CHAPTER 22

Viral Hepatitis in Travelers and Immigrants

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The various forms of viral hepatitis are a ubiquitous concern for travelers, immigrants, and the healthcare providers responsible for their care (**Table 22.1**). This chapter will cover the five hepatitis viruses that are associated with the majority of human disease: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV; formerly known as the delta agent), and hepatitis E virus (HEV), formerly known as enterically transmitted non-A, non-B hepatitis (**Table 22.1**). There is evidence to suggest that other types of viral hepatitis also exist, but they have not yet been fully characterized.

Hepatitis A virus is usually transmitted by the fecal-oral route and acquired by ingestion of contaminated food and water. Hepatitis B virus is transmitted through parenteral or mucosal exposure to blood and components, during sexual activities, or from infected mother to unborn child during the birth process. Susceptible travelers originating in areas of low endemicity for HAV and HBV infections going to areas of high endemicity can be immunized against these two vaccine-preventable diseases (**Fig. 22.1**) (Chapter 5). Hepatitis C virus transmission is predominantly through parenteral exposures to blood and components. Sexual transmission is much less common than HBV; however, travelers should be counseled about risk avoidance, as there is as yet no vaccine commercially available. Hepatitis D virus is also transmitted by routes similarly to HBV, but since infection with HBV is the prerequisite for HDV infection, HDV infection is largely prevented by prevention of HBV infection; there is no specific HDV vaccine available. Hepatitis E virus is spread by the fecal-oral route similarly to HAV, and lacking a vaccine against HEV virus (at the time of this publication), travelers need advice about prevention of this infection through selection of safe food and water.

The outcome of an acute viral hepatitis infection depends on the age, co-infections, presence of chronic liver disease, and immune status of the host. With the increasing diversity of international travelers who may have one or more risk factors that will prejudice the outcome of acute hepatitis toward serious sequelae, prevention of travel-acquired hepatitis is of prime importance. Last, in addition to considering the risks of viral hepatitis among departing international travelers, healthcare providers need to be aware of the epidemiology of the various forms of viral hepatitis, the existence of carrier states, and the differential diagnosis of hepatitis in providing care to returning travelers and to newly arrived immigrant populations.

There are many serologic studies available at this time that allow for precise diagnosis and staging of viral hepatitis, together with diagnostic tests of liver function. However, correlation of the test results with the patient's clinical status requires accurate interpretation of test results. Determining the optimal management and treatment for a given patient will often be guided by the consultation of a hepatologist. Complicating the diagnosis of acute liver inflammation, a number of other infections that may be acquired while traveling can

TABLE 22.1 Overview of Hepatitis Viruses

Virus Type	Genetic Material	Incubation Period	Transmission Routes	Risk of Chronicity	Vaccine-Preventable
A	RNA	15-45 days; mean 26 days	Fecal-oral	Absent	Yes
B	DNA	30-180 days; mean 90 days	Sexual, parenteral, blood and components, surgical/odontologic procedure, mother–fetus	High (90% in newborns; 5-10% in adults)	Yes
C	RNA	15-150 days; mean 60 days	Parenteral, blood and components, sexual	High (85%)	No
D	RNA	30-50 days	Sexual, parenteral, blood and components, surgical/odontologic procedure, skin and mucosal wound, mother–fetus	High (79% after superinfection; <5% after co-infection)	No
E	RNA	28-48 days	Fecal-oral	Absent	No

mimic the common symptoms of viral hepatitis, as can adverse effects of a number of drugs and other potential hepatotoxins (**Table 22.2**).

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis A Virus (HAV)

HAV is a 27-nm RNA virus. The transmission of hepatitis A is almost exclusively via the fecal-oral route, although parenteral transmission may occasionally occur, particularly in the setting of intravenous drug use. The virus is found throughout the world, but from the standpoint of the traveler, inadequate sewage facilities and environmental contamination with human excrement in rural tropical areas are most often responsible for hepatitis A transmission (**Fig. 22.1**). Drinking contaminated water and eating fresh fruits and vegetables grown and processed with contaminated water are major routes of infection. Consumption of shellfish grown in contaminated waters is another common etiology of hepatitis A outbreaks, such as the outbreak associated with contaminated clams that caused approximately 300,000 cases of hepatitis A infection in Shanghai in 1988.

Person-to-person transmission can occur through eating food touched by unhygienic food handlers (who failed to wash their hands after defecation) or through close personal contact involving unsanitary conditions, such as found in daycare facilities and institutional domiciles such as prisons and homes for the developmentally disabled. Epidemiologic data have shown that other high-risk populations for HAV infection are men who have sex with men, illegal drug users, and persons with clotting factor disorders. Occupational risk for HAV occurs among those who work with HAV-infected primates or with HAV in research laboratories.

As an indication of the difference in risk in developed versus developing countries, serologic evidence of prior hepatitis A infection was present in 2.3% of young Scandinavian soldiers, in 20-30% of middle-aged middle-class New Yorkers, but in almost 100% of Southeast Asian populations. Epidemiologic evidence shows that the risk of HAV infection

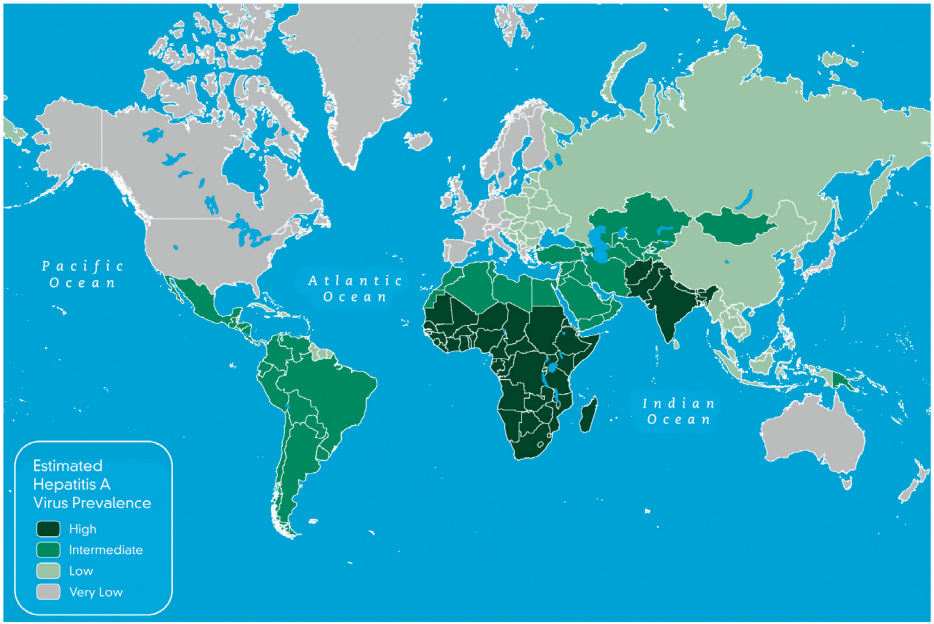


Fig. 22.1 **Geographic distribution of hepatitis A prevalence.** (From: CDC Health Information for International Travel 2008.)

TABLE 22.2 Historical Clues in Diagnosis of Hepatitis

- Recent travel history
- Ethnic background and birthplace (especially Asian, Oceanic, or North African or close exposure to these individuals)
- Sexual orientation and patterns of contact
- Known exposure to an infectious agent causing hepatitis (including healthcare workers with high-risk exposure)
- Past immunizations against hepatitis
- Past or current medical conditions
  - Previous hepatitis, including type (if known); other liver disease
  - History of, or symptoms suggestive of, biliary tract disease
  - Transfusions or administration of blood products
  - Hemodialysis
  - History of organ transplantation
  - History of recent surgery (benign postoperative jaundice?)
  - History of frequent previous jaundice (Gilbert syndrome?)
  - Current pregnancy (third trimester: consider cholestatic jaundice of pregnancy or acute fatty liver of pregnancy)
- Drug history
  - Illicit drug usage (especially parenteral)
  - Prescription medications (include oral contraceptives)
  - Over-the-counter medications (include vitamins)
- Hepatotoxic exposures
  - Alcohol usage
  - Human immunodeficiency virus infection treated with highly active antiretroviral therapy drugs
  - Occupational exposure
  - Mushroom ingestion

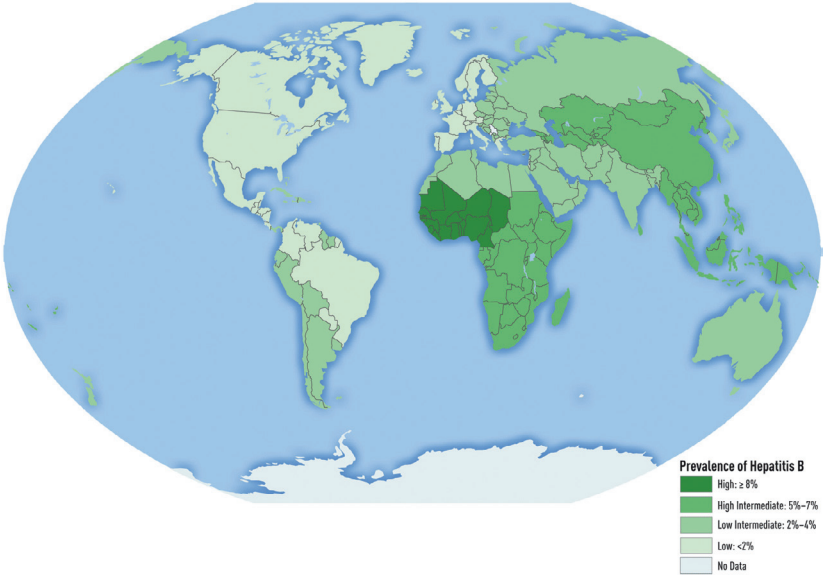
changes as formerly low-resource countries undergo modernization: only 50% of young urban Thais are seropositive, and the massive 1988 hepatitis A outbreak in China indicated that there was a large pool of susceptible young adults who had not previously been infected.

Hepatitis B Virus (HBV)

The agent of HBV is a 42-nm DNA virus. The intact virion, also known as the Dane particle, consists of identifiable sub-viral fragments, including the hepatitis B surface antigen (HBsAg), a core antigen (HBcAg), a DNA polymerase molecule, and the "e" antigen (HBeAg). Circulating HBsAg is the prime marker of active infection. HBeAg is an indicator of high infectivity, except in the setting of the precore mutation, which leads to lack of HBeAg but very high viral levels.

Identifiable groups at risk of contracting HBV include persons receiving contaminated blood products (a low risk in countries where banked blood is screened for HBsAg and other blood-borne pathogens), organ transplant recipients, healthcare workers having frequent contact with blood products, hemodialysis patients, homosexual males with multiple sexual partners, and sexual and household contacts of HBsAg-positive carriers.

The risk of transmission of HBV during travel reflects the prevalence of the disease worldwide (**Fig. 22.2**). In the United States, there is evidence of past HBV infection in 10% of the population, but the HBsAg-positive carrier rate is <2% (1.25 million people). The same figures hold for northern European countries, but areas of North Africa, sub-Saharan Africa, Oceania, and much of East Asia have much higher rates of infection: evidence for previous infection may be present in up to 70-80% of the population, and the underlying carrier rates run from 5 to 15%. An estimated 350 million persons are chronic



MAP 3-4. PREVALENCE OF CHRONIC HEPATITIS B VIRUS INFECTION AMONG ADULTS[1]

[1] Disease data source: Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012; 30(12): 2212-2219.

Fig. 22.2 Geographic distribution of hepatitis B prevalence. (From: CDC Health Information for International Travel 2008.)

carriers of HBV worldwide. One reason for the high rate of infection and carrier state in highly endemic areas is the phenomenon of peripartum maternal-fetal (vertical) transmission. As many as 30-50% of the women who are HBsAg carriers or who are acutely infected in the third trimester will transmit the infection to their offspring unless specific prophylactic measures are administered to the infant immediately following birth (see below).

Of most concern to the traveler is the risk of exposure through sexual or close personal contact with carriers in the native populations abroad and inadvertent exposure to the virus through contaminated instruments used for personal grooming, for example, haircuts, shaves, manicures, pedicures, tattooing, and waxing. Other travelers at risk include those who seek medical or dental care in countries where hepatitis B is endemic or those who receive unexpected emergency care in sub-optimal situations. The current trend in "medical tourism," that is, travel to foreign countries to obtain surgical procedures at a significantly lower cost than at home, makes the issue of effective practices by blood banks worldwide to screen for blood-borne pathogens (hepatitis B, hepatitis C, human immunodeficiency virus [HIV], West Nile virus, and Chagas disease) a topic of increasing importance.

HBV Infection in Pregnancy

As a general policy, immigrants to the United States from areas where hepatitis B is endemic should be screened for HBsAg, but the screening process becomes extremely important in pregnant women. The influx of refugees from Southeast Asia and other areas where hepatitis B is endemic has made this even more critical (Chapter 19).

The cause for concern is the risk of maternal-fetal transmission. Up to 90% of infants born to HBeAg-positive mothers will themselves become chronic carriers, with the risk of long-term complications and death and also the risk of passing the infection on to their offspring. High-dose (0.5 mL) hepatitis B immune globulin (HBIG) given within 12 hours of birth has been shown to decrease the immediate infection rate by 80%. When the passive immunity granted by HBIG disappears, significant risk of infection via maternal-fetal contact returns, so it is recommended that infants at risk also receive the first of their three hepatitis B vaccinations at birth. This combination of HBIG and HBV vaccine has been shown, in general, to be 90% effective in preventing infection in children born to mothers who are HBV carriers. However, depending on the study, in women with high viral levels the percentage of infants developing HBsAg ranges from 7 to 32%. Antiviral therapy should be considered during the third trimester in women with high-level viremia.

Hepatitis C Virus (HCV)

The HCV was identified in 1989 and proved to be the viral agent causing 96% of cases of what was previously referred to as non-A, non-B hepatitis (NANBH). HCV became the most common cause of transfusion-associated hepatitis in the United States after screening for HBsAg decreased the percentage of post-transfusion hepatitis due to HBV to 10%. Older studies suggested that as many as 3-7% of units of what would now be regarded as high-risk blood products were capable of transmission of NANBH, and rates of infection from 5 to 15% in patients receiving 1-5 units of blood were documented. The risk of post-transfusion hepatitis due to HCV initially decreased when blood was screened for surrogate markers for NANBH (using the liver enzyme alanine aminotransferase [ALT] and the core antibody to hepatitis B); it has now undergone about a 10-fold decrease with routine screening of donor blood for antibody to hepatitis C. Transmission via blood products in the United States is now rare.

Transmission of HCV also occurs with parenteral drug abuse and less often by the mechanisms by which HBV is spread. Although data from studies have been contradictory, there may be a mildly increased incidence of infection in homosexual males and in those with multiple heterosexual partners who are infected; inoculation of body fluids containing virus through mucosal lesions is presumed to be the mechanism of spread. However, this mechanism of viral spread is extremely inefficient. Sexual transmission of HCV between stable monogamous couples is uncommon. The likelihood of transmission to healthcare

workers following needle-stick or other parenteral exposure to blood or body fluids is correlated to the viral load of the source patient. Rates of transmission from 1 to 10% have been reported for HCV, in contrast to 5-30% for HBV.

Worldwide, an estimated 180 million people are infected with HCV. In the United States, it is estimated that 1.6% of the population (4.1 million persons) have antibody to hepatitis C virus, and at least 80% are chronically infected. At the time of this publication, HCV is the leading cause of death from liver disease and leading indication for liver transplantation in the United States. Unfortunately, a large proportion of infections with HCV abroad have no clear reason for transmission established; however, medical care, drug use, tattooing, body piercing, and traditional medicine (i.e., ritual scarification, acupuncture) have all been cited as causes. The traveler must be counseled to avoid risk factors for transmission similar to those with HBV. It has been established that some countries have a particularly high prevalence of anti-HCV antibody. Included in this group are certain sub-Saharan African nations, Egypt and parts of the Arabian Peninsula, Thailand, and Japan (**Fig. 22.3**).

Hepatitis D Virus (HDV)

Hepatitis D (formerly the "delta agent") is a defective RNA virus that is dependent on host enzymes and viral enzymes of HBV for its own replication. The HDV RNA is replicated by the host polymerases and requires HBV for its HBsAg coat, which is necessary for HDV assembly. Active hepatitis D is found only in patients who are positive for HBsAg, and anti-hepatitis D antibody has been found only in the sera of active HBsAg carriers or those with serologic evidence of past infection. The overall prevalence of anti-HD in HBsAg carriers is about 8-15% in Western Europe. Hepatitis D is most prevalent in southern Italy and North Africa, but increased rates are also seen in the Middle East and sub-Saharan Africa. Epidemics have also occurred in the Amazon basin, Russia, Greenland, and Mongolia. Risk factors for the transmission of the virus appear to be much the same as for HBV. In the United States, hepatitis D has been found almost exclusively in drug abusers with concomitant hepatitis B infection or in HBV carriers with a history of many transfusions. However, as immigration from endemic countries increases, this population must not be forgotten. The mortality rate in acute HBV infection appears to be greater when hepatitis D co-infection is present, but not as high as when hepatitis D superinfection of a chronic hepatitis B carrier occurs.

Hepatitis E Virus (HEV)

What had previously been called enterically transmitted non-A, non-B hepatitis is now known as hepatitis E. HEV has been demonstrated in stool using immune electron microscopy, and while the virus resembles HAV in terms of both transmission and epidemiology, it is serologically unrelated. Five genotypes have been identified, four of which infect humans, and genotype distribution varies geographically.

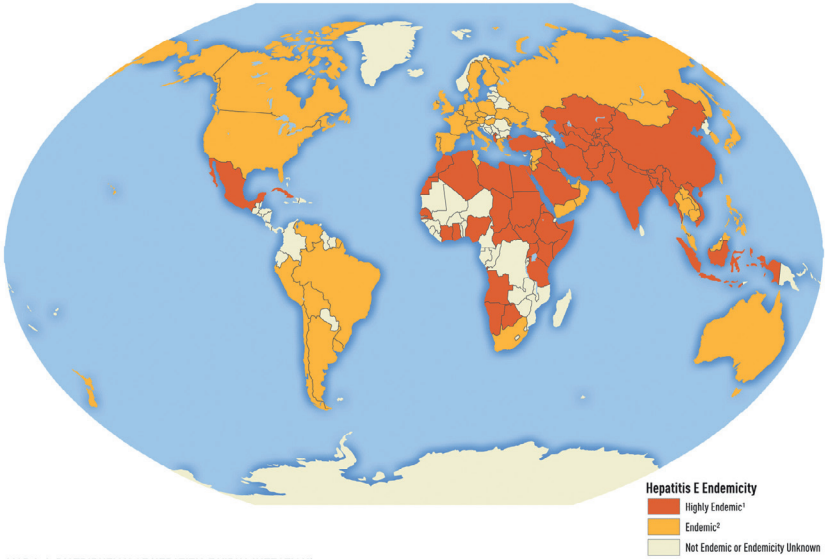
HEV is endemic in Southeast and Central Asia (**Fig. 22.4**). It has been the source of several large epidemics in India, Nepal, and Burma, usually in association with flooding or other problems with the water supply. Well-studied outbreaks have occurred in northern and western Africa, the Middle East, and Mexico. With the advent of serologic testing, evidence for frequent sporadic transmission of endemic infection has been documented in a number of countries, including Egypt, Hong Kong, and nations in sub-Saharan Africa.

Classic epidemic HEV infection is secondary to genotypes 1 or 2 HEV, which have no known animal reservoir. Patients who develop acute hepatitis after recent travel to endemic areas are generally infected with these genotypes. Studies have shown that HEV genotypes 3 and 4 are likely to be a zoonosis for which pigs are the most common reservoir. Genotype 4 has also been reported in other reservoirs such as wild boars, chickens, rodents, mongooses, shellfish, and, to a lesser extent, dogs. Based on limited serum surveys of HEV antibodies among high-risk populations in endemic regions, most zoonotic HEV infections appear to be asymptomatic among occupational risk groups where reported seroprevalence was elevated, ranging from 6% among Brazilian pig farmers up to 33% among Italian abattoir

MAP 3-5. DISTRIBUTION OF HEPATITIS C VIRUS INFECTION[1]

[1] Disease data source: Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. "Global Epidemiology of Hepatitis C Virus Infection; New Estimates of Age-Specific Antibody to HCV and Seroprevalence." Hepatology 2013; 57:1333-1342.

Fig. 22.3 Geographic distribution of hepatitis C prevalence. (From: CDC Health Information for International Travel 2008.)



MAP 3-6. DISTRIBUTION OF HEPATITIS E VIRUS INFECTION[1]

[1] Disease data adapted from: World Health Organization. "The Global Prevalence of Hepatitis E Virus Infection and Susceptibility: A Systematic Review" at http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.14_eng.pdf. Accessed November 13, 1024.
[2] Defined as waterborne outbreaks or confirmed Hepatitis E virus infection >25% of sporadic non-A, non-B hepatitis
[3] Defined as confirmed Hepatitis E virus infection in <25% of sporadic non-A, non-B hepatitis

Fig. 22.4 Geographic distribution of hepatitis E prevalence. (From: CDC Health Information for International Travel 2008.)

workers. Symptomatic cases seem to occur in young adults or older children. The very few cases of HEV in the United States have generally been imported by recent travelers from abroad, primarily Mexico and India; secondary transmission has not been documented. However, there have been reports of HEV infection secondary to undercooked deer, pig liver, and shellfish.

In general, hepatitis E is clinically similar to hepatitis A; however, the mortality in some outbreaks has been higher than that seen with hepatitis A, perhaps due to malnutrition and concomitant disease among the victims. A *mortality rate of 10-20% among women late in pregnancy* has been a consistent finding in HEV epidemics, particularly with genotypes 1 and 2. There is no commercially available vaccine against hepatitis E, although one is in development and appears promising. Administration of immune globulin derived from pooled serum banks in non-endemic regions for hepatitis E appears to offer no protection against infection.

CLINICAL SYNDROMES

Uncomplicated infections with the different viral agents have both similarities and differences but can be divided into the prodromal, icteric, and convalescent phases. Some hepatitis infections can result in either acute liver failure or chronic hepatitis, both of which can lead to complications, including death.

Prodrome

The incubation period for hepatitis A is 2-6 weeks, with a mean of 3.7, and the onset of the disease is typically rather rapid. The incubation time for hepatitis E is similar to HAV at 2-8 weeks, with a mean of 40 days. The incubation times for hepatitis B (2-6 months; mean 11.8 weeks) and hepatitis C (6-12 weeks; mean 7.8 weeks) are longer, and the onset is generally more indolent. The incubation periods for hepatitis D are less well defined, but for HDV, it appears to range from 3 to 6 weeks.

Beyond the differing incubation periods, and the rapidity of onset of symptoms, the prodrome in the different types of infections may be remarkably similar. Fatigue, flu-like myalgia, and malaise are often the initial symptoms, followed by gastrointestinal symptoms including anorexia, nausea, and occasional diarrhea. A low-grade fever may also be present. Right upper quadrant tenderness is almost universally found, and hepatomegaly is detectable in many cases.

Arthralgia and an urticarial rash are seen about 10% of the time as part of the prodrome of hepatitis B. They are thought to be due to the formation of hepatitis B antigen–antibody immune complexes. This is seen rarely in HAV infection, although may occur occasionally in hepatitis C.

Patients with hepatitis A are infectious for approximately 2 weeks before the onset of clinical disease, during which time they are shedding viral particles in their stool. Shedding declines with the onset of jaundice, and the patient is non-infectious 1-2 weeks after clinical disease develops. There is no carrier state. By contrast, patients with HBV infection may have low levels of HBsAg detectable within 1-2 weeks after infection and theoretically may be infectious; a smaller infectious inoculum will delay the appearance of HBsAg in serum. The timing for infectivity with HCV is not known.

Icteric Phase

Most cases of all three major types of hepatitis remain subclinical. In the case of hepatitis A, this is because worldwide most infections occur in children, who seldom become very ill; adults are much more likely to become jaundiced. An estimated 10-20% of HBV and 30% of HCV infections result in jaundice. Patients may first notice darkening of the urine, then the appearance of scleral or palatine icterus, and, finally, frank jaundice. Pruritus may become prominent. At this stage, symptoms of hepatitis A begin to improve, and infectivity clears as HAV disappears from the stool. However, symptoms of hepatitis B and hepatitis C may persist after the onset of jaundice, and infectivity remains.

Convalescent Phase

Gradual return to well-being is the rule in all types of hepatitis that do not become fulminant or progress to a chronic carrier state. Some 90% of cases of hepatitis A are characterized by return of liver function tests to normal within 12 weeks; the balance takes somewhat longer, but no carrier state develops. In contrast, the resolution of infection in hepatitis B typically takes 6-20 weeks, and the marker of cure is disappearance of HBsAg and appearance of antibody to it (anti-HBs); 5-10% of adult patients become chronic carriers of HBsAg. Hepatitis C symptoms may resolve quickly or may follow a smoldering course; the latter is highly associated with development of a chronic carrier state.

Acute Liver Failure

The development of acute liver failure (previously called fulminant liver failure) is the most feared complication of acute hepatitis infection. It is an overwhelming infection that results in massive hepatic necrosis, extreme initial elevation of bilirubin, and persistently abnormal bilirubin despite a return of hepatic enzymes to normal. Hepatic encephalopathy and elevated international normalized ratio (INR) develop due to the extreme liver dysfunction.

Acute liver failure (ALF) develops in only a small number of cases of acute hepatitis but is more common in hepatitis B (1-3%) than in hepatitis A (0.5-1.0%). Acute HAV superinfection in persons with chronic HCV may cause a higher rate of ALF. Regardless of viral etiology, the prognosis in cases of infectious ALF is grim: without liver transplantation, the mortality rate can be as high as 60-90%. The mortality rate for hepatitis B ALF is much higher if hepatitis D co-infection is present, and the rate in hepatitis D superinfection of chronic hepatitis B is particularly high.

Chronic Hepatitis

Chronic hepatitis does not occur after hepatitis A but can be seen following HBV, HCV, HDV, or HEV infection. Some 5-10% of people in the United States infected with HBV develop chronic hepatitis. The rate is higher (15-20%) in geographic areas with high endemic rates of disease; the development of chronic hepatitis is more likely following maternal-fetal transmission (90%). The most dreaded complication of chronic HBV is the development of hepatocellular carcinoma, which is 300 times more likely to develop in those with chronic disease compared with the general population. Additionally, those with chronic HBV can progress to cirrhosis, liver failure, and death. Chronic hepatitis develops in approximately 85% of those infected with HCV. Chronic HCV infection can lead to cirrhosis in 30-40% of infected individuals, which is then associated with the development of hepatocellular carcinoma in up to 4% per year. There is some evidence that chronic HCV co-infection may increase the likelihood of hepatocellular carcinoma in HBV carriers. Chronic HEV infection can develop in immunocompromised individuals, such as organ transplant recipients or those infected with HIV, and is associated with rapid development of cirrhosis (within 2-3 years).

Viral Hepatitis Co-Infections

Acute HAV infections in persons with chronic HBV and HCV infections are associated with more severe disease and a higher risk of death. Acute HAV infection in persons infected with HIV may result in a prolonged HAV viremic stage (median duration 53 days vs. 22 days, $p < 0.05$) and potentially more severe disease as well as increased transmissibility.

HBV and HCV co-infection may result in more serious medical complications than HCV alone, in that there is an increased chance of progression to cirrhosis and an increased risk of development of hepatocellular carcinoma.

Among HIV-infected persons, chronic HBV infection occurs in 10-15%, and up to 30% may be co-infected with HCV. An increased risk of death has been reported in HIV/HBV co-infected men. Reports from several countries have shown significantly increased rates of death from end-stage liver disease among HIV-infected persons in the era of highly active antiretroviral therapy (HAART) compared with the pre-HAART era. One hypothesis is

that chronic HBV and/or HBC infections can potentiate the inherent hepatotoxicity of the antiretroviral therapy drugs.

DIFFERENTIAL DIAGNOSIS

Before the diagnosis of a specific viral hepatitis can be made, other potential sources of hepatocellular injury must be considered. Particular attention should be paid to diseases endemic to areas from which travelers or immigrants have come, but other less exotic causes of jaundice must be considered (**Table 22.2**).

Viral Diseases

Yellow Fever

Yellow fever should be considered in any jaundiced patient who has been traveling in the endemic areas of South America or West and Central Africa. However, the incubation period of the severe, icteric form of yellow fever is 3-6 days, and the diagnosis can be effectively excluded if the patient departed from an endemic area more than a week previously. Also, the onset is quite abrupt, with marked systemic symptoms, rather than the often more insidious onset typical of viral hepatitis.

Epstein-Barr Virus (EBV)

The syndrome of mononucleosis can include hepatic enzyme abnormalities. Although they are typically low grade, serum enzyme levels as high as several thousand international units (IU) can be seen. Jaundice can also be seen with more severe inflammation.

Cytomegalovirus (CMV)

A syndrome similar to that of mononucleosis can also be seen in this infection. CMV infection generally develops in immunocompromised individuals and is rarely seen in the immunocompetent.

Herpes Simplex

Disseminated infection can result in hepatic necrosis, but this complication is generally seen only in immunocompromised patients.

Coxsackievirus

Severe infections can result in hepatitis.

Nonviral Infections

Typhoid

Diffuse hepatic involvement in typhoid may result in frank jaundice. Acute cholecystitis, with resultant biliary stasis, may also develop in the first stage of typhoid. The same risk factors that predispose a traveler to hepatitis A predispose to typhoid.

Malaria

Hepatomegaly and jaundice occasionally occur, most commonly in severe falciparum malaria.

Liver Abscess

Both bacterial and amebic liver abscess may cause focal hepatomegaly and tenderness. Amebic liver abscess is particularly a risk in travelers to underdeveloped tropical countries.

Q Fever

Hepatomegaly and jaundice may be prominent symptoms. Exposure to cows, goats, or sheep when the animals are giving birth is a major risk factor for the disease, but exposure to the animal hides of these species can also result in transmission.

Secondary Syphilis

Alkaline phosphatase levels will be markedly elevated if liver inflammation is associated with secondary syphilis.

Leptospirosis
Liver dysfunction may occur in the "immune" secondary phase of the disease.

Toxoplasmosis
The infection usually results in only mild liver function abnormalities in immunocompetent individuals.

Helminthic Infestations

Ascariasis
Hepatosplenomegaly may be seen when a patient is first infected, and biliary tract obstruction is a late complication that may occur in immigrants or returning long-time travelers.

Schistosomiasis
Marked systemic illness accompanied by hepatomegaly can be seen in acute illness due to *Schistosoma mansoni* or *Schistosoma japonicum*.

Flukes
A number of other flukes may cause infections that ultimately result in biliary tract obstruction. These include *Clonorchis sinensis*, the *Opisthorchis* species, and *Fasciola hepatica* (which may cause a picture of acute liver disease during the invasive phase).

Toxic Hepatitis
Many toxins, including prescription medications, over-the-counter medications, fat-soluble vitamins and niacin, alcohol, industrial agents, and the toxin of the mushroom *Amanita phalloides*, can cause hepatitis. A detailed drug history should be taken in any jaundiced patient.

Biliary Tract Disease
Cholecystitis or obstructive biliary tract disease should be in the differential if the diagnosis of hepatitis is considered. This can generally be excluded by imaging studies.

Gilbert Syndrome
This benign defect in hepatic glucuronyl transferase activity can cause increased bilirubin in fasting or mildly ill patients. The increase is virtually all unconjugated (indirect) bilirubin.

Pregnancy
In the third trimester of pregnancy, three syndromes can be seen. Cholestatic jaundice of pregnancy (also called intrahepatic cholestasis of pregnancy) is a benign condition without significant hepatic damage. However, acute fatty liver of pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) can result in marked hepatocellular damage and may have a high mortality rate.

DIAGNOSIS
The diagnosis of hepatitis is generally dependent on the demonstration of abnormal liver enzymes and evidence of liver cell inflammation. Hepatic function, as evidenced by the INR, is generally normal. Screening laboratory tests will usually confirm that hepatitis is present, although liver enzymes may be normal in those with chronic hepatitis.

The serum aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are the prime markers for hepatocellular injury. They will usually be quite elevated in acute hepatitis, with values as high as several thousand international units (IU). In chronic hepatitis, they may be normal or just mildly elevated until an acute exacerbation of the disease occurs, at which point they may rise dramatically. Decreasing levels of the aminotransferases will generally parallel the resolution of acute liver inflammation, although normalization in the setting of worsening INR following acute liver failure may be an ominous indicator of massive hepatocellular death.

Abnormalities in the serum bilirubin level directly reflect the functional abnormality in hepatitis. The level will generally mirror the degree of hepatic enzyme elevation. An exception to this can occur when massive cell death has occurred. The aminotransferases can be deceptively normal while the bilirubin remains quite high, reflecting the poor functional capability of the little remaining parenchymal tissue. In a mildly ill or otherwise normal patient who is jaundiced, fractionation of bilirubin to determine the proportion that is unconjugated (indirect) may be useful to establish the diagnosis of Gilbert syndrome rather than hepatitis.

Unfortunately, although these general screening tests may be of benefit in detecting that the patient's liver is diseased, they are of little benefit in identifying which type of hepatitis the patient may have. For this, more specific laboratory tests are necessary.

Hepatitis A

For the diagnosis of hepatitis A, there is an assay for antibody to the HAV (anti-HAV). In the acute disease, the anti-HAV will be of immunoglobulin class IgM, whereas within 6 months of resolution of the infection, the anti-HAV will all be IgG. If the IgM fraction is identified in the serum of the acutely jaundiced patient, a presumptive diagnosis of acute hepatitis A is made (**Fig. 22.5**).

The presence of anti-HAV IgG antibody is believed to confer immunity to reinfection, and it will generally be present for life following infection. Persistence of protective antibody levels for >10 years following hepatitis A immunization has been demonstrated; there is no official recommendation at the time of writing for additional vaccine doses after the second dose of the primary series has been received.

Hepatitis B

The diagnosis of hepatitis B infection is much more complex (**Figs. 22.6–22.8**). A number of serologic tests aid in the diagnosis. The results reflect the presence of the viral components or the immune system's response to them during the various stages of the disease. Early in the course of the acute infection, the HBsAg can be detected, often before there are any clinical signs of infection. As long as this is found in the serum, the patient remains

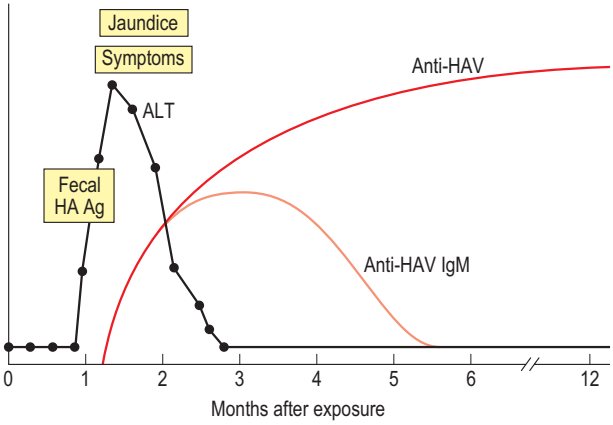


Fig. 22.5 The clinical, serologic, and biochemical course of typical type A hepatitis. *ALT*, Alanine aminotransferase; *anti-HAV*, antibody to hepatitis A virus; *HA Ag*, hepatitis A antigen; *IgM*, immunoglobulin M. (Reprinted from: Hoofnagle, J.H., 1981. Perspectives on Viral Hepatitis, Vol. 2, first ed. Abbott Laboratories, Rahway, NJ, p. 4, with permission of publisher.)

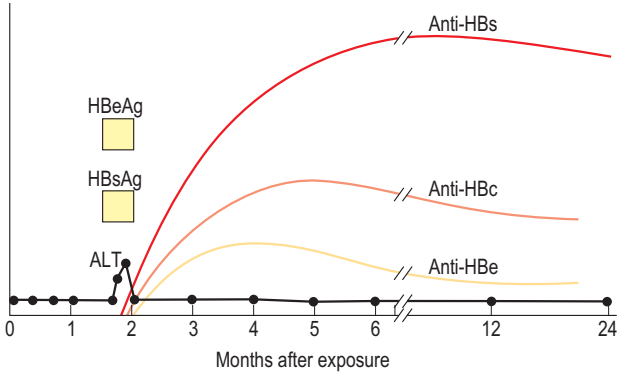


Fig. 22.6 **The clinical, serologic, and biochemical course of a subclinical asymptomatic hepatitis B virus infection. *ALT*, Alanine aminotransferase; *anti-HBc*, antibody to hepatitis B core antigen; *anti-HBe*, antibody to HBeAg; *anti-HBs*, antibody to HBsAg; *HBeAg*, hepatitis B "e" antigen; *HBsAg*, hepatitis B surface antigen.** (Reprinted from: Hoofnagle, J.H., 1981. Perspectives on Viral Hepatitis, Vol. 2, first ed. Abbott Laboratories, Rahway, NJ, p. 7, with permission of publisher.)

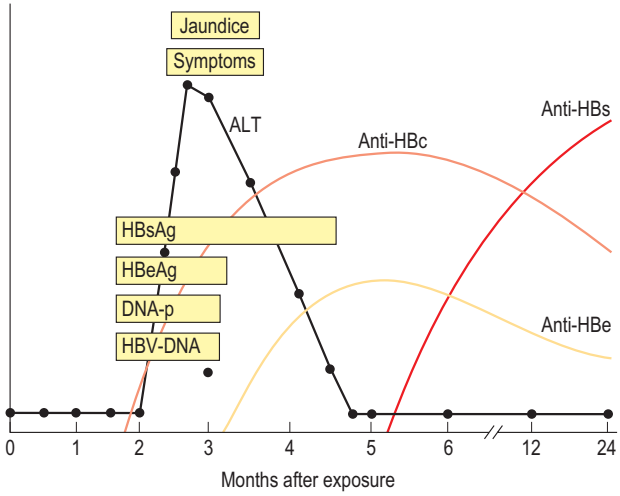


Fig. 22.7 **The clinical, serologic, and biochemical course of typical acute type B hepatitis. *ALT*, Alanine aminotransferase; *anti-HBc*, antibody to hepatitis B core antigen; *anti-HBe*, antibody to HBeAg; *anti-HBs*, antibody to HBsAg; *DNA-p*, serum hepatitis B virus DNA polymerase activity; *HBeAg*, hepatitis B "e" antigen; *HBsAg*, hepatitis B surface antigen; *HBV-DNA*, serum hepatitis B virus DNA.** (Reprinted from: Hoofnagle, J.H. 1981. Perspectives on Viral Hepatitis, Vol. 2, first ed. Abbott Laboratories, Rahway, NJ, p. 6, with permission of publisher.)

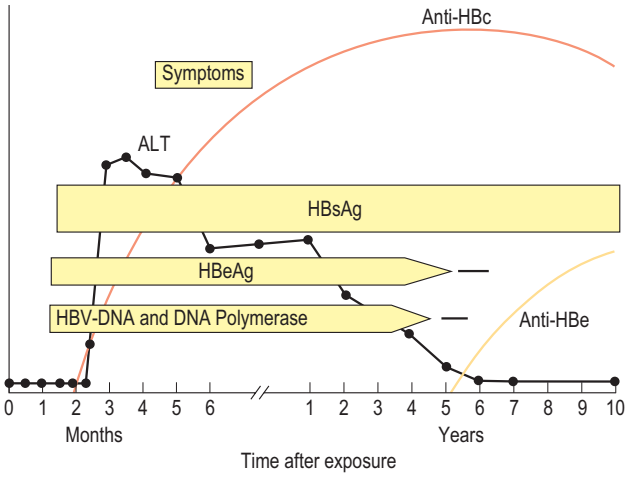


Fig. 22.8 The clinical, serologic, and biochemical course of a chronic type B hepatitis infection. *ALT*, Alanine aminotransferase; *anti-HBc*, antibody to hepatitis B core antigen; *anti-HBe*, antibody to HBeAg; *HBeAg*, hepatitis B "e" antigen; *HBsAg*, hepatitis B surface antigen; *HBV-DNA*, serum hepatitis B virus DNA. (Reprinted from: Hoofnagle, J.H., 1981. Perspectives on Viral Hepatitis, Vol. 2, first ed. Abbott Laboratories, Rahway, NJ, p. 8, with permission of publisher.)

infectious, and if it remains present at least 6 months after the onset of jaundice, the patient is presumed to be chronically infected.

Disappearance of the HBsAg from the blood is followed, after a period of several weeks, by the development of the anti-HBs antibody. This is a marker for resolution of the infection. The patient is not infectious and is considered cured. This is also the only hepatitis B serology that should be positive in the patient who has been successfully vaccinated.

Subsequent to the development of HBsAg, but before anti-HBs appears, antibody to the core of HBV develops (anti-HBc). This generally occurs at about the time of the onset of clinical illness, but it may be the only marker of HBV present if HBsAg has disappeared and anti-HBs has not yet appeared (the "core window"). An assay for IgM and IgG can determine if the anti-HBc present is due to acute or remote infection.

Another marker for hepatitis B infection is the HBeAg, or "e," antigen. This viral component is part of the nucleus and circulates freely during the acute infection. It is indicative of a high degree of infectiousness; presence of HBeAg more than 10 weeks beyond the symptomatic period indicates that the patient will probably develop chronic hepatitis (25-50% of chronic carriers are positive). By contrast, if the patient develops anti-HBe, it is a sign of either resolution of infection or development of an inactive carrier state (**Table 22.3**).

Hepatitis C

The diagnosis of hepatitis C is two-fold. The detection of HCV antibody by the enzyme-linked immunosorbent assay (ELISA) indicates exposure to the disease. This presence of acute or chronic infection is then confirmed by HCV RNA testing.

Hepatitis D

An antibody assay exists for hepatitis D, but it is often only transiently positive at the time of acute infection; it does remain persistently positive in chronic carriers of the infection.

TABLE 22.3 Interpretation of Hepatitis B Serologic Tests

HBsAg	Anti-HBs	Anti-HBc	Serologic Test
			Suggested diagnoses and follow-up
+	–	–	Early hepatitis B infection: probably pre-clinical or early clinical illness.
			HBeAg/anti-HBe testing possibly indicated: If –/– ("e window") or –/+: resolution likely. If +/–: still highly infectious.
			Needs follow-up testing until anti-HBs is positive, i.e., acute infection has resolved.
+	–	+	Diagnostic of either of the following:
			1. Acute HBV infection: has not developed anti-HBs yet. Consider "e" antigen testing as outlined above. Needs follow-up until anti-HBs positive. Anti-HBc IgM distinguishes 1 from 2.
			2. Chronic HBV carrier Consider hepatitis A, hepatitis C, or hepatitis D superinfection as diagnosis if acute hepatitis present. Consider other virus or toxin.
+	+	+	Acute hepatitis B. Atypical pattern; usually HBsAg is gone by the time anti-HBs appears; should resolve, since antibody is present.
–	+	+	Remote hepatitis B infection.
			Recovery is indicated by positive anti-HBs.
			Consider hepatitis A, hepatitis C, other virus, or other cause if acute hepatitis present.
–	–	+	One of the following:
			1. Remote HBV infection: anti-HBs now at undetectable level. If HBeAg is negative, assume remote infection and consider HAV, HCV, other virus, or other cause if acute hepatitis present.
			2. Immediate past HBV infection: the "core window" after HBsAg disappears but before anti-HBs appears. A positive test for HBeAg suggests this diagnosis: while the patient is still infectious (positive HBeAg), the infection is in the process of resolution, since HBsAg has disappeared. Follow-up is needed to be sure anti-HBs becomes positive. The immunoglobulin class of anti-HBc may distinguish 1 from 2.
			3. Low-level carrier state: HBsAg is too low to measure. If acute infection is present, consider HAV, HCV, other virus, or other cause.
–	+	–	Either of the following:
			1. Remote HBV infection: anti-HBc now too low to detect.
			2. Past immunization with hepatitis B vaccine: the vaccine contains low levels of HBsAg only. If acute infection is present, consider HAV, HCV, other virus, or other cause of hepatitis.
–	–	–	No evidence of HBV infection.
			Consider HAV, HCV, other virus, or other cause if hepatitis present.

HAV, hepatitis A virus; *HBcAg*, hepatitis B core antigen; *HBeAg*, hepatitis B "e" antigen; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCV* hepatitis C virus.

An IgM assay will be positive in acute infections and can differentiate acute from chronic disease. Hepatitis D should be considered in cases of acute liver failure or when a patient who is a known hepatitis B carrier suffers an acute exacerbation.

Hepatitis E

During the 3- to 8-week incubation period, HEV RNA can be detected in the serum or stool. By 8 weeks, anti-HEV IgM appears in the serum and persists for months, with IgG developing with resolution of disease. A commercially available HEV IgM ELISA test is available. HEV RNA is considered confirmatory, but is not yet available in the United States at the time of this publication. This can be requested through the National Institutes of Health. Serologic tests for hepatitis E have been used in studies to screen for both prevalence and incidence in countries where this disease is endemic.

Epstein-Barr Virus and Cytomegalovirus

The other viral infections that are most commonly considered in the differential diagnosis of hepatitis, EBV and CMV, can be ruled out by using acute and convalescent antibody titers. The Monospot test may be useful for the diagnosis of mononucleosis due to EBV, but it is frequently negative early in the course of the illness and may remain so.

TREATMENT

There is no specific treatment for acute viral hepatitis other than supportive care. Hospitalization is indicated for those people who are unable to care for themselves or who are unable to eat and hydrate. The other indication for hospitalization is hepatic failure, which requires intensive support and careful laboratory monitoring.

Diet was formerly a matter of great concern in treating hepatitis, but the feeling now is that a general diet with relatively high carbohydrate and low fat content is tolerated best. Activity level is also generally recommended to be as tolerated by the patient: people will usually respond more positively to being as active as possible rather than confined to bed until liver enzyme results approach normal.

Medications in acute hepatitis represent a difficult issue. In general, it is wise to avoid all medications, if possible, but especially any medications that are known to be hepatotoxic. Alcohol, even in modest quantities, should be completely avoided in the immediate period of infection, although it is probably not necessary to proscribe it for 12 months (as some urge) in the absence of evidence of severe liver disease.

The prothrombin time/INR is a functional assay of the liver's ability to synthesize coagulation factors. Vitamin K may be indicated in modest doses if it appears that acute liver infection is interfering with normal factor production. If the INR continues to rise, this is most indicative of acute liver failure, and these patients should be hospitalized.

There are several antiviral therapies currently being used for chronic hepatitis B infection, and patients with either hepatitis Be antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B are potential candidates for therapy. The drugs include tenofovir, entecavir, interferon α-2b, and peginterferon α-2a. Lamivudine, adefovir, and telbivudine are used less often due to frequent development of significant viral resistance. The goal of treatment is to suppress HBV replication, reduce progression of disease to cirrhosis with decompensation, and decrease the risk of development of hepatocellular carcinoma. Treatment is complicated and several guidelines exist. In general, treatment is indicated in those with HBV DNA levels ≥2000-20,000 IU/mL and ALT levels more than twice the upper limit of normal, and/or liver biopsies showing moderate inflammation/necrosis. Interferon had been used with moderate success in treatment of chronic hepatitis C. There now exist several direct-acting antiviral agents for chronic hepatitis C virus infection that carry cure rates of over 90-95%. Treatment of HDV infection is directed at the underlying HBV infection. The greatest experience with treatment of HEV infection is in the solid organ transplant population. Clearance of HEV can be achieved in most cases with pegylated interferon alpha monotherapy, ribavirin monotherapy, or a combination of the two.

PREVENTION

Hepatitis A Vaccine

Travelers who are at risk for hepatitis A may opt for prophylaxis with one of the inactivated hepatitis A virus vaccines currently available. The inactivated vaccines have a rate of seroconversion of >95% 1 month following immunization, but a booster dose 6-12 months after the initial dose is recommended to ensure long-lasting high levels of immunity (see Chapter 5). To avoid unnecessary immunization, if there is sufficient time before departure, it may be cost-effective to perform HAV antibody screening in travelers who are likely to have been previously infected. Examples of people in whom to consider testing would include those with a history of jaundice, natives or long-term residents of areas where hepatitis A is endemic, or those born before the close of World War II, when sanitary conditions were not as carefully maintained.

Reasonable precautions should be exercised in eating and sanitation habits, regardless of vaccine status. These include drinking hot, carbonated, or canned or bottled beverages; eating hot, well-cooked food and particularly avoiding raw or poorly cooked seafood; and avoiding unpeeled fruits and uncooked vegetables, which may be fertilized with night soil. Hepatitis A virus can be inactivated by heating at 85° C (185° F) for 1 min and partly inactivated at 60° C (140° F) for 60 min under test conditions. There is limited evidence from a food-borne outbreak that microwaving the surface-contaminated cooked food for 30 seconds or more during reheating appears inactivate the virus.

HAV Vaccine in Compromised Hosts

Patients with chronic HBV and HCV respond to hepatitis A immunization with rates of seroconversion comparable to those of healthy adults. Hepatitis A vaccine is less immunogenic in patients with decompensated cirrhosis (66% seroconversion) compared with those with compensated cirrhosis (98%) at 7 months (1 month after the second dose of vaccine). Seroconversion after two hepatitis A vaccine doses in liver transplant recipients was only in the 0-26% range. Immunogenicity of HAV vaccine in HIV-infected individuals was related to the $CD4^+$ cell count: those with $CD4^+$ >300 had seroconversion rates comparable to healthy controls, whereas individuals with $CD4^+$ <300 had a somewhat decreased response rate.

Immune Globulin

For persons unable to receive hepatitis A vaccine or who have underlying medical conditions that are predictive of a suboptimal immune response to vaccine, hepatitis A infection can be prevented through the administration of immune globulin (IG). Recipients receive protection against infection with hepatitis A virus immediately after IG administration from the transfer of pre-formed antibodies contained in the product. Recommendations are that short-term travelers receive 0.02 mL/kg (2 mL) of IG, while those contemplating stays of 3 months or longer should receive 0.06 mL/kg (4-5 mL). In those staying for prolonged periods, additional doses of IG are necessary every 5 months. Studies suggest that protective efficacy in preventing seroconversion is about 85%, and that over 1 year, about 1 in 500 people relying on IG prophylaxis will develop icteric hepatitis.

Hepatitis B

Immunization against hepatitis B is indicated for travelers depending on risk of exposure. This would include healthcare workers, those who anticipate receiving medical care in endemic regions, and those who expect to have sexual or other intimate contact with natives in countries where hepatitis B is endemic. Included in this group are families participating in international adoptions. Long-term travelers (>6 months) to endemic areas should be immunized as well, regardless of anticipated activities. If protection against both hepatitis A and hepatitis B is needed by a traveler, the hepatitis A plus hepatitis B combination vaccine may be used (see Chapter 5).

Household contacts and sexual contacts of HBV carriers should be screened and offered prophylaxis with hepatitis B vaccine when appropriate (Chapters 5 and 19). Persons who

are chronically infected with hepatitis B should receive hepatitis A vaccine to avoid more serious pathology.

HBV Vaccine in Compromised Hosts

HBV vaccine is immunogenic in patients with chronic HCV hepatitis, with seroprotection (anti-HBs ≥10 mIU/mL) after three doses comparable to healthy controls. However, several studies have shown uncertain immunogenicity of HBV vaccine administered to individuals with advanced chronic liver disease or post-liver transplant. Among HIV-infected persons, response to HBV vaccine was associated with $CD4^+$ cell counts >200 cells/μL and undetectable HIV-RNA levels, with seroconversion in up to 87.5% following three doses of HBV vaccine reported in subjects with a $CD4^+$ cell count >500/μL. However, among responders, the antibody titers were lower than in HIV-negative controls. In HIV-infected persons with <500/μL $CD4^+$ cells, one study suggested an increased number of HBV vaccine doses could be improved by administering an additional three doses of vaccine on a monthly schedule.

Hepatitis C

No hepatitis C vaccine is commercially available at the time of writing, and its development remains elusive. There are no firm data that indicate IG is protective against hepatitis C if given before exposure. Prevention consists of avoiding high-risk activities and blood products where the virus is known to be endemic. Persons who are chronically infected with hepatitis C will benefit from immunization against both hepatitis A and B, as morbidity and mortality is higher with either co-infection.

Hepatitis D

Immunity to hepatitis D is conferred with immunity to hepatitis B; the vaccine for hepatitis B should be given to those at risk. Prevention for HBV carriers is to avoid risky exposures for HDV.

Hepatitis E

Prevention of HEV consists predominantly of risk avoidance. IG manufactured in the United States and other non-endemic areas does not contain antibodies against HEV, and there is some evidence that IG manufactured where hepatitis E is endemic does not confer good protection, either. Women who are pregnant or who are of childbearing potential should be informed of the heightened risk of acute HEV infection during pregnancy and should consider deferral of travel to HEV-endemic areas as appropriate. A recombinant hepatitis E vaccine (HEV-239) has been developed. Early data have shown that the vaccine is immunogenic (87% efficacy) and provides protection for up to 4.5 years. Safety data suggest that the vaccine is well tolerated. Should this vaccine become widely available, it would be crucial in the prevention and control of hepatitis E virus disease.

FURTHER READING

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