

CLINICAL UPDATE

A Guide to Management for Health Professionals

Chronic Hepatitis B

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Digestive Health Foundation

The Digestive Health Foundation (DHF) is an educational body committed to promoting better health for all Australians by promoting education and community health programs related to the digestive system.

The DHF is the educational arm of the Gastroenterological Society of Australia, the professional body representing the specialty of gastrointestinal and liver disease in Australia. Members of the Society are drawn from physicians, surgeons, scientists and other medical specialties with an interest in GI disorders.

Since its establishment in 1990 the DHF has been involved in the development of programs to improve community awareness and the understanding of digestive diseases.

Research and education into gastrointestinal disease are essential to contain the effects of these disorders on all Australians.

Guidelines for General Practitioners and patient leaflets are available on a range of topics related to GI disorders. Copies are available by contacting the Secretariat at the address below.

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IMPORTANCE OF CHRONIC HEPATITIS B

Chronic hepatitis B is an important preventable cause of cirrhosis and liver failure. It is estimated that 90-160,000 people in Australia have chronic hepatitis B. HBV-related hepatocellular carcinoma (HCC) is rising in frequency and is the third most common cause of cancer death in the Asia-Pacific region. Hepatitis B vaccination is the most important strategy to prevent chronic hepatitis B.

With the introduction of potent HBV antivirals, treatment of HBV is entering a new era. Orally administered drugs such as adefovir, entecavir, tenofovir, telbivudine and clevudine have equal or better antiviral efficacy to lamivudine and significantly lower rates of antiviral drug resistance. Furthermore, several of these agents are effective against lamivudine-resistant HBV. Pegylated-interferon (peginterferon) has been shown to be superior to conventional interferon for obtaining sustained viral suppression, without drug resistance.

NATURAL HISTORY OF CHRONIC HEPATITIS B

HBV is a member of the hepadnavirus family, a family of hepatitis-causing DNA viruses, which use a RNA-dependent reverse transcriptase step in the replicative cycle.

Most patients with chronic hepatitis B contracted the infection in the first 3 years of life from maternal transmission or from intimate personal contact with an infected person in early childhood.

The natural history of infection acquired early in life appears to correspond to four distinct phases: immune tolerance, immune clearance, immune control and immune escape.

Phase 1: Early childhood infection is associated with a prolonged period of immune tolerance to HBV. During this phase, HBV replicates actively so that levels of circulating HBV-DNA are very high, but serum alanine aminotransferase (ALT) levels remain normal.

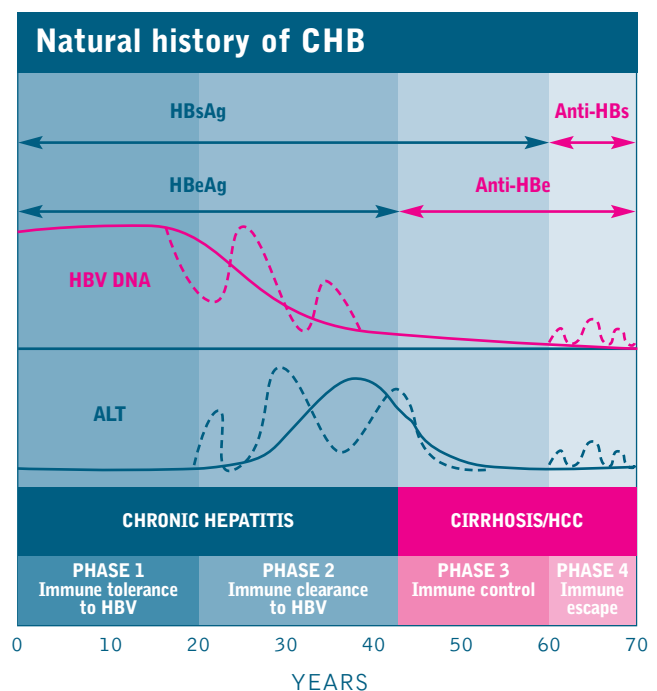
Phase 2: The most common outcome of early childhood infection is that immune tolerance wanes between the second and fourth decades

of life, resulting in the emergence of immune-mediated hepatitis flares (immune clearance). Some people however remain HBeAg positive long-term and have ongoing high-level viral replication. These individuals are at significant risk of progressive fibrosis, cirrhosis, liver failure and HCC.

Phase 3: The most favourable outcome is loss of hepatitis B e antigen and gain of hepatitis B e antibody (HBeAg to anti-HBe seroconversion) with significant reduction or disappearance of HBV-DNA from the blood (immune control). HBeAg seroconversion occurs in roughly two-thirds of individuals with chronic HBV, most often in the second or third decades of life.

Phase 4: In some patients, viral replication either persists or returns, leading to immune-mediated hepatocellular injury and fibrosis (immune escape). In the majority of these patients, immune pressure results in the emergence of a mutant virus that continues to replicate but does not produce hepatitis B e antigen (HBeAg negative or 'precore mutant' infection). Ongoing hepatitis activity may result in progressive fibrosis and cirrhosis, eventually leading to liver failure or HCC.

It has become clear that there is a threshold of HBV viral load at which liver disease occurs. It is currently thought that HBV-DNA levels over 10,000 copies/mL (2,000 IU/mL) are associated with progression of liver disease, particularly during phase 2 and 4.



Thus, *all HBsAg positive patients, regardless of HBeAg status and serum ALT levels should be assessed for viraemia and liver injury on a regular basis and be under regular specialist review.* The concept of the 'healthy carrier' is no longer supported, as all HBsAg positive patients are at risk for complications of liver disease. In all HBsAg positive patients, decisions regarding appropriate antiviral therapy will change over time and should be made in the context of the natural history of the disease.

CHRONIC HBV INFECTION AND LIVER CANCER

Viral, host genetic and environmental factors are all important in hepatocarcinogenesis. However, the risk of HCC is greatest in the setting of cirrhosis (80% of cases) and active liver disease and viral replication.

Recent cross-sectional data from a large community-based cohort in Taiwan, suggested a link between serum HBV-DNA levels and progression of liver disease and development of HCC. The therapeutic implications of these data are that cirrhosis and HCC risk may be reduced by effective antiviral therapy.

SEROLOGICAL TESTS IN HEPATITIS B

HBV has three major antigens, each of which induces an immune response. An appreciation of these responses is useful for the interpretation of serological data, for differentiating between acute and chronic infections, and for assessing which phase of infection a patient is in.

Hepatitis B surface antigen (HBsAg)

Serum HBsAg is excess viral coat material manufactured by HBV-infected hepatocyte, that passes into the blood. The presence of HBsAg in serum indicates either acute or chronic hepatitis B however HBsAg disappears from serum within months of resolution of acute hepatitis B. In a small proportion of individuals with chronic hepatitis B, HBsAg will become undetectable over time.

Hepatitis B surface antibody (anti-HBs)

Anti-HBs appears in serum following clearance of HBsAg. The presence of anti-HBs is an indication of immunity to HBV either following clearance of infection or after vaccination.

Hepatitis B core antigen (HBcAg)

This antigen is a component of the protein coat which surrounds the nucleic acid of the virus. Free HBcAg is usually confined to the liver and does not circulate in the blood.

Hepatitis B core antibody (anti-HBc)

IgM core antibody (anti-HBc IgM) is detectable in serum within several weeks of an acute infection, but only last 10 months. Thus its presence almost always indicates recent (acute) infection. IgG core antibody (anti-HBc IgG) also rises within several weeks of an acute infection and then persists indefinitely. Its presence indicates acute, previous or chronic HBV infection. It is not present in individuals with immunity following vaccination.

Hepatitis B e antigen (HBeAg)

HBeAg tends to mirror the presence of DNA polymerase, the replicative enzyme of HBV. Its presence in serum indicates active replication of HBV and is usually associated with high level viraemia. In the natural history of chronic hepatitis B, it is common for HBeAg levels to become undetectable over time. In some individuals however, the virus mutates and active viral replication continues in the absence of HBeAg (HBeAg negative or 'precore mutant' disease).

Hepatitis B e antibody (anti-HBe)

Anti-HBe develops during and after clearance of HBeAg. Seroconversion from HBeAg to anti-HBe is usually associated with loss or marked reduction in viral replication.

HBV-DNA level

Testing for the serum level HBV-DNA is available through many private and hospital laboratories. A number of HBV-DNA assays are available and there is considerable variability in the lower limit of quantitation ranging from 100 to 100,000 copies/mL (20 to 20,000 IU/mL). Increasingly HBV-DNA quantitative PCR assays are available, which are able to detect to very low levels of circulating virus. The serum HBV-DNA level is useful in assessing viral replicative status in infected individuals and in predicting and monitoring response to therapy.

PRINCIPLES OF MANAGEMENT OF CHRONIC HEPATITIS B

Management of patients with chronic hepatitis B includes prevention of HBV transmission (vaccination of sexual and household contacts), prevention and management of co-morbidities (excessive alcohol, obesity, type 2 diabetes, metabolic syndrome), and consideration of antiviral therapy. Appropriate measures should be taken to prevent hepatitis A (HAV vaccination) and hepatitis C and D virus co-infections (usually prevention of percutaneous exposure).

Vaccination of contacts

All close contacts, such as family members and sexual partners, should be tested for HBsAg and anti-HBc, and if negative for both should receive a course of three vaccinations. If a sexual partner is unlikely to have prior exposure to hepatitis B, the vaccine can be administered without testing. Following vaccination, it is useful to check for the development of anti-HBs as some people do not develop anti-HBs despite adequate vaccination. These individuals should be given a booster vaccination, although some will still fail to develop anti-HBs in their blood. Studies of health care workers suggest that these individuals are probably protected against contracting HBV, as it is probably the cellular arm of the immune system that is important in protection against infection.

All newborns are now routinely given hepatitis B vaccination, however babies born to HBsAg positive mothers must also be given passive immunisation with Hepatitis B Immunoglobulin (HBIG).

Goals of antiviral therapy

Effective viral suppression results in a reduction in necroinflammatory activity, which decreases fibrosis, and the risk of HCC and other complications of cirrhosis. Antiviral treatment is also extremely effective in preventing reactivation of hepatitis B after cancer chemotherapy or organ transplantation, a situation that can lead to fatal hepatitis B flares in the absence of antiviral prophylaxis. Unlike chronic HCV infection, it is rarely possible to permanently eliminate chronic HBV infection with antiviral therapy.

Key point:

The key objective of antiviral therapy is long-term or permanent suppression of viral replication.

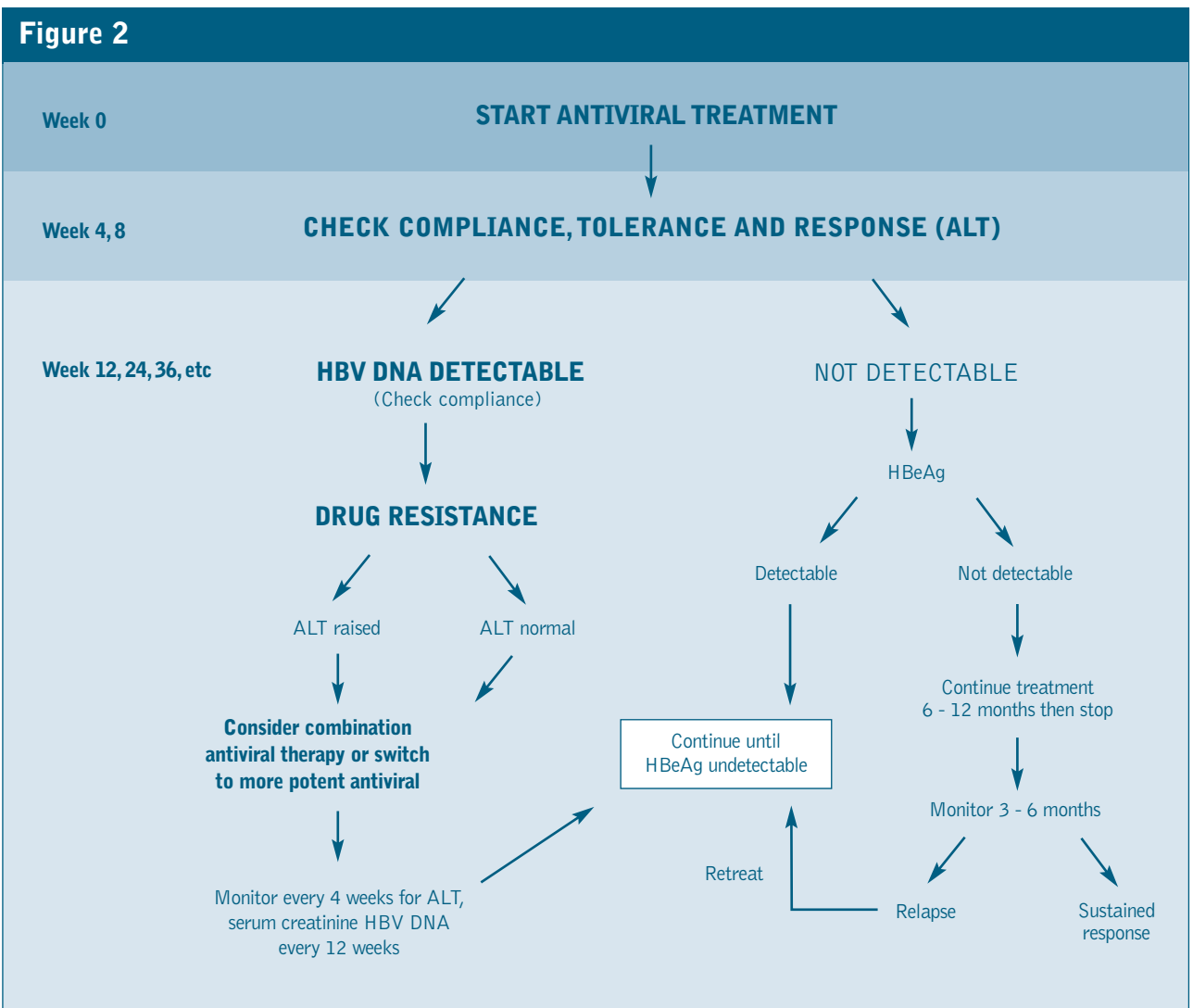
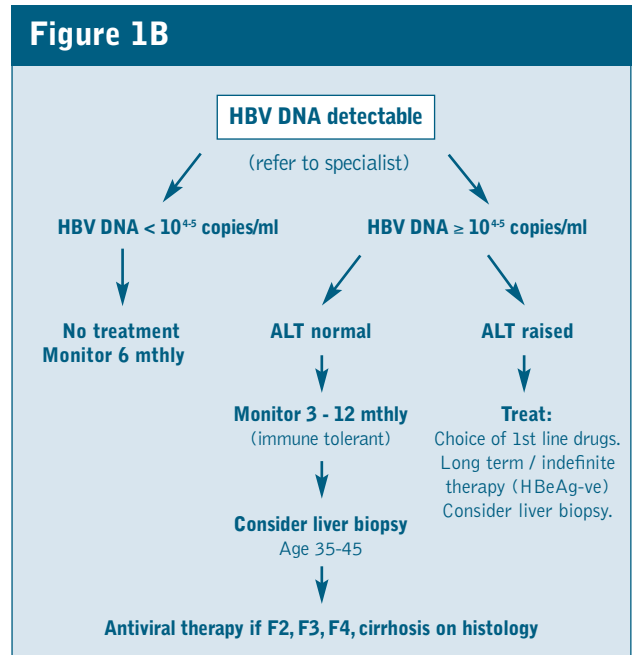
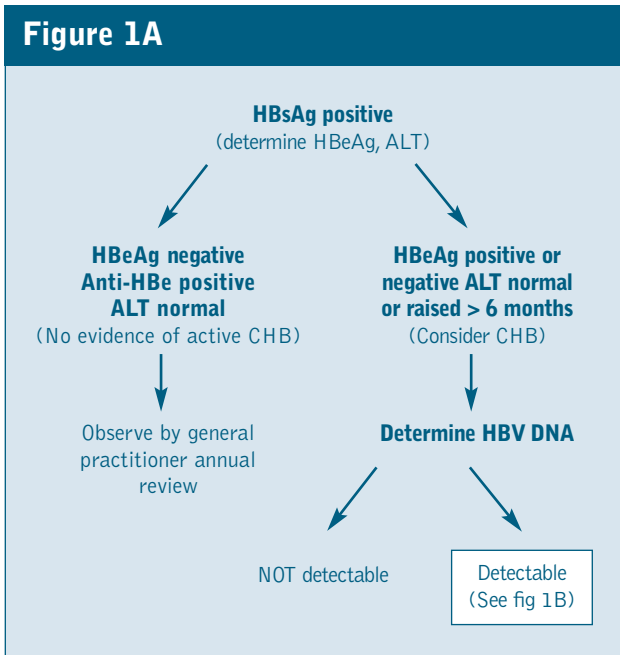
HBeAg seroconversion serves as a useful marker of sustained HBV suppression in HBeAg positive disease, and is therefore considered to be a desired endpoint of antiviral therapy. Loss of HBsAg occurs rarely, but is generally assumed to indicate a more complete state of HBV elimination.

Treatment choices

Two general categories of agents are used in the treatment of chronic hepatitis B: immunomodulatory drugs such as interferon; and direct antivirals (nucleoside and nucleotide analogues). Pegylated interferon is now registered and reimbursed for chronic hepatitis B, and has improved efficacy and ease of administration over regular interferon. Lamivudine is the prototypical HBV antiviral drug, and has advantages over interferon in terms of patient acceptability, safety and cost, however, the emergence of drug resistance is an important issue. Newer drugs available in Australia and much of the world for treatment of chronic hepatitis B include adefovir dipivoxil and entecavir. Other effective drugs in advanced stages of clinical trials include telbivudine (licensed in USA and Australia) and tenofovir (licensed for use in HIV).

Case selection for antiviral therapy

Appropriate selection of patients with chronic hepatitis B for antiviral therapy is evolving. Currently, only patients with elevated serum ALT, and histological evidence of chronic hepatitis on liver biopsy are eligible for reimbursed therapy (Section 100) in Australia (Figure 1). Patients with severe fibrosis or cirrhosis benefit from antiviral therapy at a lower HBV-DNA level and despite a normal ALT level, and should be treated. In an individual patient, the decision to treat should take into account the age of the patient, the severity of the liver disease and whether the person has HBeAg-positive or HBeAg-negative infection (Figure 1A). Detailed treatment guidelines have been issued by regional liver associations and are also available from GESA (www.gesa.org.au).¹⁻⁴



Patients with higher ALT levels, >5 x the upper limit of normal (ULN), respond the best to antiviral therapy and are also those most likely to achieve a spontaneous seroconversion. Therefore, particularly in an adolescent or young adult, it is not unreasonable to wait and observe, rather than automatically commence antiviral therapy. Liver tests should be monitored at 3 monthly intervals and if hepatitis activity continues, and HBeAg seroconversion fails to occur, then treatment can be introduced. In older HBeAg-positive patients and those with HBeAg-negative disease, liver biopsy should be performed early to assess severity of liver disease (Figure 1B) and guide treatment decisions. It is generally recommended not to start a patient with mild liver disease on lamivudine, because of concerns about emergence of lamivudine resistance (70% by 4 years). Newer antiviral agents however have very low rates of resistance in the first few years of treatment, and recommendations may change in the future.

There are particular advantages and disadvantages to be considered when choosing between peginterferon and oral antiviral agents in the treatment of chronic hepatitis B. The specific choice about therapeutic agent should be made only after discussion with the patient. Cirrhotic patients should not be given interferon therapy due to the potential to cause flares of hepatitis. Long-term oral antiviral therapy is strongly recommended in patients with cirrhosis as there are significant benefits including reduced progression to liver failure and hepatocellular carcinoma.

Monitoring disease progression and treatment response

Patients with chronic hepatitis B require regular monitoring for disease activity and progression. Monitoring of LFTs should occur 3-6 monthly and HBeAg/anti-HBe should be checked 6-12 monthly in HBeAg positive patients. HBV-DNA testing on an annual basis is recommended in untreated patients, if unavailable. If available, monitoring should include HBV-DNA levels to identify emergence of antiviral drug resistance.

During antiviral therapy, patients should initially be seen every month for clinical assessment and to enhance

compliance (Figure 2). Three monthly visits are usually appropriate for stable patients.

All HBsAg patients with F3 fibrosis or cirrhosis should be offered screening for HCC with 6 monthly liver ultrasound and alpha-fetoprotein level.

ANTIVIRAL DRUGS USED IN TREATMENT OF CHRONIC HEPATITIS B

DIRECT ANTIVIRAL DRUGS

All HBV antivirals are nucleoside or nucleotide analogues that selectively target the viral RNA-dependent DNA polymerase (reverse transcriptase).

Lamivudine

Lamivudine (dideoxy-3-thiacytidine, 3-TC) was released worldwide as the first oral HBV antiviral in 1996. In Australia, lamivudine 100mg/day is available as a PBS Section 100 drug for use in biopsy-proven, HBeAg-positive or HBeAg-negative chronic hepatitis B. The advantages include oral availability and high patient acceptability, rapid onset of antiviral efficacy, early control of hepatitis (fall of ALT) and substantial improvement in liver histology. The disadvantages are relatively low rates of post-treatment sustained response so that prolonged therapy is required for the majority of cases, and a high rate of drug resistance over time (70% in 4 years). Fortunately, newer drugs (adefovir, entecavir and tenofovir) are effective against lamivudine-resistant HBV. Despite extensive experience, there are few recorded serious adverse effects with lamivudine. Because of its renal clearance, the dose of lamivudine needs to be adjusted in those with impaired renal function. There are no important drug-drug interactions.

Adefovir dipivoxil

Adefovir dipivoxil (adefovir) acts at a different site in the viral reverse transcriptase, and is effective both in treatment-naïve patients and in those with lamivudine-resistant hepatitis B. It is reimbursed in Australia only for patients with lamivudine-resistant HBV. Adefovir is nephrotoxic at high doses (125-250 mg/day) and a dose of 10mg daily is recommended. The effects of adefovir on serum HBV-DNA, ALT and liver histology are broadly similar to lamivudine. Longterm combined lamivudine and adefovir is effective in patients with

lamivudine-resistance and so far is not associated with development of lamivudine-resistance.

Entecavir

This deoxyguanosine analogue is a highly potent and selective inhibitor of the HBV polymerase.

It exhibits superior antiviral efficacy to lamivudine and is well tolerated. Resistance is uncommon at 3 years of therapy, but is more likely in lamivudine-resistant HBV. Entecavir is reimbursed in Australia for treatment of both treatment-naïve and lamivudine-resistant hepatitis B.

NEWER HBV ANTIVIRALS

Telbivudine

This thymidine analogue (L-deoxythymidine, LdT) exhibits high potency as an HBV antiviral *in vivo*, and is specific for the HBV polymerase. It is very effective in suppressing HBV-DNA in both HBeAg positive and negative hepatitis B and has recently been approved in Australia.

Tenofovir

Tenofovir disoproxil fumarate (tenofovir), a nucleotide analogue similar in structure to adefovir, was initially developed for treatment of HIV infection. It has potent antiviral activity against HBV. Because it is less toxic than adefovir, it can be used at a more effective antiviral dose. Clinical trials of tenofovir are underway in treatment-naïve and drug-resistant HBV.

IMMUNE MODULATORS

Peginterferon

Peginterferon monotherapy is given as weekly subcutaneous injections for 48 weeks, and can be used in both HBeAg-positive and HBeAg-negative hepatitis B. It is associated with significant side effects including flu-like symptoms, mood changes, lethargy and cytopenias although the frequency and severity of side-effects appear to be less than in HCV treatment. A proportion of patients (over 40%) will develop sustained viral suppression after 48 weeks of therapy with the advantage that long-term therapy is avoided.

TREATMENT OF CHRONIC HBV INFECTION IN SPECIAL CONTEXTS

Cancer Chemotherapy and Organ Transplantation

Reactivation of hepatitis B virus infection is a well-recognised complication of cancer chemotherapy and immunosuppressive therapy, with significant liver related morbidity and mortality. Strong data support the use of prophylactic lamivudine therapy to prevent potentially fatal liver complications. It is recommended that all patients undergoing such therapies be screened for HBsAg and anti-HBc, and that all HBsAg positive patients, regardless of HBeAg and HBV-DNA status, be treated with lamivudine. The duration of lamivudine therapy should be individualised but should be for at least 12 months following completion of chemotherapy.

Children

There are relatively few data on treatment of chronic hepatitis B in children, in whom the disease is generally (but not always) mild. Typically, children have very high levels of HBV-DNA and normal ALT levels, with mild histological activity. Assessment and follow-up by a paediatric hepatologist is recommended.

Pregnancy

The standard management of pregnancy in a HBsAg positive woman is to administer hepatitis B immunoglobulin and hepatitis B vaccination to the infant at birth. It is recognised, however, that women with very high levels of viraemia may occasionally transmit infection to their baby despite such a strategy. No firm recommendation has been made on the use of nucleoside analogues in the prevention of transmission due to lack of sufficient data and conflicting results with respect to efficacy and adverse events. Lamivudine has the strongest track record however, and appears safe when used in the third trimester of pregnancy. It appears safe for women with chronic hepatitis B who become pregnant whilst on lamivudine therapy to continue treatment, although there are insufficient safety data with the newer antiviral drugs.

CONCLUSIONS AND PRACTICE POINTS

1. Age, disease activity (ALT level), viral status (HBeAg-positivity or negativity, HBV-DNA levels) and disease severity (fibrosis stage, cirrhosis) influence treatment decisions.
2. There is a threshold of HBV replication, as reflected by the HBV-DNA level, for liver disease progression. Levels of HBV-DNA greater than 10,000 copies/mL (2,000 IU/mL) appear to be associated with progression of chronic hepatitis B to cirrhosis and HCC.
3. Long-term suppression of HBV replication leads to reversal of hepatic fibrosis, prevention of cirrhosis, and, when cirrhosis is established, improvement in liver function, prevention of hepatic decompensation and reduction in the risk of liver cancer.
4. There are now a number of therapies available for the treatment of chronic hepatitis B. Clinicians should consider efficacy, safety, tolerability, cost and the likelihood of drug resistance when making treatment decisions.
5. Before embarking on cancer chemotherapy or organ transplantation in patients with chronic HBV infection, prophylactic antiviral therapy to prevent hepatitis flares is essential.
6. Treatment guidelines for both HBeAg-positive and HBeAg-negative chronic hepatitis B will evolve over the next 3 years with more widespread experience and availability of these agents. However, until effective synergistic combinations are developed, careful viral monitoring in patients on therapy is needed to ensure viral suppression.

INTERNATIONAL CONSENSUS STATEMENTS

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This third edition has been prepared by the Digestive Health Foundation, of the Gastroenterological Society of Australia. Every care has been taken in its compilation. The booklet is intended to be used as a guide only and not as an authoritative statement of every conceivable step or circumstance which may or could relate to the management of hepatitis B.

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Information leaflets on hepatitis B for patients and the general public are available through the Digestive Health Foundation, 145 Macquarie Street, Sydney, NSW, 2000.

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