

**CME Article**

# Ministry of Health Clinical Practice Guidelines: Chronic Hepatitis B Infection

Chow W C, Chong R, Guan R, Ho K Y L, Leo Y S, Loy K L, Lui H F, Ng H S, Siew W F, Teo E K, Yeo T

**ABSTRACT**

The Ministry of Health (MOH) publishes clinical practice guidelines on Chronic Hepatitis B Infection to provide doctors and patients in Singapore with evidence-based guidance on managing important medical conditions. This article reproduces the introduction and executive summary (with recommendations from the guidelines) from the MOH clinical practice guidelines on Chronic Hepatitis B Infection, for the information of readers of the Singapore Medical Journal. Chapters and page numbers mentioned in the reproduced extract refer to the full text of the guidelines, which are available from the Ministry of Health website (<http://www.moh.gov.sg/mohcorp/publications.aspx?id=26108>). The recommendations should be used with reference to the full text of the guidelines. Following this article are multiple choice questions based on the full text of the guidelines.

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**INTRODUCTION****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 MOH. 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 three years after publication, or if new evidence appears that requires substantive changes to the recommendations.

**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

Changi General Hospital  
H F Lui Digestive & Liver Clinic  
Mount Elizabeth Hospital  
National Healthcare Group Polyclinics  
National University Hospital  
National University of Singapore  
Roland Chong Gastroenterology & Medical Clinic Pte Ltd  
Singapore General Hospital  
Singapore Hepatitis Support Group  
Tan Tock Seng Hospital  
(Institutions listed in alphabetical order)

MOH Clinical Practice Guidelines Workgroup on Chronic Hepatitis B Infection

Correspondence to:  
A/Prof Chow Wan Cheng  
Tel: (65) 6321 4684  
Fax: (65) 6227 3623  
Email: chow.wan.cheng@sgh.com.sg

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 on pg 19 of full text)
- Young adults
- Healthcare 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 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 six 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 (pg 21):

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++**

**D** Babies born to HBsAg-positive mothers should be tested for seroconversion following the hepatitis B vaccination, preferably 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 three-dose vaccine series, check anti-HBs within three months after the booster dose at month 6 (pg 22).

**Grade C, Level 2+**

If anti-HBs is  $\geq 10$  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 immunocompetent 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 two 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 work-up.

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

Consider repeat vaccination with pre-S vaccine or other third-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 (pg 29):

- 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
- Participation in all activities, including contact sports
- Social interaction with others (e.g. in schools, daycare centres)

**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 six-monthly and HBeAg at least 12-monthly.
- ii) ALT 1–2 × ULN: monitor ALT 3–6 monthly and HBeAg six-monthly. Refer to specialist if persistent evidence of early deterioration of liver function or age > 40 years. Consider liver biopsy and treatment if biopsy shows significant liver damage.
- iii) ALT > 2 × ULN: repeat ALT and HBeAg within one to three 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 three months later. If still normal, monitor ALT every 6–12 monthly.
- ii) ALT 1–2 × ULN: monitor ALT 3–6 monthly. Refer to specialist if persistent, evidence of early deterioration of liver function or age > 40 years. If HBV DNA is > 2,000 IU/ml, consider liver biopsy and treat if biopsy shows significant liver damage.
- iii) ALT > 2 × ULN: repeat ALT within one to three months. Refer to specialist if persistent. If HBV DNA > 2,000 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

Six-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, the 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 six 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+**

**SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME**  
**Multiple Choice Questions (Code SMJ 201104B)**

These questions are based on the full text of the guidelines which may be found at <http://www.moh.gov.sg/mohcorp/publications.aspx?id=26108>

- |  | <b>True</b>              | <b>False</b>             |
|--|--------------------------|--------------------------|
| <b>Question 1.</b> 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"/> |
| <br><b>Question 2.</b> 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"/> |
| <br><b>Question 3.</b> Occult HBV 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"/> |
| <br><b>Question 4.</b> 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 and booster were 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 six months or later, after giving a full course of hepatitis B vaccination (three 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"/> |
| <br><b>Question 5.</b> 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 six 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"/> |
| <br><b>Question 6.</b> 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 is > 5 times the upper limit of normal.   | <input type="checkbox"/> | <input type="checkbox"/> |

**Question 7.** Surveillance of hepatocellular carcinoma for patients with chronic HBV infection should include:

- (a) Annual testing of s. alpha-fetoprotein.
- (b) 6–12 monthly US examination routinely.
- (c) 6–12 monthly CT or MRI examination routinely.
- (d) 3–6 monthly serum ALT and alkaline phosphatase.

**Question 8.** Referral to gastroenterologist should be considered:

- (a) If the patient has hepatitis B and hepatitis C or delta co-infection.
- (b) Once the HBV-infected patients are found pregnant (during first trimester).
- (c) As soon as steroidal or other immuno-suppressive treatment is given to a HBV-infected patient.
- (d) With the slightest increase in serum ALT in a HBV-infected patient.

**Question 9.** Hepatitis B vaccination for newborns, whose mothers have chronic hepatitis B virus infection, should:

- (a) Be given within one week after birth.
- (b) Include passive immunisation with immuno-globulin if the mother is HBV DNA positive.
- (c) Prevent ALL vertical transmission of hepatitis B virus infection.
- (d) Be followed by HbsAg and anti-HBs testing later in life.

**Question 10.** Women found to be HBsAg-positive during pregnancy:

- (a) Should be tested for HBeAg, anti-HBe antibody.
- (b) Should have their LFT and HBV DNA checked during pregnancy.
- (c) Should have their LFT checked after pregnancy.
- (d) Should be given anti-viral treatment routinely during pregnancy.

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**Doctor’s particulars:**

Name in full: \_\_\_\_\_

MCR number: \_\_\_\_\_ Specialty: \_\_\_\_\_

Email address: \_\_\_\_\_

**SUBMISSION INSTRUCTIONS:**

(1) Log on at the SMJ website: <http://www.sma.org.sg/cme/smj> and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on “Submit answers” to submit.

**RESULTS:**

(1) Answers will be published in the SMJ June 2011 issue. (2) The MCR numbers of successful candidates will be posted online at [www.sma.org.sg/cme/smj](http://www.sma.org.sg/cme/smj) by 01 June 2011. (3) All online submissions will receive an automatic email acknowledgement. (4) Passing mark is 60%. No mark will be deducted for incorrect answers.(5)The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

**Deadline for submission: (April 2011 SMJ 3B CME programme): 12 noon, 25 May 2011.**