



MINISTRY OF HEALTH
SINGAPORE

Chronic Hepatitis B Infection

MOH Clinical Practice Guidelines 2/2011



Academy of Medicine,
Singapore



College of Family Physicians,
Singapore



Singapore Medical
Association



Gastroenterological
Society of Singapore



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Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1+ +	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2+ +	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2+ +, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ +
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

CLINICAL PRACTICE GUIDELINES

Chronic Hepatitis B Infection

MOH Clinical Practice Guidelines 2/2011

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

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Foreword

Hepatitis B virus and its chronic sequelae (e.g. liver failure, hepatocellular carcinoma) remain major world-wide health problems. The national hepatitis B prevention and control programme in Singapore has been largely successful, as shown by the decline in hepatitis B virus carrier rate and sustained decline in liver cancer incidence. However, the hepatitis B virus is endemic in Singapore, and a large proportion (58%) of the Singaporean population remains susceptible to hepatitis B virus infection.¹

The first edition of the MOH clinical practice guidelines on chronic hepatitis B infection was published in 2003 to provide guidance on the prevention, management and treatment of chronic hepatitis B infection.

This second edition of the guidelines updates as well as expands upon the first edition. For example, the section on surveillance for exacerbation of hepatitis B has been updated to provide more detailed guidance and a discussion on the management of special groups of patients with chronic hepatitis B virus infection (e.g. pregnant patients, patients with HIV) has also been added.

I hope this set of guidelines will assist people with chronic hepatitis B infection and the healthcare professionals that work with them.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

¹ Ministry of Health, Singapore. Seroprevalence of hepatitis B virus infection in adults in Singapore. *Epidemiol News Bull* 2009; 35: 10-4.

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Epidemiology and natural history

C Patients with chronic hepatitis B virus infection and who are HBeAg negative should be checked for presence of hepatitis B virus DNA if their serum alanine aminotransferase is repeatedly or persistently above normal limits (pg 13).

Grade C, Level 2+

B Patients with chronic hepatitis B virus infection who are above 40 years of age should be followed up closely if they are still HBeAg positive or have chronic HBe-negative-hepatitis B. These patients should be actively evaluated for cirrhosis and be more readily considered for treatment of hepatitis B virus infection. Regular and frequent surveillance of hepatocellular carcinoma should be carried out in these patients (pg 14).

Grade B, Level 2++

Screening and vaccination of those at risk

C Hepatitis B vaccine should be given to protect children at birth or as soon as possible thereafter in regions where the prevalence of hepatitis B virus infection is high. Babies born to HBsAg-positive mothers are at high risk of developing chronic infection (pg 17).

Grade C, Level 2+

D Other high risk groups, including persons who come into contact with blood or blood products (e.g. laboratory staff, surgeons and dentists, hospital personnel, drug abusers) and individuals requiring repeated transfusions of blood or blood products, should also be vaccinated for hepatitis B (pg 17).

Grade D, Level 4

D The following individuals should be vaccinated for Hepatitis B:

- Sexually active individuals, especially those with multiple partners

- Close family and sexual contacts of subjects with chronic hepatitis B virus infection
- Individuals infected with human immunodeficiency virus (HIV)
- Travellers to hepatitis B endemic areas.

(pg 17)

Grade D, Level 4

Screening prior to Hepatitis B vaccination

D The following groups of people should be screened prior to hepatitis B vaccination:

- Persons born in intermediate and high endemic areas (see Fig. 1)
- Young adults
- Health care workers
- Pregnant women
- Contacts of subjects with chronic hepatitis B virus infection (family, household and sexual contacts)
- Persons with multiple sexual partners/ history of sexually transmitted diseases
- Individuals with chronically elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Individuals infected with hepatitis C virus or human immunodeficiency virus (HIV)
- Men who have sex with men
- Subjects with high risk behaviours (IV drug users, sex workers)
- Immunocompromised subjects (dialysis patients, HIV-infected patients)
- Immigrants
- Prisoners

(pg 18)

Grade D, Level 4

D The following blood tests should be done as part of serologic screening before hepatitis B vaccination:

- HBsAg
- Anti-HBs
- Anti-HBc

(pg 20)

Grade D, Level 4

D Serological screening for hepatitis B surface antigen and antibody should be done within 6 months pre-vaccination for all except newborn babies (pg 20).

Grade D, Level 4

B Based on the results of an individual’s serological screening for HBs antigen and antibody, clinicians should then act according to the table below:

HBsAg	Anti-HBs	Interpretation	Action to take
Non reactive	< 10 IU/L	i) If an individual did not have hepatitis B vaccination before, - Not immune to hepatitis B virus.	i) Administer hepatitis B vaccination
		ii) If an individual had hepatitis B vaccinations before either : a) the antibody level has waned to less than 10 IU/L, but the individual is still immune to the hepatitis B virus. OR b) the individual did not develop immunity against hepatitis B virus after the primary course of hepatitis B vaccination. NB *	ii) Offer a booster dose of hepatitis B vaccination and check anti-HBs within 3 months OR Give them another course (3 injections) of hepatitis B vaccination & recheck anti-HBs within 3 months (to discuss options with patient)
Non reactive	> 10 IU/L	Immune to hepatitis B.	Immunisation is not required.
Reactive	< 10 IU/L	Presence of hepatitis B virus infection.	Clinically assess the patient for liver disease. To repeat the HBsAg test 6 months later. If HBsAg positive 2 times, 6 months apart, chronic hepatitis B infection confirmed.

*Under rare circumstances, the emergence of hepatitis B surface mutant ('s' mutant) virus can be associated with the absence of HBsAg and a negative or low titre of anti-HBs antibody.

(pg 21)

Grade B, Level 2++

D Babies born to HBsAg-positive mothers should be tested for seroconversion following the hepatitis B vaccination, preferably 3 months after completion of course (pg 22).

Grade D, Level 4

C For children not born to HBsAg-positive mothers, as well as adults, three doses of hepatitis B vaccine should be given at months 0, 1 and 6. After the primary 3-dose vaccine series, check anti-HBs within 3 months after the booster dose at month 6 (pg 22).

Grade C, Level 2+

If anti-HBs ≥ 10 IU/L, the individual has developed immunity against hepatitis B virus.

C For individuals previously vaccinated for hepatitis B and with anti-HBs levels < 10 IU/L, consider repeat booster of hepatitis B vaccination or give a second course of hepatitis B vaccination before rechecking the anti-HBs antibody titre (pg 23).

Grade C, Level 2+

C For immuno-competent people:

- with low risk of acquiring hepatitis B *and*
 - who have completed their hepatitis B vaccination *and*
 - who had previously demonstrated immunity to hepatitis B virus after their vaccination, there is no need to check for immunity again or receive booster injections if their anti-HBs is < 10 IU/L later on.
- (pg 23)

Grade C, Level 2+

D Anti-HBc total should be checked if an otherwise Immunocompetent individual fails to seroconvert after 2 courses of hepatitis B vaccinations.

- 1) HBsAg negative, anti-HBs < 10 IU/L, anti-HBc positive
These individuals may have hepatitis B virus infection with low viral load and an undetectable level of HBsAg. Those who are tested positive for anti-HBc alone may be in the ‘window’ phase of acute hepatitis B infection or they may have chronic hepatitis B virus infection with low level viraemia. Refer them to gastroenterologists/hepatologists for further workup.
- 2) HBsAg negative, anti-HBs < 10 IU/L, anti-HBc negative
Consider repeat vaccination with pre-S vaccine or other 3rd generation vaccine, if available, especially if the individuals belong to the high-risk group. They should be advised against high risk behaviour, which may expose them to hepatitis B virus infections.
(pg 24) **Grade D, Level 3**

GPP Patients whose HBsAg is positive for the first time should be evaluated as they may be patients with undiagnosed chronic hepatitis B virus infection even if the clinical criteria may not have been met yet. The appropriate follow-up actions should then be taken:

- 1) History taking
Ask for symptoms of liver disease, family history of chronic hepatitis B virus infection, any recent travel or high risk activity.
- 2) Physical Examination
Examine the patients. Look for signs of liver disease e.g. stigmata of chronic liver disease, ascites, jaundice, etc.
- 3) Investigation
Check blood for liver function test and alpha-fetoprotein level.

If either the physical examination or the blood test results are abnormal, refer to the gastroenterologist. Consider admitting the patient to the hospital through A&E or direct access, if acute hepatitis B infection is suspected (pg 26).

GPP

Management of Chronic Hepatitis B Virus Infection

D The following advice should be given to patients with chronic hepatitis B virus infection:

- Ensure that their sexual partners are vaccinated
- No sharing of toothbrushes and razors
- Cover open wounds
- No donation of body parts
- Clean blood spills with bleach/detergents

Note: Hepatitis B virus transmission is not transmissible through:

- Sharing of utensils, food or kissing as part of social greetings
- Participating in all activities including contact sports
Social interaction with others (e.g. in schools, day care centres)

(pg 29)

Grade D, Level 4

D Management of patients with chronic hepatitis B should be tailored according to the patients' clinical state of liver disease (compensated versus decompensated liver disease) as well as their virologic and biochemical (i.e. the liver function test, in particular the serum transaminase levels) status.

- 1) For patients with HBsAg positive > 6 months and well-compensated liver disease, in association with:

(A) HBeAg-positive Hepatitis B virus infection and:

- i) Alanine aminotransferase (ALT) < Upper limit of normal (ULN): no pharmacotherapy needed. Monitor ALT at least 6 monthly and HBeAg at least 12 monthly.
- ii) ALT 1-2 X ULN: monitor ALT 3 to 6 monthly and HBeAg 6 monthly. Refer to specialist if persistent evidence of early deterioration of liver function or age > 40. Consider liver biopsy and treatment if biopsy shows significant liver damage.
- iii) ALT > 2X ULN: repeat ALT and HBeAg within 1 to 3 months. Refer to specialist if persistent. Treat immediately upon evidence of hepatic decompensation.

(B) HBeAg–negative Hepatitis B virus infection and:

- i) ALT < ULN: Monitor ALT 3 months later. If still normal, monitor ALT every 6 to 12 monthly.
 - ii) ALT 1-2X ULN: Monitor ALT 3 to 6 monthly. Refer to specialist if persistent, evidence of early deterioration of liver function or age > 40. If HBV DNA is > 2000 IU/ml, consider liver biopsy and treat if biopsy shows significant liver damage.
 - iii) ALT > 2X ULN: repeat ALT within 1 to 3 months. Refer to specialist if persistent. If HBV DNA > 2000 IU/ml, consider treatment if persistent.
- 2) For patients with decompensated hepatitis B virus–related cirrhosis:
Refer to gastroenterologist or hepatologist for management.
(pg 30) **Grade D, Level 4**

GPP Surveillance of patients with chronic hepatitis B should be carried out regularly. The required frequency of surveillance for an individual will depend on his/her risk profile, which should be determined before the start of the surveillance programme (see below):

(A) Baseline assessment to stratify risk

- check serum ALT, AST, bilirubin, albumin, prothrombin time, alpha-fetoprotein, HBsAg, HBeAg, anti-HBe and hepatitis B virus DNA
- liver imaging

(B) Periodic reassessment is necessary

Frequency of surveillance is dependent on patients' risk profile:

- i) Low-risk group
6 monthly serum ALT and bilirubin assessment - if abnormal, hepatitis B virus DNA should be checked.
- ii) Medium-risk group
4-6 monthly serum ALT and bilirubin assessment - if abnormal, hepatitis B virus DNA should be checked.

- iii) High-risk group
2-4 monthly serum ALT, bilirubin assessment, hepatitis B virus DNA assessment, appropriate to each set of circumstances. If abnormal the specialist will have to decide on further appropriate management
(pg 33) **GPP**

GPP Most patients in medium risk group and all patients in high risk group should be referred for management by a specialist (pg 33).

GPP

B For patients who have average risk of developing hepatocellular carcinoma (HCC), six-monthly blood tests for alpha-fetoprotein level and annual ultrasonographic examination of the liver is recommended.

For patients with increased risk of HCC, such as patients with cirrhosis, frequency of blood tests and ultrasonographic examination can be increased (pg 34).

Grade B, Level 2++

GPP Patients who have undergone treatment for hepatitis B within the last 6 months and developed serum ALT > ULN or patients who display evidence of hepatic decompensation should be referred to a specialist for further management immediately (pg 35).

GPP

B Patients can be considered for alternative class of therapeutic agents after they fail to respond to one class of drug.

- Patients should be actively screened for contraindications for use of interferon-alpha before they are considered for treatment with interferon-alpha as an alternative therapeutic agent
- Treatment with nucleoside/tide analogue indefinitely may be considered in patients who have persistently elevated serum ALT and evidence of active cirrhosis histologically when he/she has failed to respond to treatment with interferon-alpha previously.

These patients, however, should only be managed by specialists (pg 35).

Grade B, Level 2++

GPP Patients with HIV or hepatitis C virus co-infection should be referred for management by specialists (pg 36).

GPP

GPP Patients with chronic hepatitis B virus infection post-organ transplantation should be managed by specialists, even if the liver function test appears normal (pg 36).

GPP

C Pregnant women with replicative hepatitis B virus infection should be monitored closely after the mid-trimester and immediately postpartum for acute exacerbation of chronic hepatitis B (pg 36).

Grade C, Level 2+

1.1 Objectives

The guidelines are not to be viewed as a protocol, but provide a framework to:

- Improve primary prevention of chronic hepatitis B virus infection
- Guide the management of patients with chronic hepatitis B virus infection

1.2 Target group

The target group of these guidelines are general practitioners, non-infectious disease specialists and non-gastroenterology specialists who are involved in providing care to patients with chronic hepatitis B virus infection.

1.3 Guideline development

These guidelines have been produced by a committee made up of general practitioners, gastroenterologists, hepatologists, an infectious disease specialist, a nurse clinician as well as a patient representative appointed by the Ministry of Health. These guidelines were developed using the best available current evidence and expert opinion.

1.4 What's new in the revised guidelines

The following is a list of major revisions or additions to the guidelines:

- (1) Definition of various subgroups of patients with chronic hepatitis B virus infection
- (2) Management of chronic hepatitis B, especially its acute exacerbation
- (3) Management of special groups of patients with chronic hepatitis B virus infection

1.5 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review in 3 years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2.1 Natural history of chronic Hepatitis B

The likelihood of developing chronic hepatitis B in individuals is higher in those infected perinatally (90%) compared to those infected in adulthood (1%).¹⁻² This is due to differences in the maturity and competence of immune systems during the respective ages. Most infections acquired in Singapore are perinatal or during early childhood, though the incidence is much lower due to the advent of the hepatitis B vaccination programme in 1987.³

The natural history of perinatal and childhood-acquired infection is generally described to have three phases. The first phase (also known as the immune tolerance phase) can persist for 10-30 years. This phase is characterised by the presence of hepatitis B e Antigen (HBeAg) and high hepatitis B virus DNA (HBV-DNA) levels with persistently normal alanine aminotransferase (ALT) levels. There are usually minimal histological changes in the liver. The rate of spontaneous HBeAg seroconversion is very low and 90% of children remain HBeAg-positive by the age of 10-15 years.¹⁻²

The second phase (also known as the immune clearance phase) usually occurs during late adolescence or young adulthood. This phase is characterised by elevated ALT levels, lower hepatitis B virus DNA levels and increased histological activity. This phase is often marked by sporadic ALT elevations thought to be associated with attempts by the immune system to eliminate hepatitis B virus infected hepatocytes. Spontaneous HBeAg seroconversion occurs at an annual rate of 10-20%.⁴⁻⁶ The level of ALT is an important predictor of seroconversion, with 60-70% of patients having spontaneous seroconversion if ALT levels are more than 5 times normal.⁵⁻⁶

The mean age of spontaneous HBeAg seroconversion is about 31-35 years with most (> 90%) patients seroconverting by the age of 40 years. Persistence of HBeAg and high hepatitis B virus DNA levels beyond this age often implies a poor prognosis with worsening histology and higher incidence of hepatocellular carcinoma.⁷⁻⁹ Hepatic decompensation during acute exacerbation of hepatitis B associated with elevated serum ALT occurs in about 2.5% of patients. The annual reported incidence of cirrhosis varies from 0.5% to 9%.⁷⁻⁹

The third phase (also known as the non-replicative phase) is characterised by low levels of hepatitis B virus DNA, absence of HBeAg (i.e. HBeAg-negative) and presence of hepatitis B e antibodies (i.e., anti-HBe positive) with absence of hepatic inflammation histologically. Patients in this phase are usually asymptomatic and disease progression to cirrhosis is low, if it has not occurred yet.

HBeAg–negative Hepatitis B virus infection

In some patients, persistent hepatitis B virus DNA replication despite HBe-seroconversion gives rise to HBeAg-negative hepatitis B virus infection. This condition occurs in the older age group and significant liver disease is often present at the time of presentation.¹⁰⁻¹² It is commonly caused by a mutation in the precore codon of the virus at nucleotide 1896 with a guanine-to-adenine change.¹⁰ Other precore changes and changes in the core promoter regions have also been described.

Clinically, these patients present with lower hepatitis B virus DNA levels but have wide fluctuations in both ALT and hepatitis B virus DNA levels.¹⁰⁻¹³ Hence these patients need to be followed up closely as it can be difficult to differentiate this condition from quiescent hepatitis B virus infection.

It is important to identify and treat these patients as the incidence of cirrhosis in this group is estimated to be about 13% in 5 years, as compared to 8% in HBeAg-positive hepatitis.¹⁰⁻¹³

C Patients with chronic hepatitis B virus infection and who are HBeAg negative should be checked for presence of hepatitis B virus DNA if their serum alanine aminotransferase is repeatedly or persistently above normal limits.

Grade C, Level 2+

B Patients with chronic hepatitis B virus infection who are above 40 years of age should be followed up closely if they are still HBeAg positive or have chronic HBe-negative-hepatitis B. These patients should be actively evaluated for cirrhosis and be more readily considered for treatment of hepatitis B virus infection. Regular and frequent surveillance of hepatocellular carcinoma should be carried out in these patients.

Grade B, Level 2++

3.1 Principles of vaccination

Adult acute hepatitis B virus infection, with its attendant morbidity, can have tremendous economic implications in terms of labour costs (e.g. from time off work) and health care costs. Neonatal and childhood infections often progress to chronic disease with risk of liver cancer.

In endemic areas, a reservoir of virus is found in up to 20% of the population and maintained by intrafamilial spread. The only certain way of preventing the development of chronic hepatitis B infection and its complications is to immunise all newborns, children and susceptible young adults. Prevention of the acute infection in susceptible adults in certain high-risk groups is another indication for hepatitis B vaccination. The cost-benefit ratio is decidedly in favour of vaccination.

The long-term efficacy of hepatitis B virus vaccination is confirmed. Hepatitis B surface antibodies (anti-HBs) remain above the critical threshold for protection in 70-90% of immunised children over 10 years. Exposure to hepatitis B virus results in a secondary anti-HBs response, which effectively prevents the development of clinical disease. For instance, the average annual incidence of childhood liver cancer has declined significantly in Taiwan since the introduction of mass hepatitis B vaccination for all newborn infants in 1986.¹⁴ The decline in incidence of hepatitis B-related disease is also seen in most countries where newborns are vaccinated against hepatitis B virus infection.¹⁴⁻¹⁹

Almost all countries in the Asia-Pacific region have introduced national immunisation programs.

Vaccines available locally

Recombinant DNA (rDNA) vaccines became available in 1986. The hepatitis B vaccines available locally are all rDNA vaccines, which are highly immunogenic at the manufacturers' recommended doses. The rDNA hepatitis B vaccines are free of possible contamination with infectious agents and are safe in the developing foetus as they do not contain live viral particles. Therefore, women in high-risk groups may be vaccinated even if they may be pregnant.¹⁶⁻¹⁷

Screening is recommended in areas of high prevalence of hepatitis B virus infection. Although vaccinating a subject with chronic hepatitis B virus infection is harmless, it might give a false sense of security to an individual who is not aware of their chronic infected status that requires regular monitoring and long term follow-up. Vaccination would boost anti-HBs levels in those who are already immune.

The most economical screening test is to determine the presence of hepatitis B surface antigen (HBsAg) in the subject's serum. If HBsAg is absent, vaccination would confer immunity on those who are not immune and would boost antibody levels in those who are already immune. The presence of antibody against HBsAg (i.e. anti-HBs) signifies immunity against hepatitis B virus infection. Determining the presence of antibody against the hepatitis B core antigen (anti-HBc) alone in the serum is expensive and inadequate since a positive test indicates previous exposure but cannot distinguish the chronically infected from the protected individuals.

A repeatedly weak positive HBsAg in the serum warrants a more detailed screening procedure. The subject has chronic infection if serum hepatitis B virus DNA and anti-HBc are present. If both are absent the positive result may be a non-specific laboratory error. This can be confirmed by persistence of the positive result after treating the serum with monoclonal anti-HBs.

Concurrent presence of HBsAg and anti-HBs is found in up to 20% of local subjects with chronic hepatitis B virus infection and does not indicate protection. Levels of anti-HBs are usually below 50 IU/L in such situations, but can vary.

Indications for Hepatitis B vaccination

C Hepatitis B vaccine should be given to protect children at birth or as soon as possible thereafter in regions where the prevalence of hepatitis B virus infection is high. Babies born to HBsAg-positive mothers are at high risk of developing chronic infection.

Grade C, Level 2+

D Other high risk groups, including persons who come into contact with blood or blood products (e.g. laboratory staff, surgeons and dentists, hospital personnel, drug abusers) and individuals requiring repeated transfusions of blood or blood products, should also be vaccinated for hepatitis B.

Grade D, Level 4

D The following individuals should be vaccinated for hepatitis B:

- Sexually active individuals, especially those with multiple partners
- Close family and sexual contacts of subjects with chronic hepatitis B virus infection
- Individuals infected with human immunodeficiency virus (HIV)
- Travellers to hepatitis B endemic areas.

Grade D, Level 4

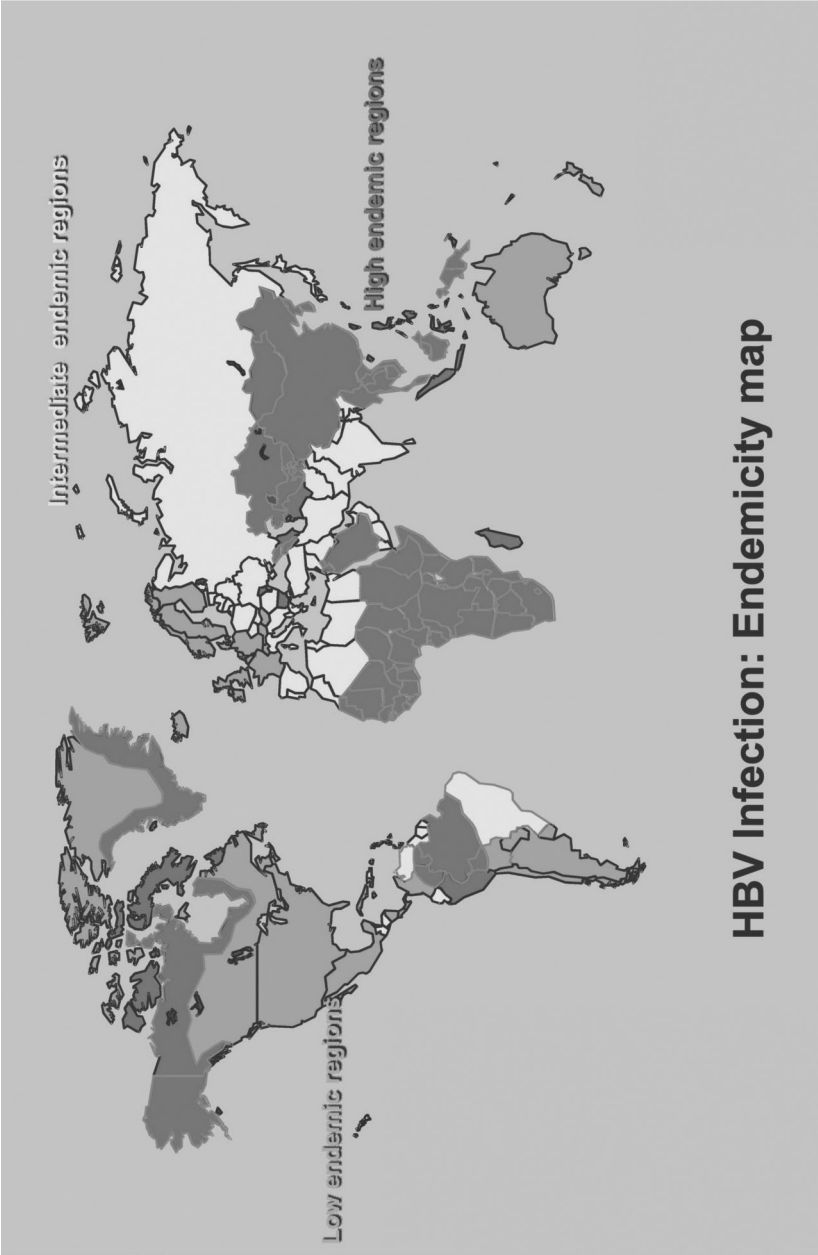
Screening prior to Hepatitis B vaccination

D The following groups of people should be screened prior to hepatitis B vaccination:¹⁷

- Persons born in intermediate and high endemic areas (see Fig. 1)
- Young adults
- Health care workers
- Pregnant women
- Contacts of subjects with chronic hepatitis B virus infection (family, household and sexual contacts)
- Persons with multiple sexual partners/ history of sexually transmitted diseases
- Individuals with chronically elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Individuals infected with hepatitis C virus or human immunodeficiency virus (HIV)
- Men who have sex with men
- Subjects with high risk behaviours (IV drug users, sex workers)
- Immunocompromised subjects (dialysis patients, HIV-infected patients)
- Immigrants
- Prisoners

Grade D, Level 4

Figure 1 Hepatitis B virus endemicity map



HBV Infection: Endemicity map

D The following blood tests should be done as part of serologic screening before hepatitis B vaccination:¹⁷

- HBsAg
- Anti-HBs
- Anti-HBc

Grade D, Level 4

3.2 Screening

With the exception of newborns, serological screening provides a basis for vaccination of an individual without giving an infected individual a false sense of security. Prophylactic vaccination is of no benefit to an individual who already has chronic hepatitis B virus infection – he/she should instead be followed up regularly and treated when indicated.

D Serological screening for hepatitis B surface antigen and antibody should be done within 6 months pre-vaccination for all except newborn babies.²⁰

Grade D, Level 4

B Based on the results of an individual's serological screening for HBs antigen and antibody, clinicians should then act according to the table below:

HBsAg	Anti-HBs	Interpretation	Action to take
Non reactive	< 10 IU/L	i) If an individual did not have hepatitis B vaccination before, - Not immune to hepatitis B virus.	i) Administer hepatitis B vaccination
		ii) If an individual had hepatitis B vaccinations before either : a) the antibody level has waned to less than 10 IU/L, but the individual is still immune to the hepatitis B virus. OR b) the individual did not develop immunity against hepatitis B virus after the primary course of hepatitis B vaccination. NB *	ii) Offer a booster dose of hepatitis B vaccination and check anti-HBs within 3 months OR Give them another course (3 injections) of hepatitis B vaccination & recheck anti-HBs within 3 months (to discuss options with patient)
Non reactive	> 10 IU/L	Immune to hepatitis B.	Immunisation is not required
Reactive	< 10 IU/L	Presence of hepatitis B virus infection.	Clinically assess the patient for liver disease. To repeat the HBsAg test 6 months later. If HBsAg positive 2 times, 6 months apart, chronic hepatitis B infection confirmed.

*Under rare circumstances, the emergence of hepatitis B surface mutant ('s' mutant) virus can be associated with the absence of HBsAg and a negative or low titre of anti-HBs antibody.

Grade B, Level 2++

3.3 Individuals with HBsAg negative and anti-HBs < 10 IU/L

3.3.1 Individuals who were not previously vaccinated

1) For newborns

Under the National Childhood Immunization Programme, all babies will be given hepatitis B vaccine at birth, 1 month and 5-6 months.

Those born to HBsAg positive mothers are given hepatitis B immunoglobulin (0.5ml) at the same time as the first dose of hepatitis B vaccine.²¹

D Babies born to HBsAg-positive mothers should be tested for seroconversion following the hepatitis B vaccination, preferably 3 months after completion of course.²²

Grade D, Level 4

2) For other children and adults

C For children not born to HBsAg-positive mothers, as well as adults, three doses of hepatitis B vaccine should be given at months 0, 1 and 6. After the primary 3-dose vaccine series, check anti-HBs within 3 months after the booster dose at month 6.²³⁻²⁴

Grade C, Level 2+

If anti-HBs > 10 IU/L, the individual has developed immunity against hepatitis B virus.

3) Contraindications for vaccination

Hepatitis B vaccination is contraindicated for those who are allergic to the hepatitis B vaccine or its preservatives.

3.3.2 Individuals who have previously received Hepatitis B vaccinations

After primary immunization with hepatitis B vaccine, anti-HBs levels decline.

Even when anti-HBs concentrations decline to <10 IU/L, nearly all vaccinated persons remain protected against hepatitis B virus infection. This is thought to be due to the preservation of immune memory through selective expansion and differentiation of clones of antigen-specific B and T lymphocytes.²⁵

Persistence of vaccine-induced immune memory among persons who responded to a primary adult vaccine series 4-23 years previously but with anti-HBs concentrations of < 10 IU/L subsequently was demonstrated by an amnestic increase in anti-HBs concentrations in 74%-100% of these persons 2-4 weeks after administration of an additional vaccine dose.²⁶

The data indicate that a high proportion of vaccinated people retain immune memory and will have an anti-HBs response when exposed to hepatitis B virus.

C For individuals previously vaccinated for hepatitis B and with anti-HBs levels < 10 IU/L, consider repeat booster of hepatitis B vaccination or give a second course of hepatitis B vaccination before rechecking the anti-HBs antibody titre.

Grade C, Level 2+

C For immuno-competent people:

- with low risk of acquiring hepatitis B and
- who have completed their hepatitis B vaccination and
- who had previously demonstrated immunity to hepatitis B virus after their vaccination, there is no need to check for immunity again or receive booster injections if their anti-HBs is < 10 IU/L later on.

Grade C, Level 2+

3.3.3 No immunity after primary course of Hepatitis B vaccination

Of those who did not respond to a primary 3-dose vaccine series with anti-HBs concentrations < 10 IU/L, 25%–50% responded to an additional vaccine dose, and 44%–100% responded to a 3-dose revaccination series.²⁷⁻³²

D Anti-HBc total should be checked if an otherwise Immunocompetent individual fails to seroconvert after 2 courses of hepatitis B vaccinations.

1) HBsAg negative, anti-HBs < 10 IU/L, anti-HBc positive

These individuals may have hepatitis B virus infection with low viral load and an undetectable level of HBsAg. Those who are tested positive for anti-HBc alone may be in the ‘window’ phase of acute hepatitis B infection or they may have chronic hepatitis B virus infection with low level viraemia. Refer them to specialists for further workup.

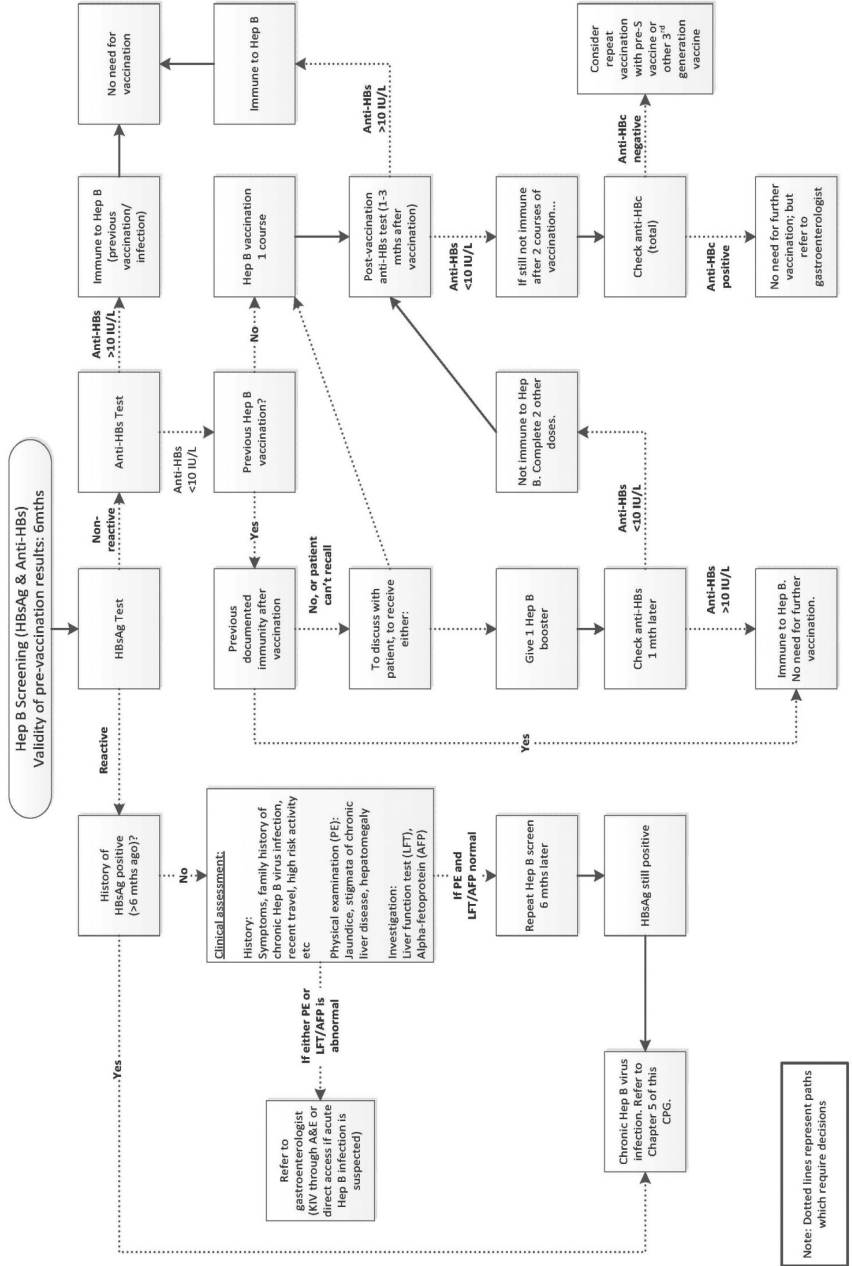
2) HBsAg negative, anti-HBs < 10 IU/L, anti-HBc negative

Consider repeat vaccination with pre-S vaccine or other 3rd generation vaccine, if available, especially if the individuals belong to the high-risk group. They should be advised against high risk behaviour, which may expose them to hepatitis B virus infections, and also counselled about post-exposure prophylaxis with hepatitis B immunoglobulin (HBIG) infection if they do sustain high risk exposure.

Grade D, Level 3

Patients with the following characteristics are less likely to respond to hepatitis B vaccination: male sex, age >45 years, smoker, obese and concurrent major medical illnesses such as chronic renal failure and immunocompromised states.

Figure 2 Algorithm for Hepatitis B screening & vaccination



Note: Dotted lines represent paths which require decisions

3.4 Individuals found to be HBsAg-positive

An individual has chronic hepatitis B virus infection if the HBsAg is positive/reactive on two occasions at least 6 months apart.

GPP Patients whose HBsAg is positive for the first time should be evaluated as they may be patients with undiagnosed chronic hepatitis B virus infection even if the clinical criteria may not have been met yet. The appropriate follow-up actions should then be taken:

- 1) History taking
Ask for symptoms of liver disease, family history of chronic hepatitis B virus infection, any recent travel or high risk activity.
- 2) Physical Examination
Examine the patients. Look for signs of liver disease e.g. stigmata of chronic liver disease, ascites, jaundice, etc.
- 3) Investigation
Check blood for liver function test and alpha-fetoprotein level.

If either the physical examination or the blood test results are abnormal, refer to the gastroenterologist. Consider admitting the patient to the hospital through A&E or direct access, if acute hepatitis B infection is suspected.

GPP

4.1 Chronic Hepatitis B virus infection

Chronic hepatitis B virus infection is defined as having positive serum HBsAg for more than 6 months.³³ The spectrum of disease manifestation is defined as below:

4.2 Patients with replicative Hepatitis B virus infection

4.2.1 HBeAg-positive chronic Hepatitis B virus infection

This is defined as chronic hepatitis B virus infection with positive HBeAg, and is usually associated with very high viral load (as measured by hepatitis B virus DNA), particularly when patient's serum ALT is still persistently within normal range.

4.2.2 HBeAg-negative chronic Hepatitis B virus infection

This is defined as chronic hepatitis B virus infection with negative HBeAg and persistently or recurrently elevated serum hepatitis B virus DNA level. Overall, patients with HBeAg-negative chronic hepatitis B virus infection tend to have lower and more fluctuant hepatitis B virus DNA levels than patients with HBeAg-positive chronic hepatitis B virus infection. The hepatitis B virus DNA level is generally considered as significant if the level is more than 4 log IU/ml. In association with the fluctuating serum hepatitis B virus DNA levels, these patients' sera ALT tend to fluctuate between normal and elevated levels too.

4.3 Hepatitis B virus DNA measurement and detection

Due to their high sensitivity, specificity and broad dynamic range, real-time PCR quantification assays are generally preferred for the measurement of hepatitis B virus DNA when treatment is considered and for assessment of subsequent response to treatment. In recent years, the World Health Organisation has defined an international standard for the expression of hepatitis B virus DNA concentrations to ensure comparability among different laboratories. Serum hepatitis B virus level should be expressed in IU/ml. A hepatitis B virus DNA level of \geq

4 log IU/ml is generally considered as significant and treatment should be considered. Preferably, the same assay should be used throughout the assessment for the same patient.

4.4 Chronic Hepatitis B

This is defined as patients that present with evidence of ongoing hepatic inflammatory activity attributed to an underlying chronic hepatitis B virus infection. This condition is usually identified clinically by intermittently or persistently raised serum transaminases and/or typical histological features associated with hepatitis B virus-related inflammation on liver biopsy.

4.5 Hepatitis B virus-related cirrhosis

This is defined as liver cirrhosis that is defined histologically and attributed to chronic hepatitis B.

4.5.1 Compensated Hepatitis B virus-related cirrhosis

This is defined as hepatitis B virus-related cirrhosis that is not associated with any clinical evidence of hepatic decompensation, such as ascites, ankle oedema, jaundice and hepatic encephalopathy. This can, however, be suspected by presence of thrombocytopenia suggestive of hypersplenism.

4.5.2 Decompensated Hepatitis B virus related cirrhosis

This is defined as hepatitis B virus-related cirrhosis in association with clinical evidence of hepatic decompensation. This can be associated with biochemical derangement, such as hypoalbuminaemia, hyperbilirubinaemia, and coagulopathy with prolonged prothrombin time.

5 Management of chronic Hepatitis B virus infection

5.1 General management

5.1.1 Serologic screening of chronic Hepatitis B virus infection amongst patient's family members

5.1.2 Prevention of transmission of Hepatitis B virus to others

D The following advice should be given to patients with chronic hepatitis B virus infection:³⁴

- Ensure that their sexual partners are vaccinated
- No sharing of toothbrushes and razors
- Cover open wounds
- No donation of body parts
- Clean blood spills with bleach/detergents

Note: Hepatitis B virus transmission is not transmissible through:

- Sharing of utensils, food or kissing as part of social greetings
- Participating in all activities including contact sports
- Social interaction with others (e.g. in schools, day care centres)

Grade D, Level 4

5.1.3 Prevention of super-infection

C Unless contraindicated, hepatitis A vaccination should be given to prevent superimposed acute hepatitis A in patients with chronic hepatitis B virus infection.³⁵⁻³⁷

Grade C, Level 2+

5.2 Specific management

5.2.1 Monitor for indications for treatment of chronic Hepatitis B

D Management of patients with chronic hepatitis B should be tailored according to the patients' clinical state of liver disease (compensated versus decompensated liver disease) as well as their virologic and biochemical (i.e. the liver function test, in particular the serum transaminase levels) status.^{34, 38}

1) For patients with HBsAg positive > 6 months and well-compensated liver disease, in association with:

(A) HBeAg-positive hepatitis B virus infection and:

- i) Alanine aminotransferase (ALT) < Upper limit of normal (ULN): no pharmacotherapy needed. Monitor ALT at least 6 monthly and HBeAg at least 12 monthly.
- ii) ALT 1-2 X ULN: monitor ALT 3 to 6 monthly and HBeAg 6 monthly. Refer to specialist if persistent evidence of early deterioration of liver function or age > 40. Consider liver biopsy and treatment if biopsy shows significant liver damage.
- iii) ALT > 2X ULN: repeat ALT and HBeAg within 1 to 3 months. Refer to specialist if persistent. Treat immediately upon evidence of hepatic decompensation.

(B) HBeAg-negative hepatitis B virus infection and:

- i) ALT < ULN: Monitor ALT 3 months later. If still normal, monitor ALT every 6 to 12 monthly.
- ii) ALT 1-2X ULN: Monitor ALT 3 to 6 monthly. Refer to specialist if persistent, evidence of early deterioration of liver function or age > 40. If HBV DNA is > 2000 IU/ml, consider liver biopsy and treat if biopsy shows significant liver damage.
- iii) ALT > 2X ULN: repeat ALT within 1 to 3 months. Refer to specialist if persistent. If HBV DNA > 2000 IU/ml, consider treatment if persistent. Note that common

conditions, such as fatty liver and commonly consumed drugs may be confounding factors giving rise to mild to moderate elevation of serum transaminases.

- 2) For patients with decompensated hepatitis B virus–related cirrhosis:
Refer to gastroenterologist or hepatologist for management.

Grade D, Level 4

5.2.2 Surveillance for exacerbation of chronic Hepatitis B

Exacerbation of hepatitis in patients with chronic hepatitis B virus infection refers to an event that is marked by significant elevation of ALT. Histologically there is associated necro-inflammation of the liver. The clinical manifestation will take on the following patterns:³⁹⁻⁴²

- (i) asymptomatic elevation of serum ALT
- (ii) symptomatic hepatitis
- (iii) acute decompensation and
- (iv) acute-on-chronic liver failure

The outcome of acute exacerbation is a function of the degree of the severity of the exacerbation and the underlying liver reserves.⁴³⁻⁴⁴

Surveillance strategy

The at-risk group includes all individuals with chronic hepatitis B virus infection. The frequency of surveillance should increase if the anticipated incidence of exacerbation is high and if the anticipated outcome of exacerbation is poor, i.e., risk stratification is important:

- 1) Risk Stratification
 - (A) Low risk group
These are patients who have seroconverted and have a non-replicative hepatitis B virus infection.
 - (B) Medium risk group
The medium risk group consists of:

- patients with replicative hepatitis B virus infection who are beyond the immuno-tolerant window
- patients with chronic hepatitis B who are not on treatment
- patients with chronic hepatitis B which is resistant to treatment
- patients who are expected to tolerate exacerbation of hepatitis B poorly, e.g. patients with liver cirrhosis

(C) High-risk group

These are patients who are at risk of developing marked hepatic injury associated with risk of acute hepatic decompensation or liver failure due to either conversion from non-replicative to replicative hepatitis B virus infection, or marked increase in viral load in patients with pre-existing replicative hepatitis B virus infection. These situations occur in patients who are:

- subjected to immunosuppressive treatment:⁴⁵⁻⁴⁹
 - (i) during immunosuppressive treatment
High viral load may lead to fibrosing cholestatic hepatitis, associated with biochemical evidence of hepatic cholestasis
 - (ii) on withdrawal of immunosuppressive treatment with agents such as steroids, cytotoxics, monoclonal antibodies with immunomodulatory activity
- withdrawn from nucleoside/tide analogue treatment for prior chronic hepatitis B
- demonstrating resistance to their ongoing nucleoside/tide analogue treatment⁵⁰⁻⁵¹ for their prior chronic hepatitis B, as suggested by the increase in viral load (hepatitis B virus DNA) after initial reduction (the risk of treatment resistance varies with different nucleoside/tide analogue agents)
- having reduced liver mass, e.g. post-hepatic resection

2) Surveillance Method

GPP Surveillance of patients with chronic hepatitis B should be carried out regularly. The required frequency of surveillance for an individual will depend on his/her risk profile (refer to page 31 for risk stratification criteria), which should be determined before the start of the surveillance programme (see below):

(A) Baseline assessment to stratify risk

- check serum ALT, AST, bilirubin, albumin, prothrombin time, alpha-fetoprotein, HBsAg, HBeAg, anti-HBe and hepatitis B virus DNA
- liver imaging

(B) Periodic reassessment is necessary

Frequency of surveillance is dependent on patients' risk profile:

i) Low-risk group

6 monthly serum ALT and bilirubin assessment

- if abnormal, hepatitis B virus DNA should be checked.

ii) Medium-risk group

4-6 monthly serum ALT and bilirubin assessment

- if abnormal, hepatitis B virus DNA should be checked.

iii) High-risk group

2-4 monthly serum ALT, bilirubin assessment, hepatitis B virus DNA assessment, appropriate to each set of circumstances. If abnormal the specialist will have to decide on further appropriate management.

GPP

GPP Most patients in medium risk group and all patients in high risk group should be referred for management by a specialist.

GPP

5.2.3 Surveillance for hepatocellular carcinoma

B For patients who have average risk of developing hepatocellular carcinoma (HCC), six-monthly blood tests for alpha-fetoprotein level and annual ultrasonographic examination of the liver is recommended.⁵²

For patients with increased risk of HCC, such as patients with cirrhosis or with family history of HCC, frequency of blood tests and ultrasonographic examination can be increased.

Grade B, Level 2++

5.3 Treatment options

Currently, the therapeutic agents available for treatment of chronic hepatitis B include interferon-alpha (both conventional interferon and pegylated interferon⁵³⁻⁵⁵) and a whole range of nucleoside/tide analogues.⁵⁶⁻⁵⁹

Thymosin alpha-1 has also been used for treatment of chronic hepatitis B with limited success.

5.4 Treatment failures

5.4.1 Definition of treatment failure

1. Non-response after 48 weeks of interferon treatment, with failure of HBe sero-conversion and/or sustained viral response (i.e. HBV DNA < 3.3 log IU/ml)⁶⁰
2. Primary non-response to nucleoside/tide analogue treatment, with < 1 log IU/ml drop in HBV DNA at 3 months of therapy
3. Partial response to nucleoside /tide analogue treatment, with > 1 log IU/ml drop but still detectable HBV DNA with real-time PCR assay at a specific time point of therapy.*

- * - Lamivudine & telbivudine: 6 months
- Adefovir: 12 months

4. Failed HBe sero-conversion at end of nucleoside/tide treatment that lasted for at least one year

5.4.2 Management of treatment failure

GPP Patients who have undergone treatment for hepatitis B within the last 6 months and developed serum ALT > ULN or patients who display evidence of hepatic decompensation should be referred to a specialist for further management immediately.

GPP

B Patients can be considered for alternative class of therapeutic agents after they fail to respond to one class of drug.

- Patients should be actively screened for contraindications for use of interferon-alpha before they are considered for treatment with interferon-alpha as an alternative therapeutic agent
- Treatment with nucleoside/tide analogue indefinitely may be considered in patients who have persistently elevated serum ALT and evidence of active cirrhosis histologically when he/she has failed to respond to treatment with interferon-alpha previously.

These patients, however, should only be managed by specialists.

Grade B, Level 2++

5.5 Management of special groups

GPP Patients with HIV or hepatitis C virus co-infection should be referred for management by specialists.

GPP

GPP Patients with chronic hepatitis B virus infection post-organ transplantation should be managed by specialists, even if the liver function test appears normal.

GPP

C Pregnant women with replicative hepatitis B virus infection should be monitored closely after the mid-trimester and immediately postpartum for acute exacerbation of chronic hepatitis B.⁶¹

Grade C, Level 2+

The following clinical quality improvement parameters, based on recommendations in these guidelines, are proposed:

Screening and vaccination

1. All newborns, children and susceptible adults should be immunised as this is the only way to prevent the development of chronic hepatitis B infection and its complications.
2. Testing for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (anti-HBs) should be performed within 6 months pre-vaccination for all except for newborn babies.
3. Appropriate follow-up actions i.e. history taking, physical examination and blood test, should be undertaken for patients whose HBsAg is positive for the first time and are yet to be diagnosed.

Chronic Hepatitis B virus infection

4. Patients with HBeAg-negative hepatitis B virus infection should be tested for hepatitis B virus DNA to exclude HBeAg-negative hepatitis if their serum aminotransferase (s.ALT or s.AST) are elevated, and treatment to be considered if diagnosed.
5. All individuals with chronic hepatitis B virus infection should be monitored for exacerbation of the infection, with an increase in frequency of surveillance if the anticipated incidence is high and if the anticipated outcome is poor.
6. Patients with average and above risk of developing hepatocellular carcinoma are recommended to undergo blood testing for alpha-fetoprotein level and ultrasonographic examination of the liver, with the frequency of testing for average risk patients set at six monthly and once yearly respectively. The frequency can be increased for higher risk patients.
7. Pregnant women with replicative hepatitis B virus infection should be monitored closely after the mid-trimester and immediately postpartum for risk of exacerbation of chronic hepatitis B infection.

Taking into consideration the different degree of endemicity of chronic hepatitis B virus infection in various parts of the world and the natural history of the disease, along with the emergence of various relatively expensive treatment options that aims to avoid the associated complications in the infected patients, cost-effectiveness of two measures that are broadly employed to manage the problem of chronic hepatitis B virus infection should be considered:

- 1) Screening for, and vaccination against, hepatitis B
- 2) Liver cancer (hepatocellular carcinoma) surveillance among patients with chronic hepatitis B infection

The benefits of hepatitis B vaccination at birth are well proven in various populations since the implementation of such programmes in various countries in the world.^{14, 62-64} Recent evidence also demonstrated the benefits of catch up vaccination programme among older children and adolescents in country of high endemicity.⁶⁵

While the likelihood of developing chronic hepatitis B virus infection and long term complication in people acquiring the infection in adulthood is low, there are other economic benefits derived from avoidance of loss of workman-hours as a consequence of acute hepatitis B-related morbidities by vaccinating the at-risk adults.⁶³⁻⁶⁴

Cost-effectiveness studies have shown the benefits of screening for chronic hepatitis B virus infection in the population, treat those who are found infected +/- screen and ring-vaccinate the close contacts of the individual who are found infected, as compared to volunteer screening +/- vaccination only.⁶⁶ While the benefit of universal vaccination (without screening) remains equivocal and may only benefit countries of high endemicity for hepatitis B virus infection, the cost-effectiveness of hepatitis B vaccination in the high-risk populations were well demonstrated.⁶⁷⁻⁶⁸

We should keep in mind that the epidemiology of any one region or country changes following large scale implementation of vaccination programme. Measures that were once appropriate for a highly endemic area may not be the most-effective measures following the drop in prevalence of chronic hepatitis B virus infection in the population. Hence, going forward, dynamic, instead of static, modeling is probably more appropriate to determine the cost-effectiveness of any public health measure in the management of chronic hepatitis B virus infection, in order to avoid underestimation.⁶⁷

On the other hand, while there were some evidence to suggest liver cancer surveillance can result in detection of early hepatocellular carcinoma among patients with chronic hepatitis B, and possibly reduce liver cancer – related mortality,⁶⁹⁻⁷⁰ there was no good cost-effectiveness study done in this area and this should be addressed in the future.

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: <http://smj.sma.org.sg/cme/smj/index.html> (*the link will only be available once the April 2011 issue of the SMJ becomes available*). The answers will be published in the SMJ June 2011 issue and at the MOH webpage for this CPG after the period for submitting answers is over.

Instruction: Indicate whether each statement is true or false.

	True	False
1. Chronic hepatitis B virus (HBV) infection can be associated with:		
A) HBsAg	<input type="checkbox"/>	<input type="checkbox"/>
B) HBeAg	<input type="checkbox"/>	<input type="checkbox"/>
C) Anti-HBe antibody	<input type="checkbox"/>	<input type="checkbox"/>
D) Anti-HBc (total) antibody	<input type="checkbox"/>	<input type="checkbox"/>
2. Patients with chronic HBV infection and are HBeAg negative may be associated with:		
A) Fluctuating viral load	<input type="checkbox"/>	<input type="checkbox"/>
B) Mutation of the precore gene of HBV	<input type="checkbox"/>	<input type="checkbox"/>
C) Viral load that tends to be much higher, compared with HBeAg-positive chronic hepatitis B	<input type="checkbox"/>	<input type="checkbox"/>
D) Normal serum ALT levels.	<input type="checkbox"/>	<input type="checkbox"/>
3. Occult hepatitis B virus infection may be (is) associated with:		
A) Positive HBsAg	<input type="checkbox"/>	<input type="checkbox"/>
B) Elevated anti-HBs titre	<input type="checkbox"/>	<input type="checkbox"/>
C) Positive HBV DNA	<input type="checkbox"/>	<input type="checkbox"/>
D) Acute exacerbation of hepatitis B in patients taking immunosuppressive treatment for rheumatoid arthritis.	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
4. Young adults who were found to be sero-negative for both HBsAg and anti-HBs should be advised:		
A) No action needs to be taken if hepatitis B vaccination & booster was once given previously	<input type="checkbox"/>	<input type="checkbox"/>
B) Consider giving one booster hepatitis B vaccine, if full course of hepatitis B vaccination was given previously	<input type="checkbox"/>	<input type="checkbox"/>
C) Check anti-HBs antibody 6 months or later, after giving a full course of hepatitis B vaccination (3 doses), if uncertain of previous vaccination history	<input type="checkbox"/>	<input type="checkbox"/>
D) Test for anti-HBc(total) antibody, if there is weak / no response to vaccination	<input type="checkbox"/>	<input type="checkbox"/>
5. Patients who are found to be HBsAg positive should be managed as follows:		
A) Advise segregation of all utensils from the rest of patients' family members and no sexual intercourse till repeat HBsAg to be done 6 months later	<input type="checkbox"/>	<input type="checkbox"/>
B) Check LFT	<input type="checkbox"/>	<input type="checkbox"/>
C) Check for jaundice and ascites	<input type="checkbox"/>	<input type="checkbox"/>
D) Check HBV DNA at the very first visit	<input type="checkbox"/>	<input type="checkbox"/>
6. Patients with chronic HBV infection should be considered for treatment of the HBV infection,		
A) As long as they are HBeAg positive	<input type="checkbox"/>	<input type="checkbox"/>
B) As long as they have PCR-detectable HBV DNA	<input type="checkbox"/>	<input type="checkbox"/>
C) If the patient has active liver cirrhosis and HBV DNA is positive	<input type="checkbox"/>	<input type="checkbox"/>
D) Only if s. ALT > five times upper limit of normal	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
7. Surveillance of hepatocellular carcinoma for patients with chronic HBV infection should include:		
A) Annual testing of s. alpha-fetoprotein	<input type="checkbox"/>	<input type="checkbox"/>
B) 6 – 12 monthly U / S examination routinely	<input type="checkbox"/>	<input type="checkbox"/>
C) 6-12 monthly CT or MRI examination routinely	<input type="checkbox"/>	<input type="checkbox"/>
D) 3-6 monthly serum ALT & alkaline phosphatase	<input type="checkbox"/>	<input type="checkbox"/>
8. Referral to gastroenterologist should be considered:		
A) If the patient has hepatitis B & hepatitis C or delta co-infection	<input type="checkbox"/>	<input type="checkbox"/>
B) Once the HBV-infected patients are found pregnant (during first trimester)	<input type="checkbox"/>	<input type="checkbox"/>
C) As soon as steroidal or other immuno-suppressive treatment is given to a HBV-infected patient.	<input type="checkbox"/>	<input type="checkbox"/>
D) With the slightest increase in serum ALT in a HBV-infected patient	<input type="checkbox"/>	<input type="checkbox"/>
9. Hepatitis B vaccination for newborns whose mothers have chronic hepatitis B virus infection, should:		
A) be given within 1 week after birth	<input type="checkbox"/>	<input type="checkbox"/>
B) include passive immunisation with immunoglobulin if the mother is HBV DNA positive	<input type="checkbox"/>	<input type="checkbox"/>
C) prevent ALL vertical transmission of hepatitis B virus infection	<input type="checkbox"/>	<input type="checkbox"/>
D) be followed by HbsAg and anti-HBs testing later in life	<input type="checkbox"/>	<input type="checkbox"/>
10. Women found to be HBsAg positive during pregnancy:		
A) should be tested for HBeAg, anti-HBe antibody	<input type="checkbox"/>	<input type="checkbox"/>
B) should have their LFT and HBV DNA checked during pregnancy	<input type="checkbox"/>	<input type="checkbox"/>
C) should have their LFT checked after pregnancy	<input type="checkbox"/>	<input type="checkbox"/>
D) should be given anti-viral treatment routinely during pregnancy	<input type="checkbox"/>	<input type="checkbox"/>

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