

MANAGING PATIENTS WITH ADVANCED LIVER DISEASE

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Robert Batey

University of New South Wales, Bankstown Hospital, Bankstown, NSW.

Links to: Chapter 7: Treatment of chronic hepatitis B virus infection
Chapter 9: Hepatitis B virus-related hepatocellular carcinoma

KEY POINTS

- Address the underlying HBV infection
 - Define the severity of disease
 - Offer anti-viral therapy where appropriate
- Minimise other hepatic injury
 - Exclude other causes of liver disease
 - Advise on healthy living
- Manage the complications of cirrhosis

People with chronic hepatitis B virus (HBV) infection are at an increased risk of developing liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), with 15–40% developing serious sequelae during their lifetime. Cirrhosis is a histopathological diagnosis, describing liver fibrosis with nodule formation subsequent to liver cell necrosis and regeneration. Fibrosis in response to hepatocyte death is due to stellate cell activation and 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 survive many years without major complications.

In HBV infection, the progression of inflammatory and fibrotic processes is more active in those with raised ALT levels and in those with a high HBV DNA.

Patients with advanced liver disease, with or without ongoing hepatic inflammation,

present clinicians with significant management challenges. The presence of untreated or untreatable HBV or hepatitis C virus (HCV) infection or continuing damage from other factors, such as alcohol use or non alcoholic fatty liver disease, or insulin resistance, adds to the complexity of the management process. If treated well, these patients may still enjoy months to years of an acceptable quality of life, even if the underlying condition cannot be cured. Ultimately, liver transplantation provides a better outcome if it can be achieved, but this is not realistic for many patients. This chapter will focus on the management of advanced liver disease in patients with chronic HBV infection. There are three issues that should be addressed in managing this group of patients.

1. Addressing the underlying HBV infection

The treatment of chronic HBV is discussed in detail in Chapter 7: Treatment of chronic hepatitis B virus infection. All patients should be evaluated for possible antiviral therapy with pegylated interferon or an oral nucleoside or a nucleotide analogue agent such as entecavir, as these drugs can significantly modify the

progression of the disease. Interferon-based therapies are contra-indicated in patients with decompensated cirrhosis, but oral antiviral agents are generally very well tolerated.

2. Reducing other hepatic insults

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

- Underlying medical conditions, including co-infection with hepatitis C, hepatitis D or the human immunodeficiency virus (HIV).
- Medication use
 - Prescribed
 - Alternative or complementary medicine and over-the-counter drugs
- Tobacco use
- Alcohol use
- Recreational drug use
- Family history of liver disease, diabetes
- Weight, body mass index (BMI)
- Evidence of diabetes or other organ system disease.

Patients with advanced liver disease should have all co-existing disorders addressed as far as possible, in addition to having the primary disease and its complications managed. Specifically, weight reduction when obesity is an issue and cessation of alcohol use (or markedly reducing alcohol consumption if abstinence is not an option) are critical processes in the management of this group of patients. Patients should also avoid excessive use of paracetamol and non steroidal anti-inflammatory therapy. Drugs known to cause liver disease should be used with caution, although underlying liver disease does not increase the risk of side effects.

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

3. Managing the complications of advanced liver disease

It is important to document the extent of liver disease through a detailed history and clinical examination. It is imperative that the patient is regularly reviewed in the same detailed manner,

as the disease process evolves over time. In the initial examination, the patient's history, his/her examination and all investigations are required to document or rule out the following conditions:

- **Chronic liver disease**
 - Hepatosplenomegaly
 - Spider naevi
 - Hepatic palms (palmar erythema)
 - Hepatic lunules (changes at nail base)
 - Loss of body hair distribution in men
 - Hirsutism in women
 - Testicular atrophy
- **Fluid and electrolyte balance problems**
 - Oedema
 - Ascites, pleural effusion
 - Decreased urine output
 - Hyponatraemia
 - Hypo/hyperkalaemia
 - Rising creatinine
- **Portal hypertension**
 - Hepatomegaly and splenomegaly
 - Collateral vessels on anterior abdominal wall
 - Caput medusae
 - Ascites
 - Overt or occult gastrointestinal haemorrhage
 - Portal systemic encephalopathy (PSE)
 - Varices (evidence by ultrasound, computed tomography or endoscopy)
- **Portal systemic encephalopathy**
 - Reversed sleep pattern (day time somnolence and nocturnal waking)
 - Metabolic flap or asterixis
 - Slowing of normal response times, reflexes
 - Impaired driving skills
 - Lack of energy
 - Confusion
 - Increasing drowsiness
 - Coma
- **Advancing hepatic decompensation**
 - Anorexia
 - Jaundice
 - Bruising and bleeding problems
 - Spontaneous bacterial peritonitis
 - Metabolic bone disease and risk of fractures
 - Impaired glucose homeostasis
 - Impaired renal function

▪ **Extrahepatic manifestations of advanced liver disease**

- Cirrhotic cardiomyopathy
- Hepatopulmonary syndromes
- Hormonal complications
 - testicular atrophy and feminisation in men
 - hirsutism, amenorrhoea in women
- Increased risk of generalized infectious complications

▪ **Hepatocellular carcinoma**

Readers are referred to Chapter 9: Hepatitis B virus-related hepatocellular carcinoma and standard texts on liver disease for a more detailed description of this condition.

Management strategies

Management strategies should address all of the conditions identified above and strategies will need to be monitored to assure treatment efficacy, to minimise complications and to allow changes to the management plan as the disease progresses or improves.

Fluid and electrolyte problems are managed by:

- Restricting salt and water intake where necessary
- Ensuring electrolyte balance
 - Cautious diuretic usage to minimise the risk of hepatorenal syndrome
 - Spironolactone is the preferred agent, in doses from 25–400 mg per day
 - Low dose frusemide
 - Potassium supplements as necessary
 - A diet low in saturated fat with adequate protein, fruit and vegetables
 - Monitoring progress with regular serum creatinine and urine electrolyte assays. When urine sodium falls below 20 mmol/day, decreased renal perfusion is likely (reduce diuretic, consider saline infusion over one hour)
- Drainage of ascites may be necessary. In some patients this may need to become a regular process, as diuretics and other conservative management approaches often fail to control the problem. The procedure is described in standard texts. 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 or diagnose spontaneous bacterial peritonitis*

Portal hypertension is managed by:

- All patients with newly diagnosed cirrhosis should undergo endoscopy to determine if varices are present
- Reducing hepatic inflammation when possible
- Prophylactically modifying portal pressure with beta-blocking agents or nitrate therapy
- Banding oesophageal varices when they are identified
- Treating acute bleeding when it occurs
- Considering more active interventions if conservative measures fail
 - TIPS (transjugular, intrahepatic portosystemic shunts)
 - Surgery for portal hypertension (rarely undertaken these days), which includes shunting procedures and oesophageal transection).

Portal systemic encephalopathy is managed by:

- Regulating protein intake ensuring a reasonable intake to maintain nutritional status, while reducing total protein and animal protein
- Maintaining optimal electrolyte balance
- Using lactulose to both clear the colon and alter ammonia metabolism and diffusion. Use doses to ensure two soft stools per day and continue use long term
- Using neomycin and metronidazole short term if lactulose is not tolerated or if it is not effective. These agents also act to reduce ammonia levels, but they have significant side effects with long-term use

Agents such as L-dopa, bromocriptine, and branch chain amino acid solutions (oral and parenteral) have been trialled in portal systemic encephalopathy, but their efficacy is not proven.

Advancing hepatic failure is managed by:

- Avoiding and managing factors that aggravate the liver disease
 - Alcohol
 - Some medications (e.g. excess paracetamol, ibuprofen, anti-tuberculosis agents)
 - Obesity
 - Injecting drug use
 - Iron overload
 - Diabetes
 - Hepatitis C infection
- Monitoring Mg, Zn, Ca, fat soluble vitamins (monthly at first to determine the patient's ability to maintain normal levels)
- Regularly checking for infection, e.g. spontaneous bacterial peritonitis (SBP)
- Avoiding certain infection risks, e.g. avoiding oysters with their risk of vibrio vulnificans infection
- Providing routine vaccination against influenza and pneumococcal disease
- Aggressively treating infections
- Managing portal hypertension
- Managing portal systemic encephalopathy
- Managing ascites
- Ongoing screening for the risk of HCC.

The risk of HCC must be addressed in patients with chronic HBV infection. Both cirrhotic and, to a lesser extent, non-cirrhotic patients are at risk of this complication.

Recommended reading

1. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-36.
2. Schiff ER, Sorrell MF, Maddrey WC. Schiff's Diseases of the Liver (10th edition); Vol 1 and 2. Philadelphia: Lippincott Williams & Wilkins; 2007.
3. Sherlock S, Summerfield JA. A colour atlas of liver disease. London: Wolfe Medical Publications Ltd; 1979.