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Despite its growing prevalence, hepatitis B is often undiagnosed. This article discusses its spread, life cycle and prevention, and groups at high risk of infection

CHRONIC HEPATITIS B: PART 1 OF 2

Hepatitis B: prevalence and pathophysiology

In this article...

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Chronic hepatitis B is a growing worldwide public health issue. Its prevalence and the mode of transmission of the virus varies greatly between parts of the world. Prevalence is rising in the UK due to an increase in migration from areas with a high prevalence of chronic hepatitis B.

This article, the first of a two-part series, discusses the prevalence and pathophysiology of chronic hepatitis B, as well as recommendations for screening high-risk groups and immunisation against the disease. Part two discusses the management of the virus.

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

"Mistakes happen – we need to learn from them to improve care"

Alicia Lucas › *p24*

TABLE 1. PREVALENCE OF HEPATITIS B INFECTION

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

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

FIG 1. HEPATITIS B VIRUS

Schematic representation of the hepatitis B virus structure

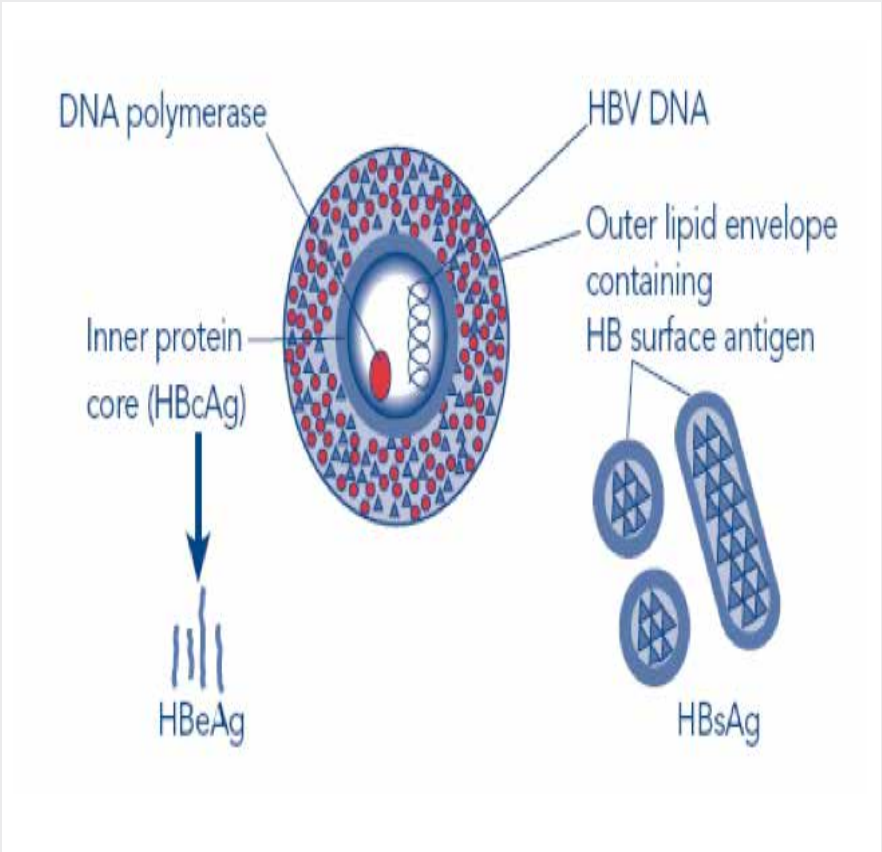


TABLE 2. FACTORS AFFECTING DISEASE PROGRESSION

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

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).

Pathophysiology

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).

Catherine Hollick

TABLE 3. HBV SEROLOGICAL MARKERS

Serological marker	Abbreviation	Indication	Stage at which marker is present in the blood
Hepatitis B surface antigen	HBsAg	Indicates HBV infection	Present 6-10 weeks after exposure to the virus. Persistence of serum HBsAg for six months or more indicates CHB
Hepatitis B surface antibodies	HBsAb or anti-HBs	Recovery from HBV or HBV vaccination	Appears during resolution of the virus (after 4-6 months), guaranteeing lifelong immunity. Also present in those vaccinated against HBV
Hepatitis B core antibody	HBcAb or anti-HBc	Current infection or previous exposure to the virus	
IgM antibody to core antigen	IgM anti-HBc (HBcAb IgM)	Acute infection	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
Hepatitis B e antigen	HBeAg		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
Hepatitis B virus DNA	HBV DNA		Represents the direct product and hallmark of viral replication and is a reliable indicator of active infection

Bonino et al (2010); Valsamakis (2007); Hatzakis et al (2006)

TABLE 4. SEROLOGICAL PROFILE AND HBV STATUS

Serological profile	Results	Indication
HBsAg HBsAb HBcAb	Negative Negative Negative	Susceptible – vaccinate
HBsAg HBsAb HBcAb	Negative Positive Negative	Vaccinated
HBsAg HBsAb HBcAb	Negative Positive Positive	Previous exposure to the virus, immune
HBsAg HBsAb HBcAb IGM antiHBc (HBcAb IGM)	Positive Negative Positive Negative	Chronically infected
HBsAg HBsAb HBcAb IGM antiHBc (HBcAb IGM)	Positive Negative Positive Positive	Acute infection
HBsAg HBsAb HBcAb	Negative Negative Positive	Four possibilities: Resolved infection (most common) False positive HBcAb – susceptible Low-level chronic infection Resolving acute infection

Centers for Disease Control and Prevention (2013)

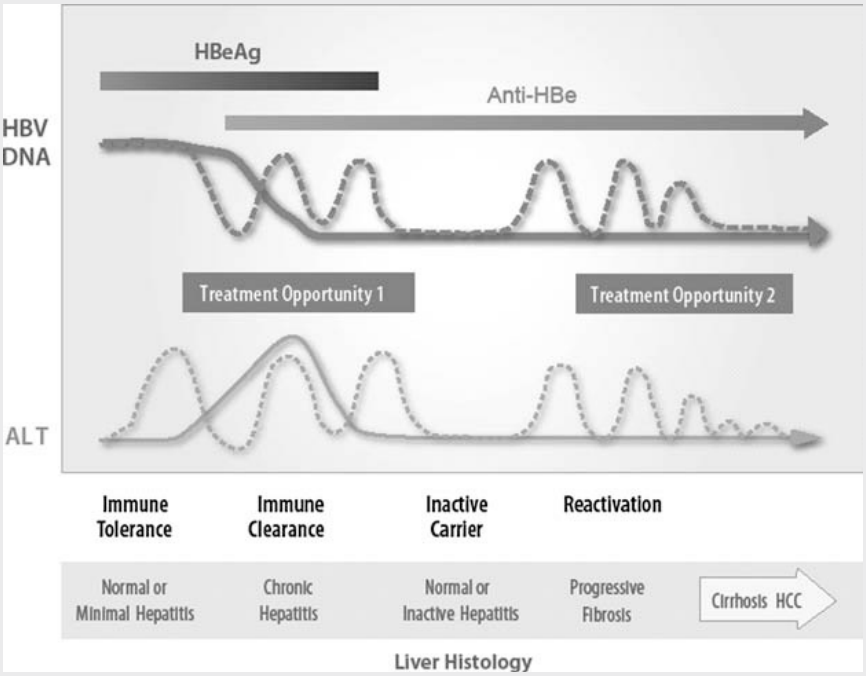
The four stages of CHB

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

FIG 2. **FOUR PHASES OF CHB**



---------- Fluctuating HBV DNA levels and fluctuating ALT levels
Perillo (2006)

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; Fattovitch 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).

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, but CHB remains an international issue and an increasing problem in the UK due to a lack of awareness and the asymptomatic nature of the disease.

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 guidance, which has been universally

welcomed, includes raising awareness measures and educational and training programmes. **NT**

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BOX 2. **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 nodule 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

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