MedicineToday | PEER REVIEWED ARTICLE | POINTS: 2 CPD/1 PDP

Digestive Health Foundation

Cirrhosis
a management guide

Treating the aetiology, managing the clinical manifestations and screening patients for life-threatening complications are key principles in the management of patients with cirrhosis.

GOKULAN PAVENDRANATHAN
MB BS

SIMONE I. STRASSER
MB BS, MD, FRACP

Dr Pavendranathan is an Advanced Trainee in Gastroenterology at the AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown, Sydney.
Associate Professor Strasser is Chair of the Digestive Health Foundation of the Gastroenterological Society of Australia, and Senior Staff Specialist at the AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown, Sydney, NSW.

Cirrhosis is a diffuse process affecting the liver in which progressive hepatic fibrosis and regenerative nodules result in distortion of the normal hepatic architecture. The most common causes of cirrhosis in Australia are alcohol consumption, viral hepatitis and nonalcoholic fatty liver disease.

Despite the wide array of causes, the progression of cirrhosis and its complications are common to all aetiologies. Patients with cirrhosis may have well compensated disease with preservation of liver function or the disease may become decompensated, with patients developing ascites, jaundice, encephalopathy and synthetic dysfunction. Decompensation can be defined as the first onset or deterioration in one of the above features. Patients with cirrhosis are also at risk of hepatocellular carcinoma.

Assessment

Determining the aetiology

Determining the cause of cirrhosis is an important part of the assessment of a cirrhotic patient. The aetiology may influence treatment decisions, prognosis, assessment for complications and screening of family members. There are many diseases in which treatment of the underlying disorder may lead to reversal of decompensation and sometimes the histological changes of cirrhosis. Examples include:

- corticosteroid treatment in cirrhotic patients with autoimmune hepatitis
- antiviral treatment in patients with hepatitis B
- alcohol abstinence in patients with alcoholic cirrhosis.

Hence, every patient with newly diagnosed cirrhosis

IN SUMMARY

- **Every patient with newly diagnosed cirrhosis warrants a thorough assessment for the aetiology.**
- **Recent deterioration in a patient or new onset ascites, jaundice or encephalopathy should prompt a thorough search for a precipitant of decompensation.**
- **A low platelet count is a very useful clue to the presence of cirrhosis and portal hypertension.**
- **Withdrawal or treatment of the aetiological factor may lead to reversal of decompensation and sometimes reversal of the histological changes of cirrhosis.**
- **Patients with cirrhosis, particularly those with ascites, are often severely malnourished.**
- **Protein intake should not be restricted in patients with severe liver disease and chronic hepatic encephalopathy.**
- **All patients with cirrhosis should be screened regularly for hepatocellular carcinoma and have an endoscopy to screen for varices.**
- **Patients aged less than 65 years with decompensated cirrhosis or early hepatocellular carcinoma should be considered for liver transplantation, unless contraindications apply.**

warrants a thorough assessment for the aetiology. The causes of cirrhosis are summarised in Table 1.

History

History is probably the most important aspect of the assessment of patients with cirrhosis. The emphasis should be on determining the aetiology and duration of disease, complications of cirrhosis, the patient's social supports and his or her nutritional status. Clues to the aetiology include:

- extent and duration of alcohol intake
- ethnicity and country of birth
- history of injecting drug use
- history of a transfusion of blood products before 1991
- family history of liver disease
- history of obesity, diabetes and the metabolic syndrome (which are all risk factors for nonalcoholic fatty liver disease).

If a patient's health has deteriorated recently or he or she has a new onset of ascites, jaundice or encephalopathy, precipitants of decompensation should be explored. These include a binge of alcohol, infection or sepsis, constipation, dehydration, a change in medication regimen (particularly diuretics and sedatives), gastrointestinal bleeding and the development of hepatocellular carcinoma.

Examination

The physical signs of chronic liver disease are easily recognisable. These include leuconychia, palmar erythema, spider naevi, jaundice, gynaecomastia, ascites, splenomegaly, oedema and the presence of a hepatic flap and foetor if the patient is encephalopathic.

The presence of ascites and splenomegaly are important clinical signs as they suggest the patient has developed portal hypertension and probably has oesophageal varices.

The presence of hepatic encephalopathy is also important to recognise and treat early, and the patient may warrant an urgent hospital admission. The early signs of encephalopathy include sleep inversion (i.e. awake at night, sleepy during day), poor concentration, mood swings and irritability. It is now appreciated that recognition and treatment of even subclinical encephalopathy, with only minor cognitive disturbance, may be beneficial.

Managing patients with cirrhosis

Despite the wide range of causes of cirrhosis, the progression of this disease and its complications are common to all aetiologies. Patients with cirrhosis may have well compensated disease with preservation of liver function or the disease may become decompensated, with patients developing ascites, jaundice, encephalopathy or synthetic dysfunction. Patients with cirrhosis are also at risk of hepatocellular carcinoma. Withdrawal or treatment of the causative factors may lead to reversal of decompensation and sometimes reversal of the histological changes of cirrhosis.

Investigations

Investigations in chronic liver disease are aimed at establishing the aetiology (see Table 1), assessing severity and screening for complications. Abnormal liver function tests may be the first indicator of the presence of chronic liver disease. The pattern of liver enzyme abnormality may give a clue to diagnosis. For instance, high gamma glutamyltransferase (GGT) and alkaline

Table 1. Cirrhosis: major causes and relevant investigations

Aetiology and examples	Investigations
Infections	
Hepatitis B	HBsAg
Hepatitis C	Anti-HCV
Toxins	
Alcohol	History
Drugs: methotrexate, isoniazid, methyldopa	History
Autoimmune diseases	
Autoimmune hepatitis	Antinuclear antibody, anti-smooth muscle antibody, anti-liver-kidney-microsomal antibody, gamma globulin levels
Primary biliary cirrhosis	Antimitochondrial antibody
Primary sclerosing cholangitis	Cholangiography, perinuclear antineutrophil cytoplasmic antibody
Coeliac disease	Coeliac serology
Metabolic disorders	
Nonalcoholic fatty liver disease	History, features of metabolic syndrome
Hereditary haemochromatosis	Iron studies, DNA testing for HFE mutation
Alpha1-antitrypsin deficiency	Alpha1-antitrypsin level and phenotype
Wilson's disease	Serum caeruloplasmin and 24-hour urinary copper levels
Vascular disorders	
Budd-Chiari syndrome	Imaging (ultrasound or CT), with or without biopsy
Veno-occlusive disease	Imaging (ultrasound or CT), with or without biopsy
Congestive cardiac failure	Imaging (ultrasound or CT), with or without biopsy

phosphatase levels may indicate the presence of a cholestatic disorder such as primary sclerosing cholangitis or primary biliary cirrhosis. As liver disease progresses, however, enzyme levels typically fall and may be unhelpful in suggesting a diagnosis. Furthermore, in patients with cirrhosis, the level of serum aspartate aminotransferase (AST) is usually higher than the alanine aminotransferase (ALT) level, regardless of aetiology.

The best clinical indicators of liver synthetic failure are the serum bilirubin concentration, INR and albumin concentration.

Electrolyte levels should be tested regularly, particularly in patients taking diuretics, as electrolyte imbalance and renal impairment are common precipitants of decompensation.

The full blood count may gives clues to gastrointestinal bleeding as well as the presence of portal hypertension and hypersplenism. A low platelet count is a very useful clue to the presence of cirrhosis and portal hypertension. Patients with a platelet count below 100 x 10^9/L should be referred for endoscopy to check for oesophageal varices.

Ultrasonography and serum alpha-fetoprotein (AFP) measurements are important screening tools for hepatocellular carcinoma and should be repeated six monthly in all patients with cirrhosis. The serum AFP level may rise with liver inflammation, particularly in patients with viral hepatitis, and give a false-positive result. A triple phase CT scan of the abdomen (noncontrast phase, hepatic arterial phase, portal venous phase) should be performed to search for hepatocellular carcinoma if AFP or ultrasound is positive or there is a high clinical suspicion of hepatocellular carcinoma.

If spontaneous bacterial peritonitis is suspected, the patient should have a diagnostic ascitic tap. The fluid should be sent for microscopy, cell count and culture.

A liver biopsy is rarely required as a diagnosis of cirrhosis can usually be made on history, examination, blood testing and imaging.

Severity scores

Several scores are used to assess the severity of liver disease (see the box on page 25). Severity assessment is particularly important in determining both prognosis and the risk of particular interventions such as general anaesthesia and major surgery. The most commonly used is the Child-Turcotte Pugh (CTP) score, which is based on clinical and biochemical parameters. The CTP score becomes less discriminatory at the severe end of the scale, and there can be vast differences in severity and prognosis for patients with CTP Class C liver disease.

The Model for End-Stage Liver Disease (MELD) score is a linear calculation based on biochemical parameters and has proven more useful for determining short-term survival in patients with severe liver disease. The MELD score is used throughout the world to prioritise patients on liver transplant waiting lists (see below).

Management of complications

Principles

Managing patients with chronic liver disease can be a challenging and sometimes frustrating task for both GPs and physicians. General principles include:

- withdrawal or treatment of the aetiological factor where possible, including abstinence from alcohol, antiviral treatment for hepatitis B infection and corticosteroid treatment for autoimmune hepatitis
- management of current manifestations of chronic liver disease such as ascites and encephalopathy
- early identification and management of potentially life-threatening complications of cirrhosis such as hepatocellular carcinoma, oesophageal varices, electrolyte disturbances and sepsis
- assessment and management of malnutrition and bone disease.

Ascites and oedema

Portal hypertension is a common complication of cirrhosis. Its pathophysiology involves splanchnic vasodilatation, relative systemic hypotension and activation of the renin–angiotensin system, the sympathetic nervous system and antidiuretic hormone release, leading to salt and water retention.[1] For unknown reasons, some patients seem to develop more ascites than peripheral oedema, whereas others primarily develop peripheral oedema. The first onset of ascites or deterioration in ascites control should prompt investigation into a cause for the decompensation, including a diagnostic tap.

Initial management of fluid retention should be salt restriction, aiming for a dietary salt intake of no more than 50 to 100 mmol/day. Fluid restriction may also be needed if patients have dilutional hyponatraemia. Consultation with a dietician regarding a no-added-salt diet and provision of written guidelines may aid compliance.

If dietary modification fails to control fluid retention, spironolactone (Aldactone, Spiractin), an irreversible aldosterone antagonist, can be commenced at an initial dosage of 50 to 100 mg daily and increased slowly (if serum electrolytes allow) to a maximum of 400 mg daily. Frusemide can be added to the diuretic regimen if adequate control is not achieved with spironolactone, starting at a dose of 20 to 40 mg daily and increasing to a maximum of 120 mg daily.

In practice, diuretic therapy is often limited by electrolyte disturbance, particularly hyponatraemia, and the maximum doses discussed above are rarely tolerated. Hyponatraemia in cirrhosis occurs in a setting of high total body sodium content, and patients should continue salt restriction while also restricting fluid intake. Electrolyte monitoring is a key part of diuretic management, particularly if there has been a change of dose. Spironolactone can cause painful gynaecomastia, in which case amiloride (Kaluril) 10 to 30 mg daily is a useful alternative.

Diuretic resistant ascites is a difficult management problem and implies a poor prognosis for patients with cirrhosis. Regular, large volume paracentesis is an effective but inconvenient option for those with resistant ascites. Another option for resistant ascites is to reduce portal pressure with a transjugular intrahepatic portosystemic shunt (TIPS), which is placed under radiological guidance via internal jugular cannulation. TIPS comprises an intrahepatic metallic mesh stent that shunts blood from the

Scoring systems used to assess liver disease severity

The Child-Turcotte Pugh (CTP) score

The sum of the points for the five clinical and biochemical parameters listed below is the CTP score. A CTP score of 5-6 is Class A, 7-9 Class B, and 10-15 Class C liver disease. Generally, patients with Class A disease have the lowest mortality, with up to 80% of those with compensated hepatitis C or alcoholic cirrhosis still being alive at 10 years' follow up. Patients with Class C liver disease have only a 20% five-year survival rate. The CTP score becomes less discriminatory at the severe end of the scale.

Parameter	1 point	2 points	3 points
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin (µmol/L)			
• noncholestatic disease	<35	35-50	>50
• cholestatic disease	<70	70-170	>170
Serum albumin (g/L)	>35	35-28	<28
INR	<1.7	1.7-2.3	>2.3

Model for Endstage Liver Disease (MELD) score equation

The MELD score is a linear calculation based on biochemical parameters:

MELD = 0.96 [Ln (creatinine (µmol/L)/88)] + 0.38 [Ln (bilirubin (µmol/L)/17)] + 11.2 [Ln INR] + 6.4, where Ln = natural logarithm

The higher the MELD score, the worse the three-month mortality. A MELD score of over 20 is associated with a 20% three-month mortality and a MELD score of over 30 is associated with a greater than 50% three-month mortality.

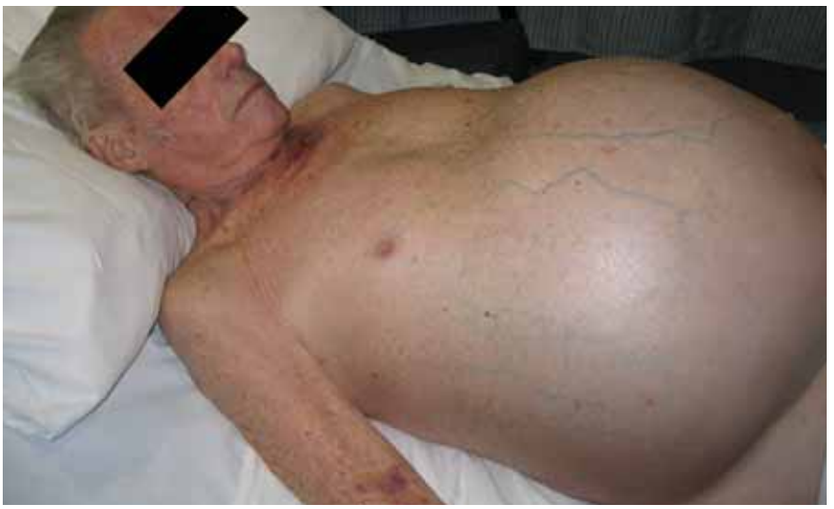


Figure 1. A patient with decompensated alcoholic cirrhosis complicated by severe protein–calorie malnutrition and tense ascites.

portal vein into the hepatic veins and is very effective in controlling ascites in well-selected patients.

Patients with diuretic resistant ascites are often significantly malnourished (Figure 1) and benefit from referral to a dietician for advice regarding a high protein, high energy diet.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is a relatively common complication of decompensated cirrhosis. The presentation is often subtle and a high index of suspicion is required for diagnosis. Patients may present with worsening ascites, subtle encephalopathy or vague abdominal discomfort, rather than frank sepsis with fevers and rigors. The diagnosis is confirmed with a diagnostic ascitic tap showing a white cell count greater 500 cells/mm^3 or neutrophil count greater than 250 cells/mm^3.[2] The Gram stain and culture are positive in only a minority of patients.

Patients with spontaneous bacterial peritonitis should be admitted to hospital and given broad-spectrum intravenous antibiotics with good Gram-negative cover. Patients who develop spontaneous bacterial peritonitis while on norfloxacin prophylaxis (see below) should receive antibiotics with broad Gram-positive as well as Gram-negative cover.[3,4] Antibiotic choices include ceftriaxone (Rocephin) 1 g daily, cefotaxime 1 g three times daily or ticarcillin/potassium clavulanate (Timentin) 3.1 g four times daily.

Patients with spontaneous bacterial peritonitis are at high risk for hepatorenal syndrome (see below), and should receive 100 to 200 mL of 20% albumin daily for three days.[5]

Prevention of complications is an important part of cirrhosis management. All patients who have had an episode of spontaneous bacterial peritonitis should receive long-term secondary prophylaxis with antibiotics such as norfloxacin 400 mg daily.[6] Primary prophylaxis of spontaneous bacterial peritonitis is indicated in the following two scenarios:

- cirrhotic patients with ascites who have been admitted to hospital for upper gastrointestinal tract bleeding
- patients with very low ascitic protein concentrations (less than 10 g/L).[7,8]

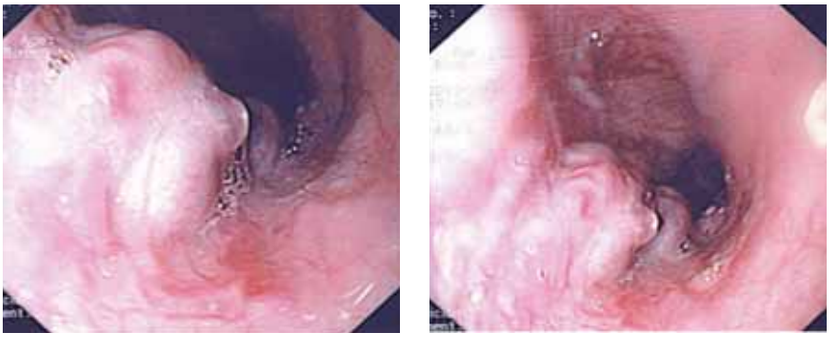
In patients with cirrhosis, an episode of spontaneous bacterial peritonitis is a poor prognostic sign. Such patients may warrant referral to a liver transplant unit.

Varices

Oesophageal varices are a common, often devastating complication of cirrhosis and portal hypertension. About 30% of patients do not survive an acute variceal haemorrhage, and of those who do survive to two weeks, half will die within a year.[9,10]

All patients with cirrhosis and features of portal hypertension, such as splenomegaly and thrombocytopenia, should be screened for oesophageal varices with endoscopy (Figures 2a and b). The risk of haemorrhage can be significantly reduced with treatment with nonselective beta blockers (such as propranolol [Deralin, Inderal]) or endoscopic band ligation.[11,12]

An acute variceal haemorrhage is a medical emergency and necessitates urgent hospitalisation. On presentation, patients should be commenced on an infusion of the somatostatin analogue octreotide (Sandostatin) to reduce portal



Figures 2a and b. Large oesophageal varices with evidence of recent haemorrhage.

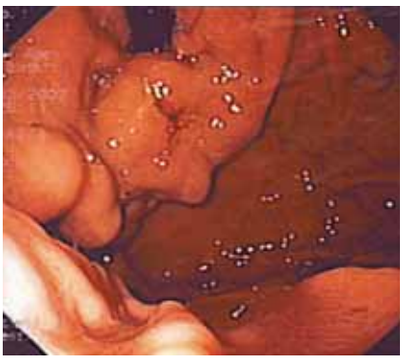


Figure 3. Large gastric varices viewed on retroflexion of the endoscope.

hypertension and antibiotics to prevent spontaneous bacterial peritonitis.[13,6] An emergency gastroscopy should be performed as soon as the patient has been adequately resuscitated and varices treated with endoscopic band ligation.

All patients who survive an acute variceal haemorrhage should receive secondary prophylaxis with propranolol and be placed on a variceal band ligation program consisting of four to six weekly banding until the varices are obliterated.

Bleeding gastric varices are an underrecognised cause of upper gastrointestinal haemorrhage in the patient with cirrhosis. They are also caused by portal hypertension and usually form in the fundus of the stomach, near the cardio-oesophageal junction (Figure 3). Gastric varices can be treated with injection of histoacryl glue.

Hepatic encephalopathy

Hepatic encephalopathy can vary in severity from a subtle change in personality or change in sleep patterns (grade 1) to coma (grade 4). Patients may have a hepatic flap (asterixis) or foetor. Subclinical encephalopathy may be difficult to diagnose but may be responsible for affected patients having severe outcomes, such as traffic accidents.

In patients with a sudden change in mental status, a precipitant such as dehydration, electrolyte imbalance, sedative use, infection or gastrointestinal bleeding may be implicated. Lactulose therapy should be administered, and relatives of patients at risk for encephalopathy should be instructed to administer a dose of lactulose when patients have any change in mental status and arrange hospitalisation if there is no rapid improvement. In the absence of a clear precipitant, empirical antibiotic treatment for infection should be commenced.

In patients with chronic encephalopathy, lactulose should be administered regularly, aiming for two to three soft bowel motions a day. Despite misconceptions, current guidelines state that oral protein intake should not be restricted in patients with severe liver disease and chronic encephalopathy, as protein–calorie malnutrition is a common finding.[14] Regular protein intake is beneficial to these patients and rarely worsens encephalopathy. Protein intakes of 1 to 1.5 g protein/kg/day are recommended, and patients may benefit from branch-chain amino acid supplementation (with Hepatamine sachets). A dietician may guide specific dietary recommendations.

Hepatorenal syndrome

Hepatorenal syndrome is a functional renal failure that occurs in patients with advanced cirrhosis, almost always in the setting of refractory ascites and hyponatraemia. It may be precipitated by infection (including spontaneous bacterial peritonitis), gastrointestinal tract bleeding, large volume paracentesis and some medications (such as diuretics, NSAIDs and aminoglycosides).

Hepatorenal syndrome is classified into two types:

- type 1, which is associated with a rapid decline in renal function and carries a very poor prognosis
- type 2, a slow, progressive deterioration in renal function over weeks, which may be reversible with withdrawal or treatment of precipitants.

Oliguria, hyponatraemia and a urine sodium concentration that is less than 10 mmol/L support a diagnosis of hepatorenal syndrome.

Management requires hospitalisation of the patient and involves correction of precipitants, correction of hypovolaemia and administration of specific vasoconstrictors such as terlipressin (accessed via the Special Access Scheme).

Nutrition

Patients with cirrhosis, particularly those with ascites, are often severely malnourished. Because of fluid retention, patients may not notice a reduction in body weight, but they may be aware of loss of muscle mass and fat stores, particularly in the face and upper body.

Patients should be commenced on a high calorie, high protein diet to improve muscle mass, mobility and overall health. Nutritional supplements such as polymeric glucose powder, protein drinks or powders and branch-chain amino acid supplements are of significant benefit but are expensive. The involvement of a dietician is very helpful as management may be complex, particularly when protein and energy requirements need to be balanced against salt and fluid restriction and against glycaemic control in patients with diabetes.

Bone disease

Up to 60% of patients with cirrhosis have significant bone disease, particularly osteoporosis. Patients with chronic liver disease are eligible for bone mineral density scans every two years on Medicare.

Vitamin D deficiency is common and multifactorial in origin. It is recommended that patients are screened for 25-hydroxyvitamin D deficiency and supplemented with vitamin D and calcium if the level is less than 60 nmol/L.[15]

Management of patients with osteoporosis may require consultation with an endocrinologist.

Hepatocellular carcinoma

All patients with cirrhosis are at risk of

continued

Recommendations for the assessment and management of patients with cirrhosis

History	Examination	Investigations	Management
• Alcohol intake	• Palmar erythema	• Synthetic function (bilirubin, INR, albumin)	• Treat the cause of liver disease
• Ethnicity	• Spider naevi	• Full blood counts (low platelet count suggests portal hypertension)	• Assess and treat precipitant of decompensation
• Country of birth	• Gynaecomastia	• Electrolytes (especially for patients on diuretics)	• Treat current manifestations or complications (e.g. ascites, oedema, encephalopathy, sudden bacterial peritonitis, varices)
• IV drug use	• Hepatomegaly	• Liver function tests	• Screen for life-threatening complications (e.g. hepatocellular carcinoma, varices)
• Family history	• Splenomegaly	• Alpha-fetoprotein measurement	• Assess and manage nutrition and bone disease
• Obesity	• Fluid retention (ascites, peripheral oedema, hydrothorax)	• Microbiology in sepsis (urine, blood, ascites, ascitic cell count)	• Liver transplantation
• Medications	• Abdominal/inguinal hernias	• Liver ultrasound	
• Precipitant of decompensation (recent alcohol abuse, sepsis, gastrointestinal tract bleeding, malnutrition)	• Encephalopathy (flap, foetor)	• Triple phase CT of the liver	
	• Cardiovascular assessment (congestive heart failure or right heart failure as a cause of ascites or cirrhosis)		
	• Nutritional status		

hepatocellular carcinoma. As the cancer is usually asymptomatic until the advanced stages, all patients with cirrhosis should be screened with six-monthly ultrasound and AFP measurements to maximise their chance of curative therapy. A raised AFP level is not specific for hepatocellular carcinoma and can be raised in viral hepatitis, cirrhosis and pregnancy. Ultrasound is a useful screening test, but in most cases the diagnosis of hepatocellular carcinoma is made on the basis of a characteristic appearance on triple phase CT or MRI scan. Biopsy of the lesion is not recommended, as there is significant risk of needle tract spread.

The management of patients with hepatocellular carcinoma depends on the size and number of lesions, presence of vascular invasion or metastatic disease and the severity of the underlying liver disease. Management should be undertaken in centres with multidisciplinary expertise.[16]

The only curative option for patients with small tumours is liver transplantation; however, this treatment is not available to all patients. Surgical resection is offered to patients with well-compensated disease without portal hypertension, but patients remain at risk of further hepatocellular carcinoma and need to be followed closely. Local therapies such as transarterial chemoembolisation, percutaneous radiofrequency ablation and percutaneous injection of alcohol offer local control and some survival advantage. Systemic chemotherapy has a limited role in the management of hepatocellular carcinoma.

Liver transplantation

Patients under the age of 65 years with advanced cirrhosis or early hepatocellular carcinoma should be considered for liver transplantation. Contraindications to transplantation include active alcohol abuse, extrahepatic sepsis or extrahepatic malignancy. The patient's mental health, coping skills and support structure are important considerations as intensive follow up and compliance are required after transplantation. Post-transplantation survival is excellent with over 90% one-year survival and over 80% five-year survival being achieved in Australia, and worldwide.

Conclusion

The management of cirrhosis is both challenging and rewarding, requiring good communication between physicians, GPs, allied health professionals and, of course, patients. The key principles in management are to treat the aetiology, manage the manifestations and screen patients for life-threatening complications (see the box on this page). MT

References

1. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. N Engl J Med 2004; 350: 1646-1654.

2. Albillos A, Cuervas-Mon SV, Millan I, et al. Ascitic fluid polymorphonuclear cell count and serum to ascites albumin gradient in the diagnosis of bacterial peritonitis. Gastroenterology 1990; 98: 134-140.

3. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites and spontaneous bacterial peritonitis. Gastroenterology 2001;

120: 726-748.
4. Cholongitas E, Papatheodoridis GV, Lahanas A, Xanthaki A, Kontou-Kastellanou C, Archimanandritis AJ. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. Liver Int 2005; 25: 57-61.
5. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341: 403-409.
6. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology 1990; 12(4 Pt 1): 716-724.
7. Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999; 29: 1655-1661.
8. Soares-Weiser K, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. Scand J Gastroenterol 2003; 38: 193-200.
9. Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med 2001; 345: 669-681.
10. Graham DY, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981; 80: 800-809.
11. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotics. Hepatology 2004; 40: 65-72.
12. Hayes PC, Davis JM, Lewis JA, Bouchier IA. Meta-analysis of value of propanolol in prevention of variceal hemorrhage. Lancet 1990; 336: 153-156.
13. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal variceal bleeding: a meta-analysis. Gastroenterology 2001; 120: 946-954.
14. Heyman J, Whitfield CJ, Brock KW, McCaughan GW, Donaghy A. Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. Med J Aust 2006; 185: 542-543.
15. Crawford BA, Labio ED, Strasser SI, McCaughan GW. Vitamin D replacement for cirrhosis-related bone disease. Nature Clin Prac Gastro Hepatol 2006; 3: 689-699.
16. Perry JF, Poustchi H, George J, Farrell GC, McCaughan GW, Strasser SI. Current approaches to the diagnosis and management of hepatocellular carcinoma. Clin Exp Med 2005; 5: 1-13.

DECLARATION OF INTEREST: None.