MANAGEMENT OF CHRONIC LIVER DISEASE

Cirrhosis is a diffuse process characterised by fibrosis and conversion of the normal liver architecture into structurally abnormal nodules.

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There are multiple causes of cirrhosis, including chronic viral hepatitis, autoimmune liver disease, alcohol, inherited metabolic disorders, biliary diseases, drugs and toxins. Although people with cirrhosis may initially be asymptomatic, compensated cirrhosis usually progresses. Ten years after the diagnosis of cirrhosis, the probability of developing decompensated cirrhosis is approximately 60% with a survival rate of approximately 50%. Major complications include portal hypertensive bleeding, ascites and spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy.

PORTAL HYPERTENSION

Portal hypertension caused by liver cirrhosis occurs as a result of fixed mechanical and reversible vascular increases in intrahepatic resistance in combination with splanchnic vasodilatation and increased portal venous inflow. The most ominous complication of portal hypertension is bleeding oesophageal varices, with a poor long-term prognosis irrespective of treatment, and few patients survive more than 5 years. At the time of diagnosis, varices are present in 40% of compensated cirrhotics and in 80% of those with Child's C cirrhosis. Only 25 - 40% of patients with oesophageal varices will bleed, and the mortality rate ranges from 30% to 50% for each bleeding episode. After a first episode of bleeding, there is a 63% rebleeding risk and a 33% risk of death within 1 year. Varices progress from small to large at a rate of 8% per year.

Risk factors for bleeding from oesophageal varices include variceal size, endoscopic features such as red wale markings and cherry-red signs, Child's C classification, alcoholic cirrhosis and portal pressure greater than 12 mmHg. The annual incidence of variceal bleeding is 2% in patients without varices, 5% in those with small varices and 15% in those with medium or large varices.

Portal hypertensive gastropathy usually presents as occult blood loss with anaemia rather than as acute gastrointestinal tract (GIT) bleeding. However, an acute bleed may occur in severe gastropathy, but there is not a clear relationship with the degree of portal hypertension. Portal hypertensive gastropathy tends to be more frequent after sclerotherapy, with mucosal changes found more commonly in the proximal stomach.

MANAGEMENT OF OESOPHAGEAL VARICES AND PORTAL HYPERTENSION

Screening for oesophageal varices and treatment of portal hypertension

Patients with cirrhosis should be screened endoscopically to determine the presence and size of varices and the need for therapeutic intervention.

Patients without varices. There is no need for β-blockers. Repeat endoscopy every 2 - 3 years, or annually if the patient is decompensated.

There are multiple causes of cirrhosis, including chronic viral hepatitis, auto-immune liver disease, alcohol, inherited metabolic disorders, biliary diseases, drugs and toxins.

Patients who present with suspected variceal bleeding need to be hospitalised, have the severity of the bleed assessed, and be resuscitated as required. Endoscopy is essential to make the diagnosis and to plan management.

Patients with small varices that have not bled. The risk of haemorrhage is so small that treatment is not cost-effective; carry out screening endoscopy every 2 - 3 years, unless the patient has decompensated cirrhosis. A recent multicentre, placebo-controlled study suggested that β-blockers prevented progression of varices, but this needs validation.

Patients with medium/large varices that have not bled. Non-selective β-blockers, e.g. propanolol or nadolol, reduce the 2-year rate of first variceal haemorrhage from 30% to 14%. The dose should be adjusted to achieve a heart rate of 55 beats/minute. If unable to tolerate, or if contraindications to β-blockers exist, the patient should be considered for variceal ligation. Variceal ligation and β-blockers are equally effective in preventing a first variceal bleed.

VARICEAL BLEEDING

Initial management

Patients who present with suspected variceal bleeding need to be hospitalised, have the severity of the bleeding assessed, and be resuscitated as required. Endoscopy is essential to make the diagnosis and to plan management. Somatostatin or octreotide can control the initial acute bleeding and may be continued for several days to prevent early rebleeding. These agents reduce splanchnic blood flow, with a resultant decrease in portal venous pressure and portal collateral blood flow. Octreotide is a synthetic analogue of somatostatin and has a longer half-life (1 - 2 hours) than somatostatin (1 - 2 minutes). Somatostatin is administered by continuous infusion at 250 µg/h and octreotide is used at a dose of 50 µg/h. Randomised clinical trials have shown octreotide to be more effective than placebo or balloon tamponade in controlling acute variceal bleeding.

Antibiotic prophylaxis. This significantly reduces the rate of bacterial infections (45 - 14%) and mortality (24 - 15%) in cirrhotics presenting with a variceal bleed and should be given to all patients presenting with a bleed.

Sclerotherapy. Controlled trials have shown that sclerotherapy is effective in controlling acute variceal bleeding in 80 - 95% of patients. However, the effect on rebleeding remains uncertain and there has been no demonstrable effect on early survival despite control of acute variceal bleeding, probably because patient demographics and the severity of liver disease varied in different published studies. Major complications including bleeding from sclerotherapy ulcers, oesophageal stenosis and oesophageal perforation occur in approximately 20% of patients, and procedure-related mortality is 1 - 3%.

Endoscopic ligation or banding of oesophageal varices. Controlled trials have shown that bleeding is controlled in approximately 90% of patients and the rebleeding rate is reduced to 30%. Comparative studies with sclerotherapy favour banding because there is less rebleeding and lower mortality. Fewer complications occur and fewer treatment sessions are required.

A meta-analysis showed that combined treatment (endoscopic therapy and pharmacological therapy) significantly improved initial control of bleeding and 5-day haemostasis, without differences in mortality compared with endoscopic therapy alone.

Transjugular intrahepatic portosystemic shunt (TIPS) should be considered if acute variceal bleeding cannot be controlled.

The risk of recurrent variceal bleeding in untreated patients ranges from 55% to 67%. Therapeutic options which have been used to prevent recurrent variceal bleeding include endoscopic ligation or sclerotherapy, β-blockers, TIPS, surgical shunts and liver transplantation.

Rebleeding rates are slightly reduced by β-blockers alone (range 37 - 57%) and endoscopic sclerotherapy (range 34 - 53%). Recommended therapy is a combination of β-blockers and surveillance endoscopy with sclerotherapy or variceal ligation to eradicate varices.

Transjugular intrahepatic portosystemic shunt. This radiological technique involves the angiographic placement of an expandable metal stent from the branch of the hepatic veins through the hepatic parenchyma into a branch of the portal vein using the transjugular approach. The aim of TIPS is to achieve a hepatic venous pressure gradient of less than 12 mmHg using variable diameter stents (8 - 12 mm). The main indications include control of recurrent portal hypertensive bleeding not responding to β-blockers and variceal ligation or refractory ascites. TIPS has also been used to control refractory hepatic hydrothorax and to stabilise the hepatorenal syndrome. It is usually (90%) effective in controlling variceal bleeding and also decreases the dosage of diuretics required to control ascites. TIPS also often leads to an improvement in nutritional status as frequent large-volume paracentesis with associated protein loss is no longer required. Contraindications to placement of TIPS include a significant Child-Pugh score > 12, MELD score > 18, right-sided heart failure, primary

Surgical shunts should only be considered in patients in whom TIPS is not possible and who are not candidates for liver transplantation.

Twenty-five per cent of cirrhotics with ascites will have an episode of spontaneous bacterial peritonitis over a 1-year follow-up period.

pulmonary hypertension, biliary obstruction, severe encephalopathy and advanced portal vein thrombosis. After insertion of TIPS for variceal bleeding the overall 1-year survival rate is 87%.

TIPS-related complications include the following:

- *Hepatic encephalopathy*. After TIPS it occurs in 20 - 30% of patients and is severe in 5 - 10%. There tends to be an increased risk of encephalopathy associated with older patients, Child's class C, hepatopetal portal flow and the use of large-diameter shunts. Lactulose is usually sufficient to control symptoms of encephalopathy, but in a small percentage reduction of the shunt diameter or shunt closure is required.
- *Shunt stenosis and occlusion*. At 1 year, the shunt occlusion risk is approximately 15% with a 75% risk of stenosis. This is diagnosed on Doppler ultrasound and can be corrected with balloon dilatation or implantation of an additional stent.

Surgical shunts. These may be non-selective, such as the end-to-side or side-to-side portocaval shunts, which are effective in controlling variceal bleeding in 95% of cases, but are associated with a 40 - 50% incidence of hepatic encephalopathy. Other non-selective shunts include the mesocaval and proximal splenorenal shunts. More commonly the selective distal splenorenal shunt is performed, which has a low risk of encephalopathy. Surgical shunts should only be considered in patients in whom TIPS is not possible and who are not candidates for liver transplantation. All patients presenting with a variceal bleed should be considered for liver transplantation.

ASCITES

In compensated cirrhotics, the 10 - 15-year risk of development of ascites is 50 - 60%. The main pathophysiological mechanism involved in ascites formation is splanchnic vasodilation. A diagnostic tap with analysis of the ascitic fluid is essential in the evaluation of a patient who presents with this condition. Indications for diagnostic paracentesis include new-onset ascites, admission to hospital, clinical deterioration and fever. The only contraindication to diagnostic paracentesis is severe coagulopathy that is not correctable with coagulation support. Fluid analysis should include a cell count, culture and albumin estimation. A Gram stain is usually uninformative. Other parameters that should be measured, depending on the clinical setting, include amylase, adenosine deaminase and triglyceride levels. Cytology and TB culture should also be performed. The cell count provides immediate information regarding the possibility of bacterial peritonitis, presumed with an absolute neutrophil count > 250/mm^3. Dipsticks can detect an elevated polymorponuclear neutrophil (PMN) count in 90 seconds and help to determine the need to treat earlier. Further confirmative information is provided by culture of 10 ml ascitic fluid directly injected into blood-culture bottles. A serum-ascites albumin gradient ≥ 11 g/l is more specific and sensitive at distinguishing portal hypertension (transudate) from exudative processes than ascitic fluid protein concentration (97% specific v. 55%).

Initial therapy

This involves restriction of dietary sodium intake (< 90 mEq/day) and oral diuretics. The most effective regimen is a combination of spironolactone and furosemide, starting with 100 mg spironolactone and 40 mg furosemide, depending on renal function. Salt restriction and a combination of antimineralocorticoid and loop diuretics are effective in 90% of patients without renal failure. Fluid intake should be restricted in patients with dilutional hyponatraemia. Recommended weight loss is 300 - 500 g/day in patients without oedema and 1 kg/day in patients with oedema. Large-volume paracentesis may be required for patients with tense ascites or for those who do not respond to, or are intolerant of, full doses of diuretic therapy. Large-volume paracentesis (5 l/day) with albumin infusion (6 - 8 g/l ascites tapped) is more effective than diuretics alone in eliminating large-volume ascites and in decreasing hospital stay. Large-volume paracentesis is safe provided the patient is not acutely ill and plasma volume expanders such as albumin, stabilised human serum (SHS) or other synthetic expanders are used. Approximately 10% of cirrhotics will have ascites refractory to medical therapy and should be considered for liver transplantation. Other treatment includes repeated large-volume paracentesis with albumin cover and TIPS. In patients with ascites, the 5-year survival is 30 - 40%.

Complications

Complications of ascites include spontaneous bacterial peritonitis, tense ascites resulting in the impairment of respiration, umbilical hernia with risk of rupture, and a hydrothorax secondary to movement of ascitic fluid across the diaphragm.

Hepatic hydrothorax. Approximately 5% of cirrhotics will develop significant pleural effusions (66% right-sided, 17% bilateral, 17% left-sided). The fluid is similar to ascites, but has a slightly higher protein content. Management involves diuretics, paracentesis, and more recently TIPS. TIPS results in resolution of hepatic hydrothorax in 70% of patients.

Umbilical hernia. This occurs in approximately 20% of cirrhotics with

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ascites. Complications include incarceration, ulceration and rupture. Treatment involves control of ascites and elective surgical repair once the ascites is controlled.

Spontaneous bacterial peritonitis. This occurs in patients with advanced cirrhosis. Approximately 50% of cases are detected during hospital admission and up to 30% may be asymptomatic. The ascites tends to be moderate to tense. Twenty-five per cent of cirrhotics with ascites will have an episode of spontaneous bacterial peritonitis over a 1-year follow-up period. The bacteria isolated from ascitic fluid are usually intestinal. It is thought that the pathogenesis of peritonitis involves translocation of intestinal bacteria from the intestinal lumen to the lymph nodes with subsequent bacteraemia and infection of ascitic fluid. Factors contributing to bacteraemia in cirrhotic patients include reduced serum-complement activity, decreased reticulo-endothelial function and invasive procedures, particularly sclerotherapy. Approximately 90% of cases of spontaneous bacterial peritonitis are monomicrobial, with *Escherichia coli* accounting for 50% of cases; other commonly grown organisms include *Streptococcus pneumoniae, Klebsiella pneumoniae* and enterococci.

Direct inoculation of 10 ml of ascitic fluid into blood-culture bottles at the bedside has improved the culture yield (91% culture positivity rate v. 42% with the conventional method). Patients with suspected spontaneous bacterial peritonitis based on an ascitic fluid polymorph count > 250 cells/mm^3 require broad-spectrum antibiotic therapy in the form of intravenous cephalosporin and ampicillin until culture and sensitivity results are available. Treatment should be continued for at least 5 days. Hepatorenal syndrome (HRS) occurs in 30% of patients and intravenous albumin (1.5 g/kg body weight at diagnosis and 1 g/kg 48 hours later) helps to prevent it. The 12-month accumulative probability of survival is 38% for patients who have experienced 1 episode of spontaneous bacterial peritonitis compared with 66% for those with no previous episodes. The risk of spontaneous bacterial peritonitis can be reduced by controlling the ascites either with diuretics or regular paracentesis. Primary antibody prophylaxis is not recommended but secondary prophylaxis using quinolones decreases the 1-year probability of recurrent peritonitis from 68% to 20%. The indiscriminate use of prophylactic quinolones leads to an increased risk of antibiotic resistance and should be reserved for patients presenting with recurrent spontaneous bacterial peritonitis.

SEPSIS IN PATIENTS WITH CHRONIC LIVER DISEASE

The prevalence of bacterial infection ranges from 20% to 67% and is related to the severity of the underlying liver disease and associated portal hypertension. The presence of bacterial infection can convert a patient from a compensated to a decompensated state, triggering encephalopathy, variceal bleeds and impaired renal function. Bacterial infection is associated with increased mortality in decompensated cirrhotics: 30-day mortality is 83% in severe sepsis and 31% in infection/sepsis. It is important to give antibiotic prophylaxis in patients presenting with GIT bleeds, to treat aggressively for occult sepsis, and to provide circulatory support in patients presenting with deteriorating renal function. The main sites of infection in cirrhotics are ascitic fluid, lung, urinary tract and blood. Factors contributing to the increased susceptibility to infection include bacterial overgrowth and translocation from the gut, impaired opsonisation of circulating antigens in cirrhotics, impaired phagocytic activity and refractory ascites.

HEPATORENAL SYNDROME

HRS is a functional renal disorder associated with severe acute or chronic liver failure. It is potentially reversible as there is no intrinsic renal disease, but usually carries a very poor prognosis and the only definitive therapy is liver transplantation. The probability of HRS in patients with cirrhosis and associated ascites is 18% at 1 year and 39% at 5 years. Clinically, HRS can be divided into 2 types. Type I is characterised by rapidly progressive deterioration in renal function, defined by the doubling of the initial serum creatinine to more than 250 µg/ml or a 50% reduction in the initial 24 h creatinine clearance to less than 20 ml/min in less than 2 weeks. Type I HRS tends to be more common in acute liver failure, acute alcoholic hepatitis or alcoholic cirrhosis, but may occur in any form of chronic liver disease and is often precipitated by spontaneous bacterial peritonitis. Type II HRS progresses more slowly, with a moderate reduction in creatinine and glomerular filtration rate. It often occurs in patients presenting with refractory ascites. The pathophysiology of renal failure is thought to be mediated by marked splanchnic vasodilatation leading to marked vasoconstriction of the renal cortical vasculature.

Without therapy, the median survival of patients with type I HRS is < 1 month and 6 - 12 months for those with type II HRS. Biochemically, hyponatraemia and azotaemia are usual. The urinary sodium concentration is < 10 mEq/l and the urine osmolality is greater than the plasma

Table I. **Four stages of hepatic encephalopathy**

Stage	Mental state	Neurological signs
1	Mild confusion, ↓attention, irritability, inverted sleep pattern	Inco-ordination, tremor, impaired handwriting
2	Drowsiness, personality changes, intermittent disorientation	Asterixis, ataxia, dysarthria
3	Somnolent, gross disorientation, marked confusion, slurred speech	Hyperreflexia, muscle rigidity, Babinski's sign
4	Coma	No response to pain, decerebrate posture

osmolality. The urinary sediment is usually inactive. Management of HRS includes identification and exclusion of other causes of renal failure such as acute tubular necrosis and drug-induced nephrotoxicity. It is important to establish an adequate circulatory volume. The usual therapy is intravenous 20% albumin and restricted sodium and water intake. Nephrotoxic agents, particularly non-steroidal anti-inflammatories and aminoglycosides, should be discontinued and avoided in patients with decompensated cirrhosis. Recent evidence from uncontrolled trials has shown that type I HRS can be reversed with prolonged treatment with vasoconstrictors such as ornipressin, terlipressin and noradrenaline, or the alpha-adrenoceptor agonist midodrine in combination with intravenous 20% albumin to increase intravascular volume. TIPS increases central blood volume and decreases production of endogenous vasoconstrictors, but a controlled trial has suggested decreased survival in patients treated with TIPS for refractory ascites. Liver transplantation is the only definitive therapy and vasoconstrictors and TIPS should be considered as a bridge to transplantation.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a spectrum of initially reversible neuropsychiatric abnormalities associated with asterixis and an abnormal EEG. It occurs in patients with acute liver failure or with portosystemic shunting associated with advanced liver disease. The degree of cerebral function impairment is extremely variable, ranging from subclinical changes to an irreversible neurological syndrome. Hepatic encephalopathy in acute liver failure is a distinct clinical entity that tends to respond poorly to the usual therapeutic regimens and is often associated with cerebral oedema.

There are a number of proposed pathogenic theories for the development of hepatic encephalopathy, the most popular involving elevated ammonia levels, abnormal tryptophan metabolism and over-activity of the major inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Neurotransmission failure is the end result of one or more of these metabolic abnormalities.

Subclinical hepatic encephalopathy occurs in 50 - 80% of cirrhotics. It is characterised by subtle neuropsychological changes without overt behavioural, neurological or EEG changes, and is typically reversible with treatment.

Recurrent, clinical hepatic encephalopathy is characterised by asterixis associated with a defined, precipitating event and reversibility with treatment. Patients with chronic hepatic encephalopathy tend to have no identifiable precipitating event but persistent hepatic encephalopathy with asterixis and incomplete response to medical therapy. These patients are also at risk of developing the irreversible neurological syndrome of hepatocerebral degeneration.

There are 4 stages of hepatic encephalopathy, shown in Table I.

A simple and reliable test for hepatic encephalopathy includes the number connection test, which allows serial testing of minimal changes in intellectual capacity, as well as asking a patient to draw a 5-pointed star or to provide a sample of his/her handwriting. Although an abnormal EEG is a classic feature of hepato-encephalopathy, the changes are nonspecific. There tends to be a temporal dissociation between blood ammonia levels and clinical symptoms of encephalopathy with the development of signs and symptoms that are likely to lag behind the progressive rise in serum ammonia levels by about 24 hours. Similarly, after therapy, the blood ammonia levels may fall before a clinical improvement in mental status. The differential diagnosis for hepatic encephalopathy is broad, including intracranial lesions, infections, metabolic disorders, alcohol and drugs. The major precipitating factors associated with the development of hepatic encephalopathy or worsening of chronic hepatic encephalopathy include excess protein, GIT bleeding, alcohol or sedative intake, overdiuresis with a consequent drop in serum potassium, decrease in circulating plasma volume and associated uraemia, infections and development of hepatocellular carcinoma.

Management of hepatic encephalopathy involves identifying and correcting any precipitating factors, restricting dietary protein and administrating lac-

tulose. Lactulose is a synthetic disaccharide composed of galactose and fructose. It is not absorbed or metabolised in the upper GIT and passes into the colon where it is degraded by anaerobic bacteria and produces several organic acids including lactic acid. It improves hepatic encephalopathy through its cathartic effect, colonic acidification with reduced ammonia absorption and altered colonic nitrogen metabolism with increased nitrogen excretion. Agents with a similar therapeutic effect include lactitol and sorbitol. If there is no response to dietary manipulation and addition of lactulose, antibiotics such as neomycin and metronidazole can be considered. However, these should only be used in the short term in order to avoid the development of neomycin-induced ototoxicity or metronidazole-associated neurotoxicity. Liver transplantation should always be considered in patients with significant or refractory hepatic encephalopathy.

Finally, it should be remembered that liver transplantation is no longer a 'last-resort' treatment and should be carried out earlier rather than later. Although it is sometimes difficult to determine the optimal timing for transplantation, the option of transplantation should be considered in patients with chronic liver disease, particularly when they have experienced any of the following complications: a major variceal bleed, refractory ascites, increasing encephalopathy and deteriorating synthetic function. Patients with chronic liver disease should be referred early to a liver transplant centre, where they can be fully assessed as to their suitability for and timing of transplantation; thereafter they can be followed up by their GP, primary physician or surgeon while waiting for transplantation.

Further reading available on request.

IN A NUTSHELL

The most ominous complication of portal hypertension is oesophageal variceal bleeding. Patients have a poor long-term prognosis irrespective of treatment and few survive more than 5 years.

Patients with cirrhosis should be screened endoscopically to determine the presence and size of varices and the need for therapeutic intervention and surveillance endoscopy.

Only 25 - 40% of patients with oesophageal varices will experience variceal bleeding.

Endoscopic banding/sclerotherapy together with pharmacological therapy, e.g. octreotide, after adequate resuscitation is the treatment of choice for an acute variceal bleed.

Indications for TIPS include: portal hypertensive bleeding, refractory ascites, refractory hepatic hydrothorax and hepatorenal syndrome.

Diagnostic paracentesis is indicated in new-onset ascites, admission to hospital, clinical deterioration and fever.

An ascitic fluid neutrophil count > 250/mm^3 is a presumptive threshold for peritonitis. Direct inoculation of 10 ml ascitic acid into blood culture bottles improves the culture yield from 42% to 91%.

Splanchnic vasodilatation and subsequent activation of a cascade of vasoconstrictors and antinatriuretic factors is the main pathophysiological factor involved in ascites formation and development of the hepatorenal syndrome.

Type I hepatorenal syndrome is characterised by rapidly progressive deterioration in renal function defined by the doubling of the initial serum creatinine to a level greater than 250 mm^3/ml or 50% reduction in the initial 24-h creatinine clearance to a level lower than 20 ml/min in less than 2 weeks. Type II hepatorenal syndrome is often associated with refractory ascites and is slowly progressive with a moderate reduction in creatinine and glomerular filtration.

Management of acute hepatic encephalopathy includes identification and correction of any precipitating factors, restriction of dietary protein and administration of lactulose.

Precipitating factors in acute encephalopathy include excess protein, GIT bleeding, ingestion of alcohol and sedatives, overdiuresis, infections and development of hepatocellular carcinoma.