42] Those born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. Testing for HBV should be done on the mother and HBIG should be given within seven days if the mother is found to be HBsAg-positive.[42]

Antiviral therapy for acute HBV has been undertaken in several studies either as a strategy to prevent fulminant hepatitis or death or to prevent the evolution to chronic HBV.[44] Most of the studies have been small, have lacked controls, and have heterogeneous patient populations.[44–46] A recent publication showed that of 17 patients with severe acute or fulminant hepatitis given lamivudine, 14, or 82%, recovered and did not need liver transplantation.[47] This compared