Viral hepatitis

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Abstract

The hepatitis A, B, C, D and E viruses primarily target the liver to cause viral hepatitis. Hepatitis A (HAV) and E (HEV) viruses are transmitted by the faecal-oral route and cause acute viral hepatitis. Acute viral hepatitis may be asymptomatic, with a rise in aminotransferase levels, it may be symptomatic, with or without jaundice, or it may present as fulminant hepatitis. The hepatitis B (HBV), C (HCV) and D viruses are parenterally transmitted and can cause acute and chronic infections. When they persist in the chronic carrier state they may cause chronic hepatitis, cirrhosis and hepatocellular carcinoma. The diagnosis of viral hepatitis is based on serology and molecular detection of the virus. There are no specific drug therapies available for patients with acute hepatitis A or hepatitis E infection, and management is based on symptomatic relief. Currently available treatments for chronic hepatitis B an C have limited efficacy, are expensive and may have severe side effects. Patients should be carefully selected and managed by a specialist with experience in this field. Vaccines are available for HAV and HBV.

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Introduction

Hepatitis is a feature of many systemic viral diseases, e.g. yellow fever, herpes simplex virus, cytomegalovirus and Epstein-Barr virus infection. However, some viruses primarily target the liver to cause viral hepatitis. As shown in Table I, the hepatitis A virus (HAV) and the hepatitis E virus (HEV) are transmitted by the faecal-oral route and cause acute viral hepatitis. The hepatitis B (HBV), hepatitis C (HCV) and hepatitis D (HDV) viruses are parenterally transmitted and can cause acute and chronic infections. There is a significant risk of the transmission of HBV or HCV with a needlestick injury, as shown in Table II.[1,2]

Acute viral hepatitis may be asymptomatic, with only a rise in aminotransferase levels, it may be symptomatic, with or without jaundice, or it may present as fulminant hepatitis. Early symptoms are non-specific and may include malaise, myalgia, joint pain, nausea and vomiting, fatigue, anorexia and abdominal or right upper quadrant discomfort. Physical findings are often minimal, but low-grade fever is usually present. A high temperature and rigors should prompt the physician to look for other causes of disease.[3,4]

HBV, HCV and HBV-associated HDV may cause chronic hepatitis. Chronic viral hepatitis may progress to cirrhosis and hepatocellular carcinoma.[2]

Hepatitis A

HAV infection is found worldwide, but is highly endemic in developing countries. Infection is spread by person-to-person contact in closed communities or by the consumption of faecally contaminated food or water. Raw shellfish is a particularly common source of infection. The incubation period varies from 15 to 50 days. HAV is excreted in the stool of infected persons as early as two to three weeks before the onset of jaundice and excretion may continue for three to four weeks after ALT levels peak.[3] Asymptomatic infections are 10 to 30 times more common than symptomatic disease. In general, the younger the patient, the milder the clinical form of hepatitis. The incidence of HAV infection is directly related to poor hygienic conditions and overcrowding. Most people infected with HAV in developing countries are children, who have mild illness. In more developed countries, infection occurs typically later in life and is thus more likely to be clinically

Table I: Characteristics of hepatitis viruses

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
DNA / RNA virus	RNA	DNA	RNA	RNA	RNA
Virus: family	Picornaviridae	Hepadnaviridae	Flaviviridae	Unassigned	Unassigned
Virus: genus	Hepatovirus	Orthohepadnavirus	Hepacivirus	Deltavirus	Hepevirus
Transmission	Faecal-oral	Parenteral	Parenteral	Parenteral	Faecal-oral
Can the virus cause chronic infection?	No	Yes	Yes	Yes (with HBV)	No

Table II: Risk of transmission after a needle-stick injury

HBV	30%
HCV	3%
HIV	0,3%

severe.[3] In South Africa an endemic pattern of HAV infection is typically found in high density, low socio-economic communities where 100% of children acquire immunity before the age of 10. However, as sanitation improves, a change takes place in the epidemic vulnerability of the South African population. A sporadic pattern of infection is mostly seen in higher socio-economic communities with an increase in symptomatic HAV among the adult population.[5] Jaundice resolves within two weeks in the majority of patients. However, complete clinical recovery may take up to six months and fatigue and weakness may persist for some weeks after apparent biochemical recovery.[3,4] Surveillance data reported to the Centers for Disease Control and Prevention show a case-fatality rate of 0,4%.[6]

Fulminant hepatic failure is defined as severe liver failure (defined as the presence of encephalopathy) that develops within eight weeks of the onset of symptoms. It is a rare complication that occurs in only 1% of hospitalised patients with HAV infections. In patients with underlying chronic HBV or HCV infection the risk of developing fulminant hepatitis is much higher.[1]

Relapsing or biphasic hepatitis has been described with HAV infection. A second episode of illness occurs four to fifteen weeks after the initial illness and is usually similar in severity. There is no association between the severity of the initial illness and the development of a relapse. The rate of relapse of HAV varies from 3 to 12%. Liver functions always return to normal within 12 months.[4].

The diagnosis of acute HAV infection is made by finding IgM anti-HAV in a patient with symptoms, or from biochemical evidence of hepatitis, as illustrated in Figure 1. Presence of total anti-HAV antibodies does not rule out acute infection as it may be positive due to an increase in IgM anti-HAV antibodies.[3,4,7]

Figure 1: Schematic representation of the HAV serological markers as a function of time after infection.

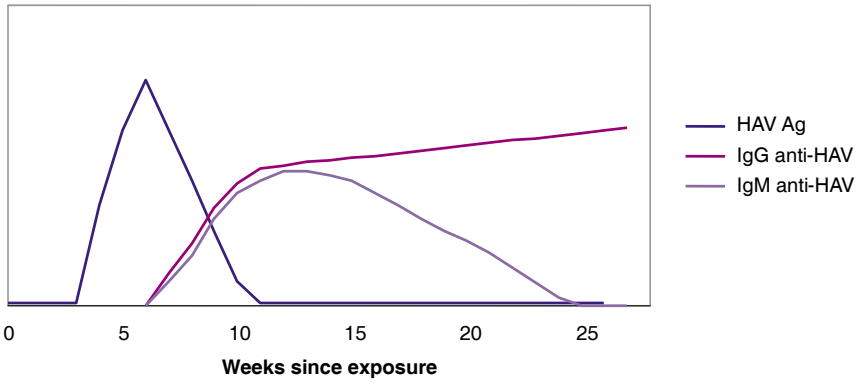
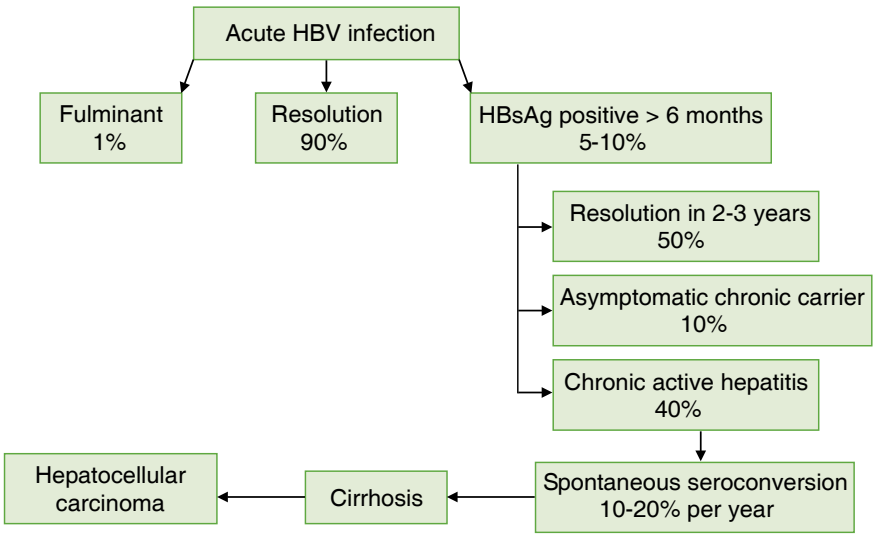


Figure 2: Progression of HBV infection acquired as an adult.



Hepatitis E

HEV is transmitted by the faecal-oral route and most epidemics have been related to the consumption of contaminated drinking water. The highest attack rates are among young adults aged 15 to 40 years. Person-to-person transmission is rare. The secondary attack rate is only 1 to 2%, compared with 15% for HAV.[7,8]

After an incubation period of 15 to 60 days, patients have a short flu-like prodrome. The majority of infections will resolve without any other symptoms. Patients may present with jaundice, malaise, anorexia and nausea. Pregnant patients have an increased risk of fulminant hepatitis, with a 20% mortality rate[7,8]

Diagnostic tests for HEV are not done routinely, as clinical cases of HEV infection are only rarely reported in South Africa. HEV serology should be requested in a patient who has travelled to the tropical or subtropical areas of Southeast or Central Asia, the Middle East, Mexico, or North or West Africa. Anti-HEV IgM becomes detectable in blood during the early phase of infection and disappears over four to six months. IgG anti-HEV represents the convalescent phase or previous exposure.[8,9]

Hepatitis B

The hepatitis B virus (HBV) is an important cause of cirrhosis and hepatocellular carcinoma. Modes of transmission include parenteral, sexual, horizontal as well as vertical transmission.[10,11]

Estimates of the prevalence of hepatitis B surface antigen (HBsAg) in South Africa range from 9,9% among adult migrant mineworkers to 10,1% among rural African children aged 0-6 years in the Eastern Cape Province.[12]

The outcome of HBV infection and the spectrum of clinical illness vary widely. The possible consequences of childhood or adult-acquired HBV infection are shown in Figure 2. The incubation period is one to four months. Symptomatic acute hepatitis develops in 30% of patients, while 70% will remain anicteric. Extrahepatic manifestations occur in 10 to 20% of cases due to immune complex formation. Patients present with serum sickness-like illness, with fever, polyarthralgia and an urticarial rash, typically occurring just before and subsiding with the onset of jaundice.

Table III: Interpretation of typical HBV serology

HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	anti-HBcIgM	Interpretation
-	+	-				Previous immunisation (vaccine consists of HBsAg and elicits an anti-HBs response in > 90 % of vacinnees)
-	+	+				Immune (patient had infection)
+	-	+	+	-	+ / -	Positive anti-HBcIgM indicates acute infection. HBeAg indicates patient is highly infectious. Repeat serology in three to six months to distinguish acute from chronic HBV infection.
+	-	+	-	+	+	Need a three- to six-month follow-up specimen to distinguish acute from chronic infection. Acute self-limited infection will lose HBsAg and develop anti-HBs.

Figure 3: Acute HBV Infection

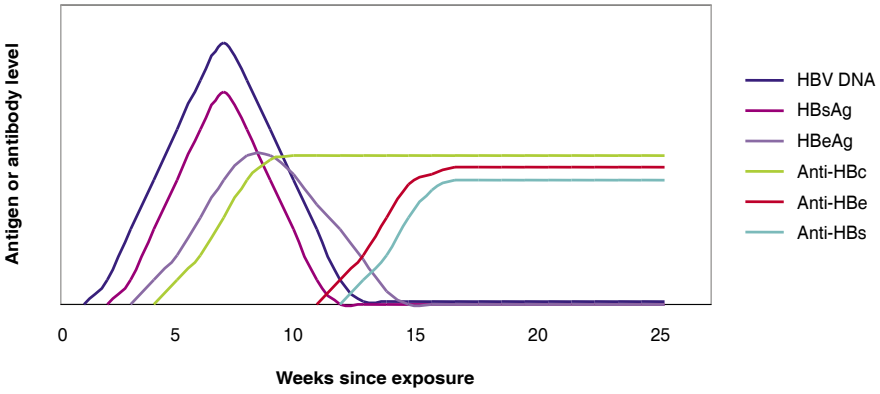


Figure 3: In a typical case of acute HBV infection, hepatitis B surface antigen (HBsAg) becomes detectable in the blood after an incubation period of four to 10 weeks, followed shortly by hepatitis B e antigen (HBeAg) and antibodies against the HBV core antigen (anti-HBc antibodies). A small proportion of individuals with anti-HBc alone are in the window phase of an HBV infection. With clearance of the infection, HBsAg and HBeAg disappear and antibodies against HBsAg (anti-HBs) and for some time against HBeAg (anti-HBe) become detectable.

Figure 4: Chronic HBV Infection

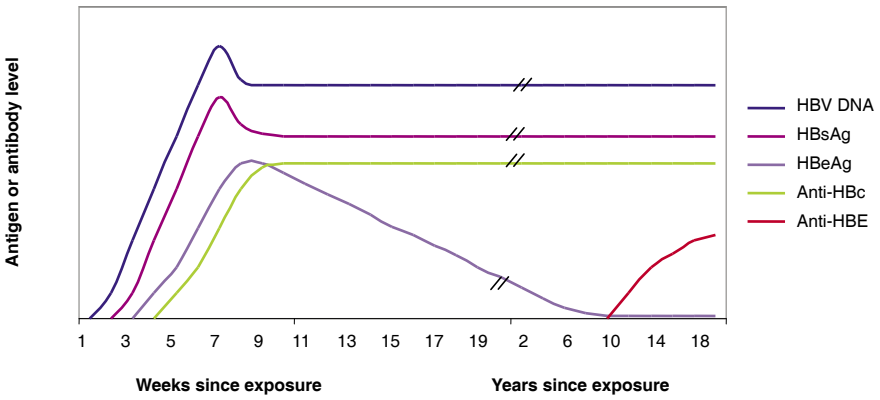


Figure 4: Diagnosis of chronic HBV. HBsAg remains positive in chronic HBV infection. The presence of HBeAg indicates a high risk of transmission. With the passage of time, HBeAg may disappear from the blood with the appearance of anti-HBe antibodies.

The emergence of HBV genetic variants is the result of the "immune escape" phenomenon. Some of these genetic variants, for example the surface antigen mutants, may have implications for the accuracy of laboratory diagnosis and may reduce the effectiveness of vaccination.[15]

Glomerular disease, with development of nephrotic syndrome, may also occur as a manifestation of HBV. Fulminant hepatitis is rare, although it is more likely to occur with hepatitis D co-infection or underlying conditions such as alcoholic liver disease.[1,10,11]

Chronic hepatitis is defined by at least six months of persistent HBV disease (HBV surface antigen (HBsAg) positive > six months). The symptoms do not correlate with the severity of disease. Serum aminotransferases may be normal, although most patients have mild to moderate elevations. During flares of disease, serum aminotransferases may be elevated 20 times normal. The spontaneous rate of seroconversion is 10 to 20% per year and patients with flares should be observed for the development of antibodies against hepatitis B e antigen (anti-HBe). The prognosis of chronic HBV is directly related to the development of cirrhosis.[11,13]

Childhood and adult infections have a much better prognosis than infections acquired perinatally. Only about 10% of children infected perinatally will clear the virus, while 90% of all patients with childhood and adult infections will clear the virus. Rates are similar whether or not there is symptomatic acute disease. Patients who have acquired natural immunity through infection develop both anti-HBs and anti-HBc antibodies. They have life-long immunity against disease unless there is significant immunosuppression, such as human immunodeficiency virus type 1 (HIV-1) infection. Of the 10% of adults who develop chronic hepatitis, 50% will show resolution within two to three years. Forty per cent will develop chronic active hepatitis and many of these will progress to cirrhosis and hepatocellular carcinoma.

Ten per cent will become chronic a-symptomatic carriers, with minimal symptoms.[11]

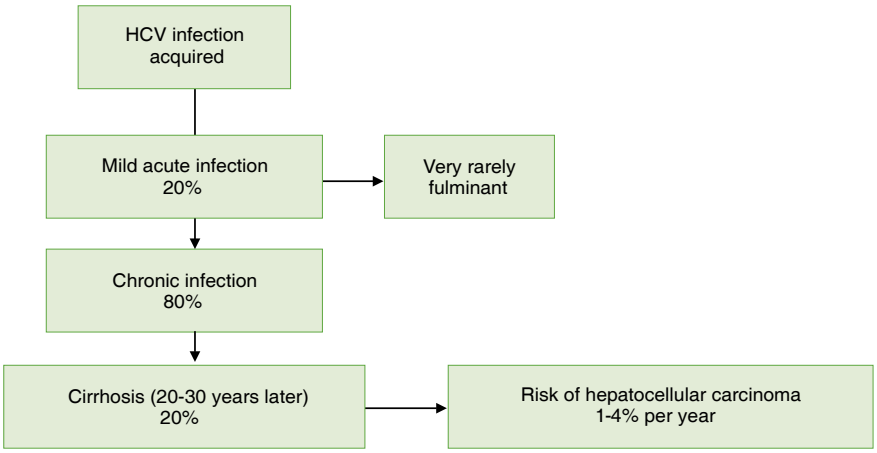
The laboratory diagnosis of HBV is based on serology and is summarised in Table III. At least 4 ml of clotted blood is required for a complete viral hepatitis profile. The appearance and disappearance of serological markers can be used to diagnose the status of disease progression.[11] The course of a typical acute HBV infection is shown in Figure 3, and a chronic HBV infection is shown in Figure 4. Molecular testing has revealed patients who are HBV-DNA positive but HBsAg negative. These patients are referred to as having occult hepatitis B.

The prevalence of occult HBV infection is higher in patients co-infected with HCV or HIV, and in patients with hepatocellular carcinoma. The presence of occult HBV infection has important therapeutic implications. It has been associated with advanced fibrosis and diminished response to interferon α.[14]

Hepatitis C

HCV shows considerable genetic variation. The virus exists as a group of diverse but related quasi-species within an infected individual. This presents a major challenge to the immune system, as well as for vaccine design. There are at least six genotypes and multiple subtypes, of which genotype five is most common in South Africa.[16,17]

Figure 5: Progression of HCV infection in an infected adult.



HCV infects 170 million people worldwide and is one of the main indications for liver transplantation in developed countries. HCV prevalence in South Africa is estimated at 1,8%.[18] Infection is mainly spread through percutaneous exposure to blood.[16]

Although HCV is shed in semen and saliva, sexual transmission seems to be less efficient than in the case of HBV. Maternal-foetal transmission occurs infrequently (risk estimated at 0 to 8%). Co-infection with HIV-1 increases the risk of both sexual and maternal-foetal transmission. The virus is shed in milk, but breastfeeding is not contraindicated. Household contacts should not share razors, toothbrushes, etc.[17]

The incubation period varies from six to twelve weeks. As shown in Figure 5, only 20% of patients will develop mild symptoms of acute hepatitis. Fulminant hepatitis is very rare. The infection becomes chronic in most cases, with a prolonged asymptomatic period of 20 to 30 years. Eighty percent of patients will have persistent viraemia. Of these, cirrhosis will develop in 20% and the risk of developing hepatocellular carcinoma is 1 to 4% per year. Co-infection

Table IV: Management of acute viral hepatitis

• Identify patients who may experience fulminant hepatic failure and refer to specialist care immediately.
  ○ Patients with underlying HBV or HCV infection who develop acute HAV
  ○ Pregnant patients with acute viral hepatitis
  ○ Patients co-infected with HBV and HDV with symptoms of acute viral hepatitis

• Most patients do not require hospitalisation. Consider admission when:
  ○ Patient has dehydration due to persistent anorexia or vomiting
  ○ Patient has progressive prolongation of the prothrombin time
  ○ Patient has any sign of liver failure, such as mental status changes

• Bed rest is recommended during the symptomatic phase of the illness.

• All but clearly necessary medication should be stopped.
  ○ Nausea should be managed with metocloperamide. Chlorpromasine should be avoided, as it may cause drug-induced cholestasis.
  ○ Pain should be managed with paracetemol (< 2 gram / day).
  ○ Pruritis can be managed with cholestyramine.

• Alcohol should be avoided during symptomatic illness, but it is not necessary to impose abstinence after symptomatic recovery.
• Dietary manipulation has not been shown to improve symptoms or outcome.
• There are no specific drug therapies available for patients with acute HAV or HEV.

Table V: Management of chronic viral hepatitis

• Currently available treatments for HBV and HCV have limited efficacy, are expensive and may have severe side effects. Patients should be managed by a specialist with experience in this field.
• Major predictors of treatment response in chronic HBV infection include high ALT levels, low HBV DNA levels and greater degree of activity on liver biopsy. • Antiviral treatment is not recommended for patients with inactive HBsAg carrier state or patients with occult HBV. • Options available for treatment are the immunomodulatory agent, interferon α, and the antiviral drugs lamivudine, adefovir, tenofovir and entecavir.
• HCV infection treatment decisions are based on quantitative HCV RNA analysis, staging on liver biopsy and viral genotype. • Treatment is based on a combination of interferon α and Ribavirin.

with HIV-1 or HBV increases the risk for cirrhosis and carcinoma and accelerates the clinical progression of the disease.[16]

Extrahepatic manifestations of HCV include cryoglobulinemia, which results in immune complex-mediated vasculitis. Patients will present with weakness, arthralgia and purpura. Severe cases may be associated with membranoproliferative glomerulonephritis.[16]

The laboratory diagnosis of HCV infection is based on serological assays to detect antibodies and molecular tests for viral RNA. Enzyme immunoassay (EIA) for HCV antibodies measures HCV exposure, not immunity. It does not differentiate between acute, chronic and resolved infection. False positive HCV antibodies may occur in populations with a low (<10%) prevalence of HCV infection. Low positive EIA results need to be confirmed with a second EIA test. If HCV infection is clinically suspected, an EDTA specimen must be submitted for HCV RNA detection by PCR. Qualitative as well as quantitative molecular tests are available to detect HCV RNA. HCV viral load determination is useful before providing and monitoring treatment. Liver biopsy is the only definitive method to assess the stage of disease. Liver function tests fluctuate with time and do not correlate with the severity of liver injury in HCV infection.[16,19]

Hepatitis D

Hepatitis D only occurs in patients with acute or chronic HBV infection. HDV is a defective virus and needs HBV to replicate. If HBV resolves and HBsAg is cleared from the serum, the HDV will also resolve. HBV-immune individuals cannot contract HDV infection. HDV occurs most commonly in patients who have had multiple parenteral exposures, e.g. intravenous drug users. Acute infection has a mortality of 2 to 20%. Chronic infection is more likely to result in cirrhosis than either chronic HBV alone or chronic HCV.[11,20]

Management and prevention of viral hepatitis

There are no specific drug therapies available for patients with acute hepatitis A or hepatitis E infection, and management is based on symptomatic relief.[7,8] Currently available treatments for HBV and HCV have limited efficacy, are expensive and may have severe side effects.[11,17,21] Patients should be carefully selected and managed by a specialist with experience in this field. The management of acute and chronic viral hepatitis is summarised in Tables IV and V respectively.

Vaccines are available for HAV and HBV. Prevention is discussed elsewhere in this publication.

See CPD Questionnaire, page 44

This article has been peer reviewed

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