Hepatitis B: prevalence and pathophysiology

In this article...

- Epidemiology of chronic hepatitis B
- Life cycle of hepatitis B
- How the virus is diagnosed

Hepatitis B virus (HBV) is an immense global public health problem, with more than two billion people worldwide living with it (Long et al, 2008). Current estimates suggest that around 350 million of these have developed chronic hepatitis B (CHB) virus infection (Tillmann et al, 2012). This can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC), resulting in one million deaths worldwide annually (Thursz et al, 2006).

Epidemiology

Worldwide prevalence

The prevalence of CHB and the age at which infection occurs varies dramatically between different parts of the world. There is a high prevalence (8-15%) in South East Asia, Africa, the Pacific islands, and the Amazon Basin and pockets of the Middle East and North and South America; the prevalence is generally low (less than 2%) in western populations (Table 1).

UK prevalence

In recent years, the number of people with CHB in the UK has risen sharply from 180,000 (Foundation for Liver Research, 2004) to 326,000 (Hepatitis B Foundation, 2007), due to people migrating to the UK from areas with a high CHB prevalence. Health Protection Agency reports (2011) show an antenatal HBV prevalence of 0.42% across England.

People infected with CHB often have no symptoms so many remain undiagnosed, both worldwide and in the UK.

Transmission

HBV is a bloodborne virus that can be found in low concentrations in semen, vaginal fluids, saliva, tears, sweat, urine and breast milk. The virus is 100 times more infectious than HIV and can live outside the body for seven days.

In areas of high prevalence, HBV is generally transmitted from mother to child (perinatal or vertical transmission) during childbirth rather than via the placenta. Transmission from child to child (horizontal transmission) is also common. The tradition of scarification may also be a significant source of transmission in African countries (Kim et al, 2011).

In countries with a low HBV prevalence, the condition tends to affect mainly young adults and is usually transmitted through injecting drug use or unprotected sexual contact (Liaw et al, 2010).

5 key points

1. Hepatitis B virus infection is a growing problem worldwide and in the UK
2. HBV is mainly transmitted through sexual contact or drug use in western countries and through vertical or horizontal transmission in developing countries
3. The age at which HBV is contracted affects prognosis
4. Chronic hepatitis B is often asymptomatic and can go undiagnosed, so high-risk groups should be tested routinely for HBV
5. HBV infection is preventable with a safe and effective vaccine
Hepatitis B life cycle

The life cycle of HBV is complex but, essentially, it acts as a stealth virus by evading the immune system (Chisari et al, 2010). During the first stage of infection, the HBV virion (virus particle) attaches to a liver cell (hepatocyte) then penetrates the hepatocyte's cytoplasm (Locarnini et al, 2010). The HBV virion is uncoated (Fig 1), which means that nucleocapsids can move into the hepatocyte's nucleus and convert the DNA to covalently closed circular DNA (cccDNA) – a double-stranded DNA structure (Valsamakis, 2007). The cccDNA is very stable and can stay in the host nucleus for many months in chronic disease (Jeulin et al, 2013). The virus makes copies of itself in a process that lacks "proof reading ability", which allows the virus to mutate (Horvat, 2011). The newly formed HBV virions are released into the bloodstream, from where they invade other hepatocytes and repeat the replication process.

It is thought that HBV causes inflammation and progressive fibrosis in the infected liver by triggering the immune system to attack the hepatocytes (Nebbia et al, 2012).

Natural history

The incubation period for HBV is 30-180 days. The age at which a person is infected with the virus determines the disease outcome; 90% of those who acquire HBV perinatally or in early childhood will develop CHB, as their immune system cannot destroy and clear infected hepatocytes (Lee et al, 2010).

In adults, 90% of infections are acute and only 5-10% develop into CHB (Shi et al, 2009). Acute liver failure occurs in 1% of acute HBV infections (Liang, 2009). Very rarely (in 1-2% of cases), people with CHB may lose the HBV surface antigen, which is considered to be a definitive recovery. However, the virus can reactivate if they become immunosuppressed (Larrubia, 2011).

**Pathophysiology**

**Hepatitis B life cycle**

**Natural history**

**TABLE 1. PREVALENCE OF HEPATITIS B INFECTION**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Area</th>
<th>% of global population</th>
<th>Lifetime risk of infection</th>
<th>Age of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (8-15%)</td>
<td>South East Asia, China, most of Africa and the Pacific islands, Amazon Basin; parts of the Middle East and North and South America</td>
<td>45%</td>
<td>Greater than 60%</td>
<td>Early childhood</td>
</tr>
<tr>
<td>Intermediate (2-7%)</td>
<td>Parts of South America and western Europe, North Africa, eastern Europe and the Indian subcontinent</td>
<td>43%</td>
<td>20-60%</td>
<td>All age groups</td>
</tr>
<tr>
<td>Less than 2%</td>
<td>Parts of North America, Australia, most of western Europe including the UK</td>
<td>12%</td>
<td>Less than 20%</td>
<td>Adult risk groups</td>
</tr>
</tbody>
</table>

Centers for Disease Control and Prevention (2012); Health Protection Agency (2006)

**FIG 1. HEPATITIS B VIRUS**

Schematic representation of the hepatitis B virus structure

**TABLE 2. FACTORS AFFECTING DISEASE PROGRESSION**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Increased disease progression due to chronic hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>HBV DNA level &gt;2 x 1,000–10,000, genotype C or D, mutations</td>
</tr>
<tr>
<td>Host</td>
<td>Age greater than 40, male, immune status (HIV, infancy, receiving immunosuppressants), family history of cirrhosis and HCC, diabetes, elevated body mass index</td>
</tr>
<tr>
<td>Other</td>
<td>Co-infection with HIV, HDV* or HCV, habitual alcohol consumption, habitual smoking, aflatoxin exposure</td>
</tr>
</tbody>
</table>

Liaw (2009)

*Hepatitis D (delta) virus cannot exist without HBV and is acquired simultaneously with HBV (co-infection) or later (super infection). The former is usually self-limiting but causes more severe disease than HBV alone; a super infection can cause acute liver failure, usually becomes chronic and causes a rapid progression to cirrhosis (Karayiannis, 1998).
The four stages of CHB

The lifetime risk of developing cirrhosis with CHB is 15-40%, with a 2-5% risk of HCC in those with cirrhosis (Nebbia et al, 2012). Many factors affect the rate of disease progression in CHB (Table 2).

It is understood that CHB has four distinct phases with different durations and outcomes (Fig 2). Stages are linked to the degree of HBV replication and the way in which the immune system responds.

» Immune-tolerant phase: this stage lasts for 10-30 years in perinatally acquired HBV but is absent or has a shorter duration for those infected as children or adults. The hepatitis B viral protein, HBeAg, a marker of active viral replication, is present with high levels of HBV DNA and a normal level of alanine aminotransferase (ALT), a liver enzyme. There is minimal liver damage as the immune system tolerates the virus.

» Immune clearance phase (immuno-active): those who acquire HBV in late childhood, adolescence or adulthood often present in this phase. When immunotolerance is lost, the immune system attacks infected hepatocytes, resulting in elevated ALT levels and fluctuating HBV DNA levels, and causing liver fibrosis.

### TABLE 3. HBV SEROLOGICAL MARKERS

<table>
<thead>
<tr>
<th>Serological marker</th>
<th>Abbreviation</th>
<th>Indication</th>
<th>Stage at which marker is present in the blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B surface antigen</td>
<td>HBsAg</td>
<td>Indicates HBV infection</td>
<td>Present 6-10 weeks after exposure to the virus. Persistence of serum HBsAg for six months or more indicates CHB</td>
</tr>
<tr>
<td>Hepatitis B surface antibodies</td>
<td>HBsAb or anti-HBs</td>
<td>Recovery from HBV or HBV vaccination</td>
<td>Appears during resolution of the virus (after 4-6 months), guaranteeing lifelong immunity. Also present in those vaccinated against HBV</td>
</tr>
<tr>
<td>Hepatitis B core antibody</td>
<td>HBcAb or anti-HBc</td>
<td>Current infection or previous exposure to the virus</td>
<td></td>
</tr>
<tr>
<td>IgM antibody to core antigen</td>
<td>IgM anti-HBc (HBcAb IgM)</td>
<td>Acute infection</td>
<td>Appears shortly after surface antigen and persists for 6-24 months; can also be present during flares of hepatitis. IgM anti-HBc gives place to IgG anti-HBc as infection resolves</td>
</tr>
<tr>
<td>Hepatitis B e antigen</td>
<td>HBeAg</td>
<td></td>
<td>A protein that appears 6-12 weeks after exposure to the virus. Presence for 3-4 months suggests progression to chronic disease. Connected with high transmissibility, infectivity and active viral replication</td>
</tr>
<tr>
<td>Hepatitis B virus DNA</td>
<td>HBV DNA</td>
<td></td>
<td>Represents the direct product and hallmark of viral replication and is a reliable indicator of active infection</td>
</tr>
</tbody>
</table>


### TABLE 4. SEROLOGICAL PROFILE AND HBV STATUS

<table>
<thead>
<tr>
<th>Serological profile</th>
<th>Results</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Susceptible – vaccinate</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Negative</td>
<td>Vaccinated</td>
</tr>
<tr>
<td>HBcAb</td>
<td>Negative</td>
<td>Previous exposure to the virus, immune</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBcAb</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IGM antiHBc (HBcAb IG M)</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Acute infection</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBcAb</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IGM antiHBc (HBcAb IG M)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Four possibilities:</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Negative</td>
<td>Resolved infection (most common)</td>
</tr>
<tr>
<td>HBcAb</td>
<td>Positive</td>
<td>False positive HBcAb - susceptible</td>
</tr>
<tr>
<td>IGM antiHBc (HBcAb IG M)</td>
<td>Positive</td>
<td>Low-level chronic infection</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Resolving acute infection</td>
</tr>
</tbody>
</table>

Centers for Disease Control and Prevention (2013)
The following at-risk groups should be tested for HBV:

- People born or brought up in an area of intermediate or high HBV prevalence
- Babies born to HBV-infected mothers
- People who have ever injected drugs
- Men who have sex with men
- Anyone who has had unprotected sex, particularly with multiple sexual partners; people who have had unprotected sex with someone from an area with intermediate or high HBV prevalence; people presenting at sexual health clinics; people diagnosed with a sexually transmitted infection; commercial sex workers
- Looked-after children and young people, including those in care homes
- Prisoners, including young offenders
- Immigration detainees
- Close contacts of someone known to be chronically infected with HBV

**Signs and symptoms of chronic HBV**

People with CHB often do not have symptoms, so those with the disease may have no way of knowing that they are infected. However, some complain of fatigue, aches and pains, fever, loss of appetite, nausea and abdominal pain.

The majority of acute HBV infections are also asymptomatic but around 30% of adults will present with jaundice, fatigue, poor appetite, weight loss, nausea and vomiting, abdominal pain, pyrexia, dark urine and light stools (Aspinall et al, 2011).

**Diagnosis**

HBV is diagnosed with a blood test to detect hepatitis B surface antigen (HBsAg). The different HBV serological markers (Table 3) may be used collectively to determine a person’s HBV status. These are shown in Table 4.

**HBV testing**

Since 2000, all pregnant women have been tested for HBV. The National Institute for Health and Care Excellence (2012) has published a new guideline to promote HBV and hepatitis C virus testing. The guideline recommends that the at-risk groups listed in Box 1 are tested for HBV, and given counselling before and afterwards.

All those who test positive for HBV surface antigen should be referred to a specialist centre within six weeks. Pregnant women should be assessed by a specialist within six weeks of receiving the screening test result so treatment can be offered in the third trimester if necessary (NICE, 2013).

**Vaccination**

HBV is preventable through vaccination; this is generally a course of three injections given over six months, although accelerated courses are available. NICE (2012) and The Green Book (HM Government, 2009) both recommend that high-risk groups are vaccinated against HBV.

**Conclusion**

HBV infection can be prevented through vaccination; this is generally a course of three injections given over six months, although accelerated courses are available. NICE (2012) and The Green Book (HM Government, 2009) both recommend that high-risk groups are vaccinated against HBV.

The future financial implications of CHB to the health service could potentially be huge if action is not taken.

NICE (2012) has produced guidance to promote and offer testing to people at increased risk of HBV infection. The guideline, which has been universally

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**FIG 2. FOUR PHASES OF CHB**

- Fluctuating HBV DNA levels and fluctuating ALT levels

Perillo (2006)

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**BOX 1. WHO TO SCREEN**

The following at-risk groups should be tested for HBV:

- People born or brought up in an area of intermediate or high HBV prevalence
- Babies born to HBV-infected mothers
- People who have ever injected drugs
- Men who have sex with men
- Anyone who has had unprotected sex, particularly with multiple sexual partners; people who have had unprotected sex with someone from an area with intermediate or high HBV prevalence; people presenting at sexual health clinics; people diagnosed with a sexually transmitted infection; commercial sex workers
- Looked-after children and young people, including those in care homes
- Prisoners, including young offenders
- Immigration detainees
- Close contacts of someone known to be chronically infected with HBV

Seroconversion – loss of HBeAg and formation of the antibody to HBeAg (HBeAb) – takes place in 50% of children and adults within five years of entering this phase, and 70% of children and adults by 10 years, resulting in transition to the third phase.

- Inactive carrier phase (immune control): this is an inactive phase of HBeAg negative HBV with low or undetectable HBV DNA levels, a normal ALT and no damage to the liver. Occasional surface antigen loss occurs. Patients in this phase form the largest group with HBV.
- Reactivation phase: this phase can be spontaneous or can be triggered by immunosuppression. Patients can revert to HBeAg positivity but most are HBeAg negative with detectable DNA levels, high ALT and moderate to severe necro-inflammation with variable amounts of fibrosis on liver biopsy (Chen, 2010; Pattovitch et al, 2008; McMahon, 2004). The management of HBV will be discussed in the second part of the series.

**HBV genotypes**

There are 10 HBV geographically distributed genotypes (A-J): B and C in Asia; A, E and D in Africa; and A and D in Western Europe and North America (Kao, 2011).

Genotypes A and B have a more favourable response to treatment with pegylated interferon than other types. Genotypes C and D are associated with more serious disease and HCC (Bonino et al, 2010).
References


Centers for Disease Control and Prevention (2013) Interpretation of Hepatitis B Serological Results. Atlanta: CDCP. tinyurl.com/CDC-HepB-Serological


# KEY TERMS

Alanine aminotransferase (ALT) – an enzyme normally found in low levels in the liver; higher levels can be produced when there is injury to the liver

Antigen – a toxic or other foreign substance within the body that produces an immune response, especially the production of antibodies

Capsid – protein coat or shell of a virus particle

Chronic – disease or illness lasting for longer than six months

Cirrhosis – normal liver tissue being replaced by structurally abnormal nodules due to progressive and severe fibrosis

Cytoplasm – the material within a cell excluding the nucleus

Genome – the complete set of genes in an organism (coded into the DNA in viruses)

Hepatocellular carcinoma – a cancer arising from the liver cells (hepatocytes)

Liver fibrosis – progressive build-up of scar tissue within the liver, caused by the immune system attacking hepatocytes in the case of HBV

Mode of transmission – the route by which an organism is transferred from one host to another

Nucleocapsid – capsid with enclosed nucleic acid

Nucleus – part of the cell containing RNA and DNA, and responsible for growth and production

Prevalence – the total number of cases of a disease in a given population at a specific time

Viron – the complete infectious form of a virus outside a host cell, with a core of RNA or DNA with within a capsid

Mark and David are two year old twin boys and they are looking for their forever family.

Their foster carer describes them as a ‘delight to care for and easy to fall in love with.’

The boys enjoy playing with their toys, especially musical ones, and trips to the local park and a local toddler group where they play with other children.

Mark is an affectionate, cheerful little boy. His verbal and physical development is slow compared to other children of his age, as a result of his early life experiences. However, he is thriving with his foster carer compared to other children of his age, as a result of his early life experiences. He is walking

and is keen to explore.

If you want to find out more about them call Adoption in Somerset on 0800 587 9900 or email childrens@somerset.gov.uk