Hepatitis, a general term meaning inflammation of the liver, can be caused by viral infection. The most serious viral cause is hepatitis B — a life-threatening liver infection caused by the hepatitis B virus (HBV). It can cause chronic liver disease, progressive hepatic fibrosis, hepatocellular carcinoma and end-stage liver disease.

HBV can cause acute illness or chronic infection. Despite the availability of a highly effective vaccine (see p16) and improvements in antiviral therapy, it remains a major public health problem globally. The prevalence of HBV infection varies in different parts of the world — from as low as 0.1% to as high as 20%. Figure 1 (p12) indicates how prevalence rates vary across the globe.

Population movements and migration are changing the prevalence and incidence of the disease. Immigration from high or medium prevalence areas is leading to increased incidence of disease in low prevalence areas. According to the World Health Organization, an estimated two billion people have been infected with HBV at some point in their lives. Approximately 350 million remain infected chronically and, of these, 25–40% will die of cirrhosis or liver cancer that is related directly to their infection.

The virus
HBV is an enveloped virus containing a partially double-stranded, circular DNA genome and is classified within the hepadnavirus family. It replicates within hepatocytes (see Box 1, p12) and, consequently, interferes with the function of the liver. The immune system tries to combat and eradicate the virus but this response, and the consequent release of inflammatory mediators, leads to liver inflammation and damage.

Eight different genotypes of HBV have been identified (A–H), the prevalence of which vary within different countries. In Europe, genotypes A, D and G are most common. Data suggest that progression of the disease and responsiveness to treatment are related to the genotype identified (investigations to determine which genotypes are most difficult to treat are ongoing).2,3

Transmission
HBV transmission can occur in several ways, including:

- Through using contaminated injecting equipment, sustaining a needlestick injury or receiving a tattoo or body piercing (percutaneous or parenteral transmission)
- Through sexual intercourse with infected individuals
- Through contact with infected bodily secretions or blood
- From mother to child during childbirth

HBV is too large to cross the placenta so it cannot be transferred during gestation unless there is a break in the

Some 350 million people across the world are infected chronically with hepatitis B. Despite global control of the disease being achievable through widespread vaccination, this has not yet been attained.
maternal-fetal barrier (eg, due to amniocentesis). However, the most common mode of transmission is perinatal transmission from mother to baby at birth. Around 90% of those infected at birth will go on to develop chronic HBV infection. Where infection occurs later in life, only 5–10% of patients develop chronic infection.

It is recommended that the offspring of infected women be treated with hepatitis B immunoglobulin at birth (to provide immediate protection). They should also be given the HBV vaccine as soon as possible after birth to improve long-term immunity.

**Detection**

Hepatitis B is a complex disease and diagnosis is made by assessment of biochemical, serological, virological and histological parameters. The parameters used to define and characterise HBV infection are listed in Box 2 (p15).

Hepatitis B surface antigen (HBsAg) is used to screen for the presence of infection. It is the first viral antigen to be detectable in the blood after infection — appearing during the virus's incubation period. In 10% of patients, HBsAg is cleared early and may not be detectable when these patients are screened for HBV infection.

Shortly after HBsAg is detected, a second antigen (hepatitis B e antigen; HBeAg) becomes detectable. The presence of HBeAg signifies HBV replication and, along with the presence of HBV DNA (detected using polymerase chain reaction-based assays), indicates an active infection.

Antibodies to the hepatitis B core antigen are detectable in the blood after the onset of acute hepatitis B symptoms. These antibodies (anti-HBc) persist for life and their presence indicates previous or ongoing infection. The relative concentrations of anti-HBc immunoglobulin M and immunoglobulin G indicate the timeframe of infection (see comment on anti-HBc, Box 2, p15).

During the natural course of an infection, the HBeAg is sometimes cleared with a corresponding rise in its antibodies (anti-HBe). This is usually associated with a dramatic decline in viral replication and indicates resolution of acute hepatitis B infection. In patients who develop chronic hepatitis B, HBsAg and HBV DNA remain high for more than six months.

**Acute hepatitis B**

The course of hepatitis B infection can be highly variable and different clinical manifestations present depending on the patient's age (at the time of infection) and immune status and the extent to which the disease has progressed when it is identified.

In adults, acute hepatitis B infection has an incubation period of 6–24 weeks. Following this period, acute hepatitis develops — patients will have elevated aminotransferase levels that can persist for four to 12 weeks. Affected adults can develop symptoms of jaundice, anorexia, nausea, liver discomfort (usually originating in the right upper quadrant) and fatigue. This acute form of the disease often resolves spontaneously after four to eight weeks of illness. Most of those infected during adulthood clear the virus without significant consequences and without its recurrence.

In about 1% of cases, fulminant hepatitis B develops causing extensive liver necrosis. This form of the disease is normally fatal.
Chronic hepatitis B

Chronic HBV infection develops in 90% of those who are infected at birth. It also occurs in older patients whose immune systems fail to eradicate the virus completely after acute infection. It is diagnosed by the persistence of HBsAg in a patient’s bloodstream for more than six months.

The clinical features of hepatitis B are a result of the interaction between HBV and the host's immune system. The immune system attacks the hepatocytes that harbour the virus and thus causes liver injury. The WHO has reported that approximately one million deaths occur worldwide each year due to chronic forms of HBV infection — generally due to cirrhosis or cancer of the liver.

Patients with chronic HBV infection can progress through up to five phases of disease. Understanding these phases is critical to determining the risk of liver damage. During acute infection, the virus is not recognised as a foreign body because the immune system has not matured fully. Consequently, the immune system does not attempt to remove it. Minimal damage occurs to the liver so treatment is not recommended. However, patients should have their liver function tested periodically so that any rise in ALT is detected early.

Typically, chronic infection acquired perinatally or during infancy has all five phases — the first of which (the immune tolerant phase, see below) can last for decades. Adult-acquired chronic infection has a similar clinical course but there is often no obvious immune tolerant phase. The five phases are described hereafter.\(^{11}\)

### Phase 1: Immune tolerant phase

This phase is characterised by high levels of viral replication (patients’ blood tests are positive for HBeAg) and normal alanine aminotransferase (ALT) levels. As discussed, this phase usually only occurs in patients who acquire the infection at birth.

During this phase, the virus is not recognised as a foreign body because the immune system has not matured fully. Consequently, the immune system does not attempt to remove it. Minimal damage occurs to the liver so treatment is not recommended. However, patients should have their liver function tested periodically so that any rise in ALT is detected early.

### Phase 2: Immune clearance phase

The immune clearance phase signifies a vigorous immune response resulting in liver damage. It is characterised by the presence of HBeAg in the blood along with fluctuating and elevated levels of ALT, and high levels of viral DNA. Repeated episodes of inflammation lead to liver fibrosis and the duration and severity of this phase determine the degree of long-term liver damage.

Treatment should be started as soon as possible to prevent progressive liver fibrosis. Left untreated, patients are more likely to develop cirrhosis, liver failure and cancer.

### Phase 3: Immune control phase

During the immune control phase, the host’s immune response suppresses viral replication to low or undetectable levels. As a result, inflammation reduces and serum ALT normalises. The establishment of immune control is associated with

### Box 2: Markers of infection with hepatitis B virus

<table>
<thead>
<tr>
<th>MARKER</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEROLOGICAL MARKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface antigen (HBsAg)</td>
<td>Used to screen for the presence of recent infection since it is the first hepatitis B virus antigen to be detectable — usually evident four to 10 weeks after infection. It also indicates chronic infection if present for more than six months. Useful marker for diagnosis.</td>
</tr>
<tr>
<td>Hepatitis B core antigen (HBeAg)</td>
<td>This antigen is first detectable in the blood during weeks 3 to 6 of an acute infection. The presence of HBeAg correlates with HBV replication and, along with the presence of HBV DNA, indicates an active infection.</td>
</tr>
<tr>
<td>Hepatitis B core antibody (anti-HBc)</td>
<td>The antibody to HBcAg is first present at the onset of acute hepatitis B symptoms and persists for life. It indicates previous or ongoing infection with HBV. During acute infection, anti-HBc immunoglobulin M (IgM) is detected in the blood in high concentrations. This gradually declines over the next three to six months, corresponding with an increase in immunoglobulin G (IgG). The presence of anti-HBc IgG indicates that HBV infection has occurred within the previous six months; the presence of anti-HBc IgM indicates that HBV infection occurred more than six months previously.</td>
</tr>
<tr>
<td>Hepatitis B e antibody (anti-HBe)</td>
<td>The antibody to the “e antigen” does not help fight infection (the reason for which is unclear) but its presence in the blood corresponds with a considerable reduction in HBV DNA replication.</td>
</tr>
<tr>
<td><strong>VIROLOGICAL MARKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B viral DNA</td>
<td>Present in the blood of an infected individual regardless of the phase of infection and used as a marker for infection. Measuring its level in the blood can help identify a patient’s phase of infection.</td>
</tr>
<tr>
<td><strong>BIOCHEMICAL MARKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Main biochemical marker used for determining the severity of hepatitis. Surrogate marker for indicating the degree of necrosis and inflammation in the liver.</td>
</tr>
<tr>
<td><strong>HISTOLOGICAL MARKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Grade of liver fibrosis</td>
<td>Following a liver biopsy, liver fibrosis is graded 0–4, where 0 represents no fibrosis and 4 represents cirrhosis.</td>
</tr>
</tbody>
</table>

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**Most of those infected during adulthood clear the virus without significant consequences and without its recurrence.**
HBeAg seroconversion — anti-HBe is present in the blood, corresponding with the removal of HBeAg. This phase does not require antiviral treatment; however, the infection can reactivate at any time and patients in this phase should still undergo regular monitoring. Prophylactic treatment (see p21 of accompanying article) is recommended if patients require immunosuppressive therapy, such as chemotherapy.

Immune escape phase During the immune escape phase, the virus mutates and no longer expresses the HBeAg protein. However, it can still replicate so recurrence of active liver disease and progressive fibrosis occurs. This phase is characterised by persistently elevated or fluctuating levels of ALT and elevated viral DNA in the blood, but no HBeAg. Patients experiencing this stage of disease require long-term treatment to suppress viral replication.

Occult HBV infection Occult HBV infection refers to the presence of viral DNA in the blood or liver without levels of the HBSAg being detectable. The presence of the DNA may be related to the long-term persistence of a HBV DNA reservoir in hepatocytes.

The reactivation of hepatitis B infection following immunosuppression has been described in patients with occult infection although the clinical relevance of this phase is unclear.9

Effects on health As the clinical course of chronic HBV infection varies between patients, clinical outcome and prognosis also vary. The lifetime risk of death caused by a liver-related complication has been estimated to be 40–50% for men and around 15% for women.1

Morbidity and mortality are linked to the persistence of viral replication and the development of cirrhosis or hepatocellular carcinoma. Studies suggest that 15–20% of chronic hepatitis B patients develop cirrhosis within five years of their diagnosis.

Whether cirrhosis is compensated or decompensated (see Box 4) has a significant impact on a patient’s chances of survival. Around 15% of patients with compensated cirrhosis will die within five years, compared with 60% of those with decompensated cirrhosis.

### References