Standard Operative Procedure

Management of Chronic Hepatitis B in adults

Special Region (1)

Union of Myanmar

Version 1.0

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Approved by: Internal Medicine Unit

1. Overview

The main goal of chronic hepatitis B(CHB) treatment is to improve survival and quality of life by preventing disease progression, and consequently HCC development.

Untreated people with CHB show an 8–20% cumulative risk of developing cirrhosis over five years. Those with cirrhosis have an approximately 20% annual risk of hepatic decompensation, and the risk of developing hepatitis B–related hepatocellular carcinoma (HCC) ranges from <1% to 5 %. Untreated people with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years. HCC may still develop even after spontaneous HBsAg loss (annual rate approximately 0.55%). The PAGE-B score appears to predict HCC development even in untreated CHB patients.

2. Clinical features of chronic hepatitis B

Most people are asymptomatic and unaware of their diagnosis. Symptoms when present tend to be mild and nonspecific, such as fatigue and right upper quadrant or epigastric discomfort or ache. Symptoms are more likely to be present once cirrhosis is present. Common symptoms of chronic hepatitis may include fatigue, weakness, nausea, and right upper quadrant pain.

Features of decompensated cirrhosis on clinical examination are portal hypertension (ascites, variceal hemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

3. Investigation for firstly noticed untreated CHB

- Cp auto
- Serum creatinine
- Serum electrolytes
- HBV profile
- Liver function test
- APRI – aspartate platelet ratio index (AST/Plt) {APRI > 0.5 = liver fibrosis and APRI>1 = liver cirrhosis}
- AFP (investigate only if there is history, clinical or radiological features of cirrhosis)
- USG abdomen – to screen for steatotic liver disease, cirrhosis or hepatocellular carcinoma
- transient elastography and HBV viral load (if available)

4. Indications to start antiviral therapy

Any of the following

- Features of decompensated cirrhosis on clinical examination
- coinfections (such as HIV, hepatitis D or hepatitis C)
- family history of liver cancer or cirrhosis
- immune suppression (such as long-term steroids, solid organ or stem cell transplant)
- comorbidities (such as diabetes or metabolic dysfunction—associated steatotic liver disease)
- extrahepatic manifestations (such as glomerulonephritis or vasculitis)
- APRI score >0.5
- Persistence abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period)
- Ultrasonography evidence of cirrhosis of liver

- transient elastography>7 kPa
- HBV DNA>2000 IU/mL AND ALT level > ULN

Note

- metabolic dysfunction associated steatotic liver diseases are dyslipidaemia or obesity associated liver diseases.

5. Antiviral treatment

TDF, ETV and TAF are recommended antiviral drugs for people with CHB.

ETV and TAF (if available) are recommended for people with established osteoporosis and/or impaired kidney function.

Antiviral doses according to creatinine clearance

Drug	**CrCl (mL/min) by using the Cockcroft–Gault (CG) or MDRD formulas**			
	>50	30–49	10–29	<10, Hemodialysis or continuous ambulatory peritoneal dialysis
TDF	300 mg OD	300 mg every 48 hours	300-mg every 72–96 hours	Every seven days or one 300-mg tablet following completion of approximately every 12 hours of dialysis
ETV	0.5 mg OD	0.25 mg OD **OR** 0.5 mg every 48 hours	0.15 mg OD **OR** 0.5 mg every 72 hours	0.05 mg OD **OR** 0.5 mg every 7 days
ETV (decompensated liver disease)	1 mg OD	0.5 mg OD **OR** 1 mg every 48 hours	0.3 mg OD **OR** 1 mg every 72 hours	0.1 mg OD **OR** 1 mg every 7 days
TAF	25 mg OD	25 mg OD	25 mg OD at CrCl 15-29 mL/min Not recommended for CrCl < 15 mL/min	CrCl less than 15 mL/ min) not receiving chronic hemodialysis: not recommended.

6. Duration of treatment

	Duration of antiviral therapy
CHB with cirrhosis	Lifelong
Non-cirrhotic CHB	Can be discontinued until met the discontinuation criteria (mention below)

Discontinuation of oral antiviral therapy may be considered exceptionally for:

1. people without clinical evidence of cirrhosis

   and

   people who can be followed carefully after discontinuation and long term for reactivation

   and

   if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment

   and

   in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

2. If HBV DNA testing is not available: discontinuing oral antiviral may be considered for people who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of previous HBeAg status.

7. Treatment response

	HBe Ag positive		HBe Ag negative	
Tenofovir	Virological response	97 % after 5 years	Virological response after 5 years	98 %
	ALT normalization	73 % after 5 years	normal ALT after 5 years	95 %
	HBe Ag loss	49 % after 5 years		
	HBs Ag loss	10 % after 5 years 3 % after 48 - 52 weeks	HBs Ag loss after 8 years	1 %
	HBs Ag seroconversion	8 % after 5 years		
Entecavir	Virological response	67% after 48-52 weeks	Virological response after 48-52 weeks	90%
	HBs Ag loss	2 % after 48-52 weeks	HBs Ag loss after 48-52 weeks	0%
	ALT normalization	68% after 48-52 weeks	ALT normalization after 48-52 weeks	78%
	Anti-HBe-seroconversion	21% after 48-52 weeks		
TAF	Virological response at 48 weeks	64 %	Virological response at 48-52 weeks	94%
	Virological response at 96 weeks	75 %		
	HBeAg loss at 48-52weeks	14 % and 22 %		
	Anti- HBe seroconversion at 48-52 weeks	10 % and 18 %		
	ALT normalization at week 96	72 %	ALT normalization after 48-52 weeks	83%
	HBsAg loss after 48-52 weeks	1%	HBsAg loss after 48-52 weeks	0%

Note - Rate of HBeAg seroconversion with present antivirals closely related to pre-treatment ALT (<10% if ALT < x2 ULN, >50% if ALT > x5 ULN).

8. Treatment failure and management

Primary antiviral therapy failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by >1 $\log_{10}$ IU/mL within three months. Secondary antiviral therapy failure may be defined as a rebound of HBV DNA levels of >1$\log_{10}$ IU/mL from the nadir among people with an initial antiviral therapy effect (>1 $\log_{10}$ IU/mL decrease in serum HBV DNA).

Management of antiviral resistance

Antiviral drug	Recommended management
Lamivudine	Swift to tenofovir
Tenofovir	No resistance to date
Entecavir	Swift to tenofovir

9. Management of Mother to child transmission for CHB

	Indication to start antiviral treatment	Antiviral drug
Pregnancy already on antiviral treatment		Continue current antiviral treatment
Pregnancy without antiviral treatment	HBV DNA > 200,000 IU/ml Or Positive HBe Ag Or HBs Ag alone (if HBV DNA and HBe Ag are not available)	• Start TDF from second trimester until at least delivery or completion of the infant HBV vaccination series • antiviral drugs ➢ TDF – recommended ➢ TAF – not recommended ➢ ETV – category C for pregnancy

Note

- Starting prophylaxis during the second trimester has been shown to be more efficacious than starting during the third trimester.

10. Management of HBV and HCV coinfection

The frequency of HCV-HBV dual infection ranges between 1% and 15% globally, depending on research populations and geographic areas. Hepatitis C and B viruses are the two most prevalent causes of liver disease in the whole globe. Individuals who have both HCV and HBV are more probable to develop cirrhosis, have more severe liver disease, and are at a higher risk of developing hepatocellular carcinoma In many instances of coinfection, HCV is the dominant virus and may in fact suppress levels of HBV DNA. People with both HCV and HBV have a much higher risk of developing HCC, and this is more likely to be an infiltrating and aggressive form of HCC and to occur at a younger age than those with nodular HCC, suggesting accelerated hepatocarcinogenesis with coinfection. Treatment for both infections is generally required.
The presence of active or past hepatitis B is not an impediment to HCV therapy, but those starting HCV direct-acting antiviral therapy should be assessed for current or past HBV infection and monitored for potential post-therapy HBV reactivation. There is a moderate risk of HBV reactivation among HBsAg-positive

people receiving HCV direct-acting antiviral therapy, and HBsAg-positive people should therefore be treated with a nucleoside analogue during and after direct-acting HCV antiviral therapy. All coinfected people should be monitored by measuring serum ALT and HBV DNA during HCV infection.

HBsAg-positive people should be treated with oral antiviral drug during and after direct-acting HCV antiviral therapy.

11. Monitoring for people with CHB

	Investigation	Frequency
For CHB (currently not meet for indication of antiviral drug)	APRI (transient elastography if available), CP (auto), ALT, AST, SB, PT, creatinine, HBV DNA (if available), HBs Ag and HBeAg/anti HBe	3 monthly* - APRI (transient elastography if available), CP (auto), ALT, AST, SB, PT, creatinine, USG (abdomen) Annually - HBs Ag and HBeAg/anti HBe, HBV DNA (if available)
For CHB (non-cirrhosis) on antiviral drug	APRI (transient elastography if available), CP (auto), ALT, AST, SB, PT, creatinine, HBV DNA (if available), HBs Ag and HBeAg/anti HBe	Annually
For CHB (compensated or decompensated cirrhosis)	APRI (transient elastography if available), CP (auto), ALT, AST, SB, PT, creatinine, HBV DNA (if available), HBs Ag and HBeAg/anti HBe, USG (abdomen) and AFP	6 monthly (note – HBV DNA annually)
Treatment adherence should be monitored regularly and at each visit. ***3 monthly during 1st year of enrollment followed by 6 monthly**		

Surveillance for hepatocellular carcinoma (HCC) among people with CHB
Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:

- people with cirrhosis, regardless of age or other risk factors;
- people with a family history of HCC; and
- people older than 40 years and with HBV DNA level >20,000 IU/mL

12. Abbreviation

AFB – alpfafeto protein

ALT – alanine aminotransferase

APRI – aspartate platelet ratio index

AST – aspartate aminotransferase

CCG - Cockcroft and Gault

CHB – chronic hepatitis B

CrCl – creatinine clearence

ETV – entecavir

HCC – hepatocellular carcinoma

MDRD - Modification of Diet in Renal Disease Study Group

MTCT – mother to child transmission

Plt – platelet

SB – serum bilirubin

TAF - Tenofovir alafenamide

TDF - Tenofovir disoproxil

ULN -upper limit of normal

13. Online calculators

APRI - AST to Platelet Ratio Index (APRI) Calculator - Clinical Calculators - Hepatitis C Online

CCG - https://www.mdcalc.com/calc/43/creatinine-clearance-cockcroft-gault-equation?uuid=18a0126b-1dc6-40f2-9f95-7f5b681a90fe&utm_source=mdcalc

MDRD -- https://www.mdcalc.com/calc/76/mdrd-gfr-equation?uuid=99800e55-a77b-4440-913c-163194b43870&utm_source=mdcalc

PAGE -B https://mdac.cuhk.edu.hk/calculators/page-b/

14. Reference

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