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Managing patients with advanced liver disease

KEY POINTS

- Determine the phase of the hepatitis B virus (HBV) infection.
- Determine the severity of the liver disease.
- Fully evaluate the patient to identify factors contributing to liver damage.
- Minimise other hepatic injury:
  - manage other causes of liver disease or damage
  - advise on healthy living.
- Offer antiviral therapy where appropriate – treat all cirrhotic patients with antiviral therapy.
- Manage the complications of cirrhosis.
- Implement screening for hepatocellular carcinoma as recommended in Hepatitis B related hepatocellular carcinoma.

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Introduction

People with chronic hepatitis B (CHB) virus infection are at an increased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), with 15–40% developing complications during their lifetime (1). Cirrhosis is a histopathological diagnosis, describing liver fibrosis with nodule formation, due to liver cell necrosis and regeneration. Cirrhosis also refers to a clinical condition, and can either be compensated, where liver function is relatively preserved, or decompensated. Decompensated cirrhosis refers to the complications of jaundice, ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, associated renal impairment or HCC. If the cause of the liver disease can be removed, early cirrhosis may reverse in some patients.

The pathological process in cirrhosis is increased hepatic fibrosis by activated stellate cells in response to hepatocyte death; it is at first limited in extent, then forms portal-to-portal or portal-to-central vein bridging, finally leading to nodule formation. Cirrhosis leads to altered liver perfusion, with a decrease in portal vein flow and a compensatory increase in hepatic artery input. This adversely affects hepatocyte function over time. Nevertheless, patients with stable cirrhosis may live for many years without major complications. In hepatitis B virus (HBV) infection, progression of the inflammatory and fibrotic processes is more rapid in those with raised alanine aminotransferase (ALT) levels and in those with detectable HBV DNA.

Patients with advanced liver disease, with or without ongoing hepatic inflammation, present clinicians with significant management challenges. Adding to the complexity of the management process are untreated cofactors such as hepatitis C virus (HCV) infection, alcohol use, non-alcoholic fatty liver disease (NAFLD), with its associated insulin resistance, and smoking. With treatment, these patients may still enjoy months or years of an acceptable quality of life, even if the underlying condition cannot be reversed. Liver transplantation can provide a better quality of life, but availability is limited. This chapter focuses on the management of advanced liver disease in patients with CHB infection, assuming that HBV has been identified as an issue.

Determine the phase of the hepatitis B virus infection

The phase of the disease must be established, so that appropriate decisions on antiviral therapy can be made (see: "Virology: viral replication and drug resistance" and "Hepatitis B virus testing and interpreting test results"). Despite barriers to initiating and maintaining therapy, all patients with advanced liver disease should be treated with an oral antiviral agent. Suppression of HBV DNA to undetectable levels is an important goal in treatment of cirrhosis caused by CHB. Engaging the patient in a management plan may increase the possibility of ultimately being able to use antiviral therapy.

Determine the presence or absence of cirrhosis and the severity of the liver disease

Cirrhosis may be present in the absence of symptoms, clinical signs or abnormal liver tests. It is therefore important to determine, where possible, the presence or absence of cirrhosis. Liver biopsy has been the gold standard for quantifying hepatic fibrosis, but is much less frequently undertaken now given increasing availability of non-invasive means of assessing fibrosis. Transient elastography (FibroScan®, Echosens) is the most commonly used test for determining fibrosis stage. A liver stiffness measurement more than 12 kPa at a reliable measurement can be considered diagnostic of severe fibrosis or cirrhosis. (2)

Ultrasound technology using shear wave elastography is becoming more widely available, including acoustic radiation force impulse (ARFI, Siemans), and Aixplorer (SuperSonic Imagine). Emerging data suggest their accuracy may be similar to FibroScan. In addition, shear wave elastography performed by Hitachi, Toshiba or GE is becoming more widely available. Data for these novel modalities may become useful. However, equivalent cut-off measurements have not yet been validated in patients with CHB.

Where FibroScan is unavailable and the patient declines a biopsy, ultrasound performed by experienced technicians may identify cirrhosis and portal hypertension. However, the sensitivity of ultrasound in detecting cirrhosis may be as low as 50%; hence, a normal liver ultrasound cannot be used to exclude the presence of cirrhosis. Serum biomarkers, including aspartate aminotransferase (AST) to platelet ratio index (APRI) and Fibrosis-4 Index for Liver Fibrosis (FIB-4) also provide information on fibrosis severity.

Having established the presence or absence of cirrhosis, the severity of the liver disease should be assessed. A full physical and laboratory work-up is needed, so that signs of cirrhosis and portal hypertension, and their complications, can be documented at baseline. Documentation allows relevant management strategies to be offered and progress to be evaluated appropriately.

Assessment of cirrhosis and severity of liver disease
Assessment for the following is required:
Chronic liver disease – spider naevi

– hepatic palms (palmar erythema)
– nail changes (leukonychia)
– gynaecomastia
– hepatomegaly
Portal hypertension
– splenomegaly
– collateral vessels on abdominal wall or caput medusae (around umbilicus)
– ascites
– varices (evidenced by ultrasound, computed tomography and endoscopy)
Fluid and electrolyte and renal impairment
– oedema
– pleural effusion
– decreased urine output
– hyponatraemia
– hypo/hyperkalaemia
– elevated serum creatinine
Portal systemic encephalopathy (PSE)
– minimal (sub-clinical) PSE may be subtle and require number-connection tests, the sANT1 test or STROOP testing for detection
– reversed sleep-wake cycle (daytime somnolence and nocturnal waking)
– slowing of normal response times, reflexes
– impaired driving skills
– lack of energy
– metabolic flap (asterixis)
– confusion, disorientation
– increasing drowsiness
– coma (hepatic failure) is a late sign
Hepatic decompensation
– jaundice
– bruising, bleeding
– spontaneous bacterial peritonitis
– hepatocellular carcinoma
– impaired renal function (hepatorenal syndrome)
Extrahepatic manifestations of advanced liver disease
– cardiomyopathy
– hepatopulmonary syndrome
– metabolic bone disease and risk of fractures
– hormonal complications
* testicular atrophy and feminisation in men
* hirsutism and amenorrhoea in women
– increased risk of serious infections
Nutritional assessment
– body mass index (may not be useful if there is significant fluid retention)
– waist circumference (may not be useful if ascites)
– proximal muscle wasting.
See standard texts on liver disease for a more detailed description of these manifestations (3–7).

Fully evaluate the patient to identify all factors contributing to liver damage

All patients should have a detailed history and examination performed to establish:

- underlying medical conditions including co-infection with hepatitis C or D viruses, or human immunodeficiency virus (HIV), which will influence the course of the disease
- medication use
  – prescribed
  – alternative or complementary medicine and over-the-counter drugs
- tobacco use
- alcohol use (there is no safe alcohol consumption in cirrhosis)
- recreational drug use (especially cannabis which may promote fibrosis)
- family history of liver disease, diabetes
- weight, body mass index
- evidence of diabetes or other organ system disease
- other forms of liver disease (e.g. haemochromatosis, autoimmune liver disease).

Cofactors for liver disease should be addressed in patients with advanced liver disease, as far as possible. Specifically, obesity should be controlled, and alcohol and cannabis use ceased (or markedly reduced if abstinence is not an option). Paracetamol can be used at a reduced dose (< 2 g a day), and non-steroidal anti-inflammatory therapy should be avoided due to the increased risk of nephrotoxicity. Medications may require dose reduction or may be contraindicated due to pharmacokinetics or risk of hepatotoxicity. Exercise should be maintained, where possible, to help preserve muscle mass, cardiovascular fitness, functional status and quality of life.

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Having advised the patient about other factors that can aggravate liver disease, the clinician must then focus on a specific management plan for the advanced liver disease.

Offer antiviral therapy where appropriate

The treatment of CHB is discussed in detail in Treatment of chronic hepatitis B virus infection. All patients should be evaluated for possible antiviral therapy with an oral nucleos(t)ide analogue (NA), entecavir or tenofovir, because these drugs will significantly modify disease progression. Pegylated interferon is rarely used in patients with compensated cirrhosis and is contraindicated in those with decompensated cirrhosis, but NAs are generally well tolerated. All cirrhotic patients with detectable HBV DNA should be treated with NAs.

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Manage and prevent the complications of advanced liver disease

Management strategies

Following the diagnosis of cirrhosis, the following steps should be taken.

1. Upper gastro-intestinal endoscopy (UGIE or gastroscopy)
Gastroscopy is important to screen for the presence of gastroesophageal varices in patients with cirrhosis. However, recent guidelines and consensus statements suggest that patients with both liver stiffness measurements below 20 kPa on transient elastography (FibroScan) and platelet counts above 150 / $mm^3$are very unlikely (< 5%) to have high-risk varices. In these patients, gastroscopy can safely be avoided (8).

2. HCC screening (see: Hepatitis B related hepatocellular carcinoma)
The risk of HCC must be addressed in patients with CHB infection. Patients with CHB remain at risk of HCC, including those on long-term suppression with NAs and those without cirrhosis. In fact, HCC may be the only factor affecting survival in patients with CHB on long-term therapy with NA (9). Patients with CHB and cirrhosis should undergo screening for HCC at baseline and ongoing surveillance with 6-monthly abdominal ultrasound examinations. The role of 6-monthly serum alpha-fetoprotein (AFP) levels remains controversial, with some practitioners preferring to use both ultrasound and AFP to screen particularly where ultrasound is less available such as in remote Australia.

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3. Referral to a liver transplant unit
Not all patients will be suitable for transplant or even for referral to a transplant unit. However, this decision should be considered and documented. Two means of objectively assessing severity of liver disease are the Child-Turcotte-Pugh score and the Model of End-Stage Liver Disease (MELD) score. The scoring system for the Child Pugh Turcotte model is shown in Table 8.1. The MELD score is calculated using data for serum bilirubin, serum creatinine and the international normalised ratio (INR). Online calculators can easily provide a score if these results are available. Patients who have a high Child-Pugh class B or Child-Pugh class C cirrhosis and MELD score of over 15 should be referred for consideration of transplantation if there are no contraindications. Table 8.2demonstrates the link between MELD scores and life expectancies.

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Table 8.1 Child-Turcotte-Pugh scoring system for cirrhosis

Measure	1 point	2 points	3 points	Units
Bilirubin (total)	< 35 (< 2)	35–51 (2–3)	> 51 (> 3)	µmol/L (mg/dL)
Serum albumin	> 35	28–35	< 28	g/L
International normalised ratio	< 1.7	1.71–2.20	> 2.20	-
Ascites	None	Mild	Moderate/severe	-
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)	-

Points	Class	1-year survival (%)	2-year survival (%)
5-6	A	100	85
7-9	B	81	57
10-15	C	45	35

Table 8.2 Model of End-Stage Liver Disease (MELD) score and prognosis in chronic liver disease

Score	Predicted 6-month survival (%)	Predicted 12-month survival (%)	Predicted 24-month survival (%)
0-9	98	93	90
10-19	92	86	80
20-29	78	71	66
30-39	40	37	33

Dietary modification in advanced liver disease

Patients with advanced liver disease often eat poorly, and in the past this has been complicated by advice to reduce protein and sodium intake. It is clear that patients do better if they can eat frequent small meals daily, low in saturated fat but with adequate dietary protein, fruit and vegetables. Evening food intake enhances hepatic regeneration and recovery from hepatic insults and, in hospital patients, it reduces morbidity and mortality.

Fluid and electrolyte abnormalities (including ascites)

Fluid and electrolyte abnormalities in patients with cirrhosis are common and include:

- abnormal serum sodium, especially hyponatraemia
- abnormal serum potassium, particularly hypokalaemia due to diuretics
- metabolic alkalosis, often associated with hypokalaemia
- fluid retention, such as ascites or peripheral oedema
- renal impairment, including hepatorenal syndrome.

Management involves correcting fluid and electrolyte imbalances, and may include:

- potassium supplementation
- salt restriction
- water restriction
- reducing or ceasing diuretics to avoid hepatorenal syndrome.

Additional therapy for ascites may be required with regular large volume paracentesis (ascitic tap). Medications to avoid in ascites include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs (NSAIDs) and beta blockers. Some patients are treated with transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressure and decrease ascites accumulation.

– All patients presenting with ascites should have a diagnostic tap to exclude spontaneous bacterial peritonitis.
– Patients with recurrent ascites should be referred to a specialist unit or for consideration of transplantation.

Portal hypertension

Portal hypertension is managed by:

- non-selective beta blockers (propranolol or carvedilol)
- prophylactic variceal band ligation of high-risk oesophageal varices
- treating acute bleeding when it occurs
- considering TIPS if conservative measures fail.

Cirrhotic patients with portal hypertension have an increased risk of portal vein thrombosis (PVT). Currently, there are no formal recommendations about use of low molecular weight heparin in this situation, but there is increasing interest in its use, because it appears to reduce risk of both PVT and mortality from other causes (5).

Portal systemic encephalopathy

Portal systemic encephalopathy is managed by:

- maintaining electrolyte balance
- using lactulose to clear the colon and alter ammonia metabolism and diffusion (use doses to ensure two to three soft stools per day, and continue use long term)
- considering use of rifaximin, a non-absorbable antibiotic; available on PBS Authority for the prevention of hepatic encephalopathy in patients with a prior episode and in whom lactulose is not tolerated or is ineffective
- continuing normal protein intake, which is critical for hepatic regeneration.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is managed by:

- having a low threshold of suspicion in a patient with onset or worsening of encephalopathy, deteriorating renal function, renal failure or generally unwell. Ascites presenting with fever, abdominal pain and vomiting is an uncommon presentation of SBP.
- early referral to emergency department or for hospital admission if diagnosis is suspected
- confirmation of diagnosis by ascitic tap (white cell count > 500/mm^3or neutrophils > 250/mm^3)
- treatment of acute episode with appropriate IV antibiotics, with or without albumin
- prophylaxis with co-trimoxazole (alternative norfloxacin) for all patients with previous proven episode of SBP, and patients with ascites and low ascitic protein concentration (< 10 g/L).

Advancing hepatic failure

Advancing hepatic failure is managed by:

- avoiding and managing factors that aggravate the liver disease
  – alcohol, cannabis, tobacco
  – some medications (e.g. excess paracetamol, NSAIDs)
  – obesity
  – injecting drug use
  – iron overload
  – diabetes
  – hepatitis C infection
- monitoring magnesium (Mg), zinc (Zn), calcium (Ca) and fat-soluble vitamins
- regularly checking for infection (e.g. cellulitis, chest infection)
- avoiding certain infection risks (e.g. avoid uncooked oysters because of the risk of *Vibrio vulnificus*infection)
- providing routine vaccination against influenza and pneumonia

Summary

The management of patients living with CHB cirrhosis remains challenging. While effective antiviral therapy with NA reduces the risk of cirrhosis progression, cofactors such as NAFLD or alcohol can lead to ongoing liver damage. Clinical presentation with decompensated cirrhosis frequently involves multiple organ systems, and management frequently involves several specialty disciplines, allied health and nursing support. Regular ultrasound scanning (USS) surveillance for HCC should be emphasised.

Hepatitis B related hepatocellular carcinoma

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