Investigating the patient who has hepatitis B

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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It is not uncommon for GPs to be faced with a patient who has tested positive for hepatitis B virus (HBV) serology. The fundamental rules are:

- positive hepatitis B surface antigen (HBsAg) indicates current HBV infection
- positive hepatitis B antibodies only indicate an absence of current HBV infection (see the flowchart on page 73).

It is the patient who is HBsAg positive (i.e. with HBV infection) who requires investigation so that appropriate management and advice can be given. How we investigate depends upon the clinical scenario. Most patients will fall into one of the following groups:

- patients with acute symptomatic hepatitis
- asymptomatic patients whose HBsAg is an 'incidental' finding, serological tests being performed, for example, as a screen in patients at risk of HBV infection, in patients donating blood at the blood bank, or in those presenting with abnormal liver function tests
- patients with clinically evident, advanced chronic liver disease, presenting, for example, with complications of chronic liver disease such as ascites, confusion or bleeding.

This review does not address the third group; such patients should be referred for specialist management.

The appropriate selection of investigations and their interpretation depend on an understanding of the virus itself, how illness occurs, and the natural history of the infection.

IN SUMMARY

- **Hepatitis B virus (HBV) infection is present when HBsAg is detectable in the serum.**
- **Appropriate investigation of a patient who is HBsAg positive depends on the clinical scenario, and relies upon an understanding of the virus, the serological markers used, how illness occurs, and the natural history of HBV infection.**
- **In acute hepatitis, investigation is directed towards deciding whether the episode is due to HBV or another cause; if HBsAg is detected, whether the episode represents a new infection or a flare of chronic HBV infection needs to be considered.**
- **Investigation in the more common scenario of chronic infection in an asymptomatic person is directed mainly towards defining the stage in the natural history of HBV infection and the state of the liver.**
- **In chronic infection, active liver disease (abnormal ALT) and viral replication (positive HBeAg or HBV DNA) identifies patients who are at increased risk of liver injury but may respond well to antiviral therapy.**
- **Specialist referral is important when active liver disease is present, irrespective of the state of viral replication, and when cirrhosis or hepatic decompensation is evident.**

HBV and its many parts

HBV belongs to the family of Hapadnaviridae. It is a partially double-stranded, circular DNA virus that consists of two parts: an envelope and a nucleocapsid core.

Envelope

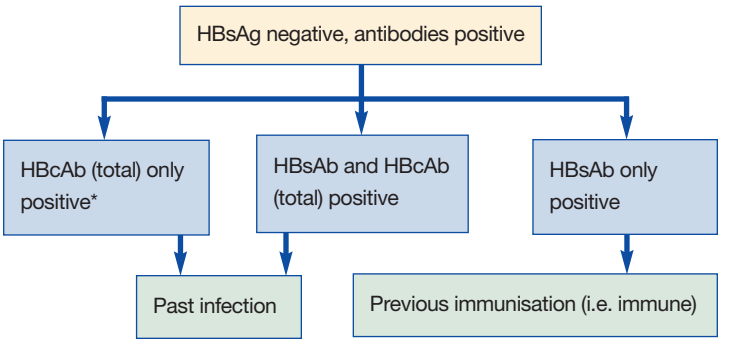
The envelope contains surface antigen (HBsAg). When HBV is present in the liver, HBsAg is produced in excess and released into the circulation, thus providing a useful marker for serological detection of HBV infection. As noted above, a positive result indicates current HBV infection, a negative result no active infection. Antibodies to surface antigen (HBsAb) bind to the external surface of the virus and prevent infection by HBV, thus conferring protective immunity. HBsAb can also be induced by HBV vaccination.

Nucleocapsid core

The nucleocapsid core contains the viral genome and polymerase protein, and is surrounded by a protein coat comprising core antigen (HBcAg). The following antigens are found in, or associated with, the nucleocapsid core:

- **HBcAg** is expressed on the surface of infected liver cells with actively replicating virus. It is not secreted into the circulation and is never found in the serum. HBcAg is very immunogenic and antibodies are readily produced to it (called HBcAb). HBcAb persists even after the infection has resolved. Thus, HBcAb can be used as a marker of exposure to HBV. It has no role in eradicating the virus and does not confer protection against HBV.
- **HBeAg** is a soluble protein that is expressed during viral replication, secreted into the circulation and readily detectable. It indicates active viral replication and infectivity. HBeAg is also immunogenic; the antibody to eAg (HBeAb) has no protective role. The presence of HBeAb is used clinically to indicate the loss of HBeAg (so-called 'eAg seroconversion').
- **HBV DNA** is readily measured in the serum and is the best indicator of active viral replication. Its quantification indicates the amount of virus present (i.e. the 'viral load'). HBV DNA can be detected by two methods. The first is hydridisation. A positive result (i.e. 'detected') indicates that there is clinically significant viral replication occurring. The second method is the polymerase chain reaction (PCR), which is ultrasensitive. It can be positive even when clinically we consider active viral replication not to be occurring. The hybridisation test is the appropriate clinical test, PCR being used for more esoteric reasons by hepatologists and virologists. Most patients with positive HBeAg will have detectable HBV DNA. The main clinical role of HBV DNA in the management of patients with chronic infection is in its use by the hepatologist to predict response to interferon therapy and to monitor response to antiviral therapy.

Interpretation of serology results: when hepatitis B antibodies only are positive



* When HBcAb only is positive this represents resolved infection in most patients. In rare cases, current infection may be present, with the levels of HBsAg being below the detectable range; further serological investigation will be necessary, especially if the alanine aminotransferase level is abnormal.

Mutations in HBV

Like most viruses, mutations occur in association with chronic infection. Some mutations might be responsible for changes in immune response (e.g. a change from immune tolerance to the development of liver injury). Of clinical significance is disease caused by 'HBeAg-negative mutants'. This is characterised by the absence of 'eAg' production in the presence of ongoing active viral replication and liver inflammation. This condition is more prevalent in Mediterranean countries and Asia.

The significance for serological assessment is that HBeAg will be negative and HBeAb positive even though active viral replication is occurring. HBV DNA will readily detect the presence of HBeAg-negative mutant infection.

How HBV causes liver injury

HBV is not usually a cytotoxic virus. The liver injury is a result of immune-mediated injury. The immune system (especially T cells) targets the HBcAg expressed on infected liver cells with active viral replication, leading to cell death. Thus, there are two major factors that determine whether there is liver injury:

- the presence of actively replicating HBV within liver cells
- an immune system able to generate cytotoxic cells to HBcAg.

The differences in immune responses across patients account for the different clinical outcomes. If there is a high degree of recognition between the immune system and HBV, all liver cells containing replicating HBV will be targeted, acute hepatitis will become clinically evident, and the virus will be destroyed. This situation is usually observed when infection occurs in people with a mature immune system, and helps to explain why more than 95% of adult-acquired HBV infections are cleared.

In the absence of immune recognition to the virus, persistent infection with no liver injury will result; this is referred to as immune tolerance (see below). This situation invariably occurs when neonates, with their immature immune system, are infected. In the presence of immune recognition to HBcAg, but with insufficient ability to clear the virus, persistent infection results with ongoing immune-mediated injury to the liver; this may lead eventually to cirrhosis.

Natural history and clinical outcomes

The natural course of chronic HBV can be considered in stages of immune response, and are readily recognised by simple clinical evaluation. The four stages are identified by serological testing and repeated evaluation of the alanine aminotransferase (ALT) level (see the box below). Defining the stage at which an individual patient lies gives an excellent guide to appropriate management decisions and to counselling regarding infectivity and prognosis.

Immune tolerance

Immune tolerance can persist for 10 to 30 years in patients with perinatally acquired infection, but would rarely be observed in adult-acquired disease where there is a mature immune system. This stage is characterised by active viral replication with the absence of active liver disease. Patients are asymptomatic, have normal liver function tests and minimal changes on liver biopsy.

Replicative (immune clearance) stage

Immune clearance occurs once an immune response develops in an attempt to clear the virus, leading to liver cell injury and subsequent inflammation. This stage corresponds to the period of symptomatic hepatitis in patients with acute hepatitis and typically lasts up to four weeks. In chronic

Serology and staging of chronic HBV infection

	Immune tolerance stage	Immune clearance stage	Nonreplicative 'latent' infection	Resolution stage
Baseline serology				
• HBsAg	Positive	Positive	Positive	Negative
• HBsAb	Negative	Negative	Negative	Positive
• HBcAb	Positive	Positive	Positive	Positive
Liver function				
• ALT	Normal	Elevated	Normal	Normal
Indicators of viral replication				
• HBV DNA	Positive	Positive	Negative†	Negative
• HBeAg	Positive	Positive*	Negative	Negative
• HBeAb	Negative	Negative*	Positive	Positive
	Infectivity			

* Patients with HBeAg-negative mutants will be HBeAg negative and HBeAb positive; HBV DNA will be detectable. †HBV DNA may still be detectable with PCR testing.
ALT = alanine aminotransferase.

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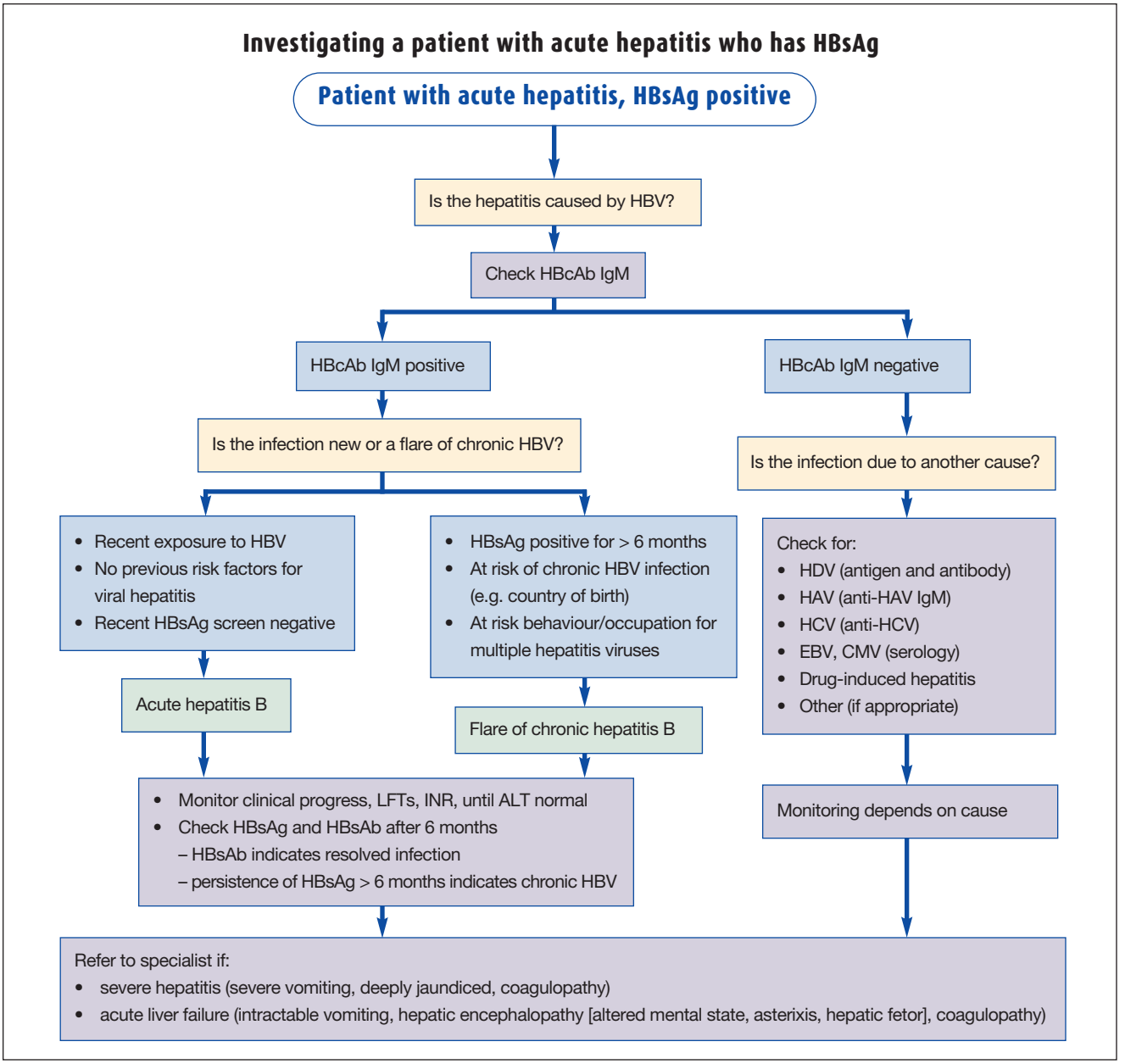


disease, this may persist for decades with cycles of inflammation and repair. Active liver disease is present, flares of elevated ALT occur and HBV DNA may decline as the number of infected cells decline. During this stage the patient is at risk of developing cirrhosis due to prolonged episodes of inflammation. Antiviral therapy is most effective when given in this phase.

Nonreplicative 'latent' infection

If the immune response is sufficient to suppress viral replication, the nonreplicative stage is reached. Remission in liver disease occurs with normalisation of ALT levels and the disappearance of HBeAg. Antibodies to 'e' antigen emerge with 'eAg seroconversion'. HBV DNA is usually absent, but HBsAg is still detectable. Occasionally patients may experience reactivation of their disease (usually in association with marked immune suppression, such as during immunosuppressive therapy or cancer chemotherapy) with detectable viral replication and a flare in their liver function tests, and thus regression to the replicative phase.

Resolution stage

Some patients with chronic HBV infection

Table 1. Interpretation of HBV serological tests

Serological marker	Interpretation
HBsAg	Hallmark of current HBV infection, either acute or chronic (if present for >6 months)
HBsAb	Confers immunity and protection against infection
HBcAg	An intracellular antigen expressed in infected liver cells, not detectable in serum
HBcAb (total)	Indicates exposure to HBV, cannot distinguish between current or past infection
HBcAb IgM	Indicates acute infection but may also be present during flares in chronic disease
HBeAg	Marker of active viral replication and increased risk of infectivity, except in patients with HBeAg-negative mutants, in whom HBeAg is negative but HBV DNA is detectable
HBeAb	Indicates 'e' antigen seroconversion and remission in liver disease. HBV DNA will disappear (except in patients with HBeAg-negative mutants)
HBV DNA	Indicates active viral replication and increased infectivity risk

eventually develop antibodies to HBsAg and clear HBsAg. The annual rate of seroconversion has been estimated at less than 2% per year.

How to investigate HBV infection

A basic understanding of key concepts in pathogenesis is essential to enable the appropriate use and interpretation of serological tests for HBV infection. A summary of the tests and their interpretation is shown in Table 1.

Patient with acute hepatitis

In the investigation of the patient with acute hepatitis, three questions need to be answered.

Is this acute HBV infection?

Acute HBV infection is diagnosed on the detection of HBsAg and HBcAb IgM. Markers of replication are also detectable during the early phase of infection, but testing for this is seldom necessary. Occasionally HBsAg is below the detectable range and HBsAb has yet to appear. This is referred to as the 'window' period. HBcAb IgM will confirm HBV infection. Other causes should also be sought. The differential diagnosis of acute hepatitis in an HBsAg positive patient and the investigative approach is outlined in the flowchart on page 77.

Is this a flare of chronic HBV infection?

In patients from endemic regions and in those who engage in high-risk occupations or activities, there may be a higher index of suspicion of chronic HBV infection. Past medical history may indicate chronic infection with previously detectable HBsAg for over six months. In the patient who is known to have chronic HBV infection, an acute flare could be associated with detectable HBcAb IgM.

How severe is the hepatitis – is referral needed?

Worsening jaundice, intractable vomiting and coagulopathy indicate severe hepatitis; patients with these signs should be referred to a specialist.

Patients with acute hepatitis B should have their ALT level monitored until it normalises. The viral serology should be followed for at least six months, since persistence of HBsAg beyond that time indicates chronic infection.

In the typical patient in whom the hepatitis resolves, serology should be conducted for diagnosis (as above), and HBsAg and HBsAb checked after six months. There is no need to perform tests for HBV DNA, HBeAg or HBeAb unless HBsAg persists.

Chronic infection in an asymptomatic patient

There are four major questions that need to be addressed when investigating the asymptomatic patient with chronic infection.

Is this really chronic infection?

As mentioned above, chronic HBV infection is confirmed by the demonstration of HBsAg over a six-month period.

At what stage is the HBV infection?

The stage of the HBV infection in a particular patient can be determined by looking at the ALT level and serological markers for viral replication (HBeAg and HBV DNA). Since liver function tests may fluctuate over time, ALT is considered normal when it has been persistently normal on three occasions over three to six months.

The clinical significance of staging chronic HBV infection is to enable the institution of appropriate management and counselling, as shown in the flowchart on page 81. It is of particular importance to identify patients in the replicative stage, since they are at risk of serious ongoing liver injury and thus may be eligible for antiviral therapy. These patients should be referred for specialist assessment and management.

What is the state of the liver?

Clues that there may already be serious liver injury (namely cirrhosis) should be sought. Clinical examination may reveal signs of chronic liver disease and/or decompensation. However, since peripheral manifestations of cirrhosis appear late in the course of HBV-induced cirrhosis compared with alcoholic liver disease, most patients with cirrhosis will not have such signs.

Blood tests offer important clues. A low serum albumin and/or prolonged prothrombin time or INR indicates reduced hepatic synthetic function. A reduced platelet count may result from hypersplenism. A raised alpha fetoprotein (AFP) level is highly suggestive of a hepatoma, necessitating further investigation with a triple phase CT scan.

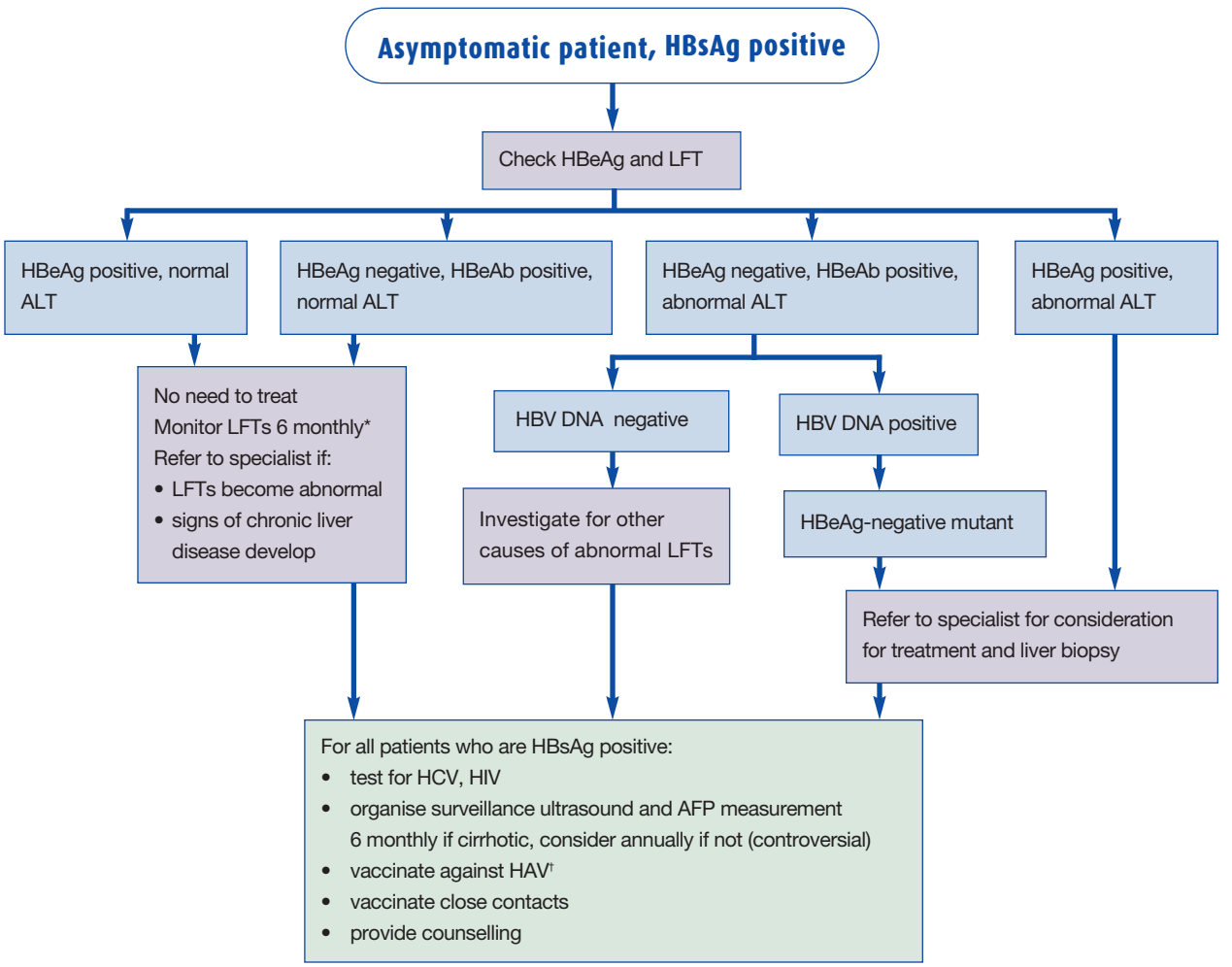
Liver ultrasound with Doppler examination may reveal an irregular liver contour, signs of portal hypertension, or a complicating hepatoma.

The above signs are good predictors of the presence of cirrhosis, but a normal examination does not exclude this condition. Any features suggestive of cirrhosis should prompt specialist referral, irrespective of the liver function tests and viral serology.

Are there any other risk factors for liver disease?

Evidence of other factors that might be associated with liver disease usually

Investigation of a patient with chronic hepatitis B



* Patients positive for HBsAg with negative HBeAg and persistently normal ALT are at lower risk of long term complications and require only periodic monitoring 6 to 12 monthly.
† It is reasonable to vaccinate empirically against HAV without first performing HAV serology. LFT = liver function test; ALT = alanine aminotransferase; AFP = alpha fetoprotein; HCV = hepatitis C virus; HAV = hepatitis A virus.

Table 2. When to refer patients with chronic HBV infection

- Abnormal ALT level (irrespective of state of viral replication)
- Features suggestive of cirrhosis (clinical signs, low albumin, coagulopathy, low platelet count, suggestive ultrasound findings)
- Hepatic decompensation (jaundice, ascites, peripheral oedema, confusion)
- Interpretation of results, staging or prognosis unclear
- Anxious patient in need of further reassurance

Table 3. Chronic HBV infection: pre-referral investigations

- Three sets of liver function tests over 3 – 6 months
- HBV serology (HBsAg, HBsAb, HBeAg, HBeAb)
- HAV serology
- HCV serology
- Full blood examination, prothrombin time/INR, urea and electrolytes
- Alpha fetoprotein level
- Liver ultrasound

Table 4. Chronic HBV infection: monitoring and referral triggers

Assessment method	Frequency	Trigger for referral
Physical examination for signs of chronic liver disease or decompensation	3 – 6 monthly*	Appearance of new signs
Liver function tests	3 – 6 monthly*	Abnormal ALT (especially if on >1 occasion)
Full blood examination, prothrombin time/INR	6 monthly	Thrombocytopenia or coagulopathy
Alpha fetoprotein level	6 monthly	Abnormal/increasing values
Liver ultrasound (triple phase CT scan if patient is obese)	Patients with cirrhosis 6 monthly; patients without cirrhosis 12 monthly†	Suspicious space-occupying lesion

* Patients positive for HBsAg with HBeAg and persistently normal ALT are at a lower risk of long term complications and require only periodic monitoring 6 to 12 monthly.
† Surveillance in patients without cirrhosis is controversial.

prompt a more aggressive approach to investigation and management of the patient, especially if the ALT is abnormal in the absence of viral replication, or features suggestive of cirrhosis are noted. Family history and alcohol intake are important factors.

Other issues require laboratory investigations and these are best conducted by specialists; however, it is recommended that patients have hepatitis C serology checked before referral.

The role of the specialist in investigation

Situations that should prompt referral to a specialist have been outlined above and, for chronic HBV infection, are summarised in Table 2. To enable efficient assessment by the specialist, it is desirable that a minimum of investigation be carried out before referral. Table 3 summarises investigations recommended before referral.

Further monitoring

All patients with chronic HBV infection require ongoing surveillance irrespective of the degree of liver disease or whether they are on antiviral therapy. Suggested regimens for those not undergoing evaluation for therapy and for those without serious liver disease are shown in Table 4. It is reasonable and appropriate for these monitoring schedules to be applied by the GP, provided that the trigger points for further investigation or referral are understood. MT

Further information

1. Dore G, Grulich A, Kidd M, et al (eds). HIV/Viral hepatitis: a guide for primary care. Sydney: Australasian Society for HIV Medicine (ASHM), 2001 (available via ASHM website: www.ashm.org.au).
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