Managing Cirrhosis

By Cameron Ghent, MD, FRCPC

Cirrhosis of the liver is a progressive, fibrosing process resulting in nodule formation and microvascular distortion. Almost 40% of patients with cirrhosis are asymptomatic at diagnosis but the majority become symptomatic as a consequence of the disease's progression and the development of complications.[1] These sequelae are characterized into portal hypertensive and non-portal hypertensive (Table 1). The diagnosis of cirrhosis is an indication to assess the need for preventive or proactive therapy to prevent complications.

Cirrhosis without portal hypertensive complications requires specific treatment directed at the underlying cause of the liver disease rather than the fibrosis itself. Nevertheless, many of these therapies (*i.e.*, immunosuppressive therapy for autoimmune hepatitis, alcohol abstention in alcoholic liver disease, antiviral therapy for hepatitis B and C) have been shown to reverse the extent of the fibrosis. Reluctance to treat patients with established cirrhosis in these diseases has been overcome by controlled trials showing improved outcomes. The emphasis here will be on management of portal hypertensive complications.

Table 1

Complications of Cirrhosis

Portal Hypertensive	Non-Portal Hypertensive
Ascites	Altered drug metabolism
Primary peritonitis	Hepatic osteodystrophy
Hepatorenal syndrome	Coagulopathy
Variceal hemorrhage, hypertensive gastropathy	Hepatocellular carcinoma
Portosystemic encephalopathy	Feminization
Hepatic hydrothorax	Malnutrition

Ascites

Portal hypertension may be manifested in various ways. The most common presentation is the development of ascites. About half of patients with compensated cirrhosis at diagnosis develop ascites within 10 years.[2] Rapid accumulation of ascites should trigger a search for possi-

Table 2

Classification of Ascites Based on Serum-Ascites Albumin Gradient (SAAG)

SAAG > 11 g/L	SAAG < 11 g/L
Cirrhosis	Peritoneal carcinomatosis
Fulminant hepatic failure	Nephrotic syndrome
Cardiac ascites	Tuberculous peritonitis
Myxedema	Serositis of connective tissue disease
Primary peritonitis in cirrhosis	Perforated viscus
Budd-Chiari syndrome	Pancreatic or biliary ascites

ble underlying hepatocellular carcinoma or portal vein thrombosis, but is most commonly due to progression of the underlying disease, alcohol abuse or excessive salt intake. In situations where the clinical detection of ascites is difficult or equivocal, ultrasonography may assist the diagnosis and guide the paracentesis. Analysis of the fluid is essential. The serum albumin-ascites gradient (SAAG) is highly accurate in distinguishing between portal hypertensive and non-portal hypertensive ascites. This gradient, which is a subtraction and not a fraction, has an accuracy of 97% in confirming portal hypertension when it has a value greater than 1.1 g/dl or 11 g/L.[3]

Most patients will respond to dietary sodium restriction (2 gm Na daily) and natriuretic use. A combination of loop and potassium-sparing diuretics is usually successful in relieving the ascites and associated edema. Monitoring of 24-hour urine sodium excretion will distinguish between inadequate diuretic doses (urine Na will be < 80 mmol/d) and noncompliance with salt restriction (urine Na > 80 mmol/d). Ascites is considered refractory if it fails to respond to spironolactone 400 mg daily and frusemide 160 mg daily or if lesser doses of diuretics cause renal dysfunction necessitating their discontinuation. Fluid restriction is not required unless severe hyponatremia (serum sodium <120 mmol/L) ensues.

Refractoriness of ascites portends a one-year survival of less than 25% and is an indication for liver transplantation.[4] Repeated large volume paracenteses (LVP) may serve as a bridge to transplantation. Diuretics may be continued in addition to the LVP if the urine sodium measurements indicate some response. The need for albumin infusion at the time of paracentesis remains controversial. We use albumin infusion (6 g/L to 8 g/L of ascites removed) only in those patients undergoing LVP of six litres or more, in the absence of peripheral edema.[5,6] Alternatives to LVP include transjugular intrahepatic portosystemic shunt (TIPS) and various surgical shunts. TIPS is preferred over surgical shunts due to its feasibility, low cost, favorable complication profile and minimal alteration of the regional anatomy which is of paramount importance to possible future transplantation.

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Primary Peritonitis

Infection of ascites is a serious complication of cirrhosis with a less than 50% chance of a two-year survival.[7] A low threshold for diagnostic paracentesis is necessary for early diagnosis and treatment. When first described, its mortality exceeded 90%. However, better management has now reduced the in-hospital mortality rate to around 20%.[8] Diagnosis is established when the fluid polymorphonuclear count exceeds 250 cells/mm^3 or by positive culture of fluid. The use of direct inoculation of fluid into blood culture bottles has enhanced the diagnostic sensitivity of ascites culture to around 90% from a previous rate of 50%.

Third generation cephalosporins (*i.e.*, cefotaxime 2 gm *tid*) or four aminoquinolones (ciprofloxacin 200 mg *bid*) are the antibiotics of choice. Five-day treatment has been shown to be as effective as 10-day treatment.[9] Diuretics should be discontinued and LVP is to be discouraged.

Furthermore, expanding the intravascular volume is essential in managing these patients. A recent study has demonstrated a lower incidence of renal failure and mortality when the antibiotic was combined with albumin infusion.[10] Recurrence of infection occurs in almost 70% of patients within one year. Therefore, antibiotic prophylaxis should be maintained indefinitely. Ciprofloxacin 750 mg once weekly or norfloxacin 400 mg daily are the recommended prophylactic regimens.

Hepatorenal Syndrome

The International Ascites Club has laid down new criteria for the diagnosis of hepatorenal syndrome (HRS) (Table 3). HRS has been further reclassified into two clinical types — HRS 1 and HRS 2.[11] Type 1 is the more severe form characterized by a rapidly progressive impairment in circulatory and renal function while Type 2 is more slowly progressive. In the presence of decompensated liver cirrhosis, there is a one- and five-year probability of developing HRS of approximately 20% and 40% respectively.[12] Historically, this disease resulted in almost certain death. Newer therapies have greatly changed the outlook of this illness, but it is still usually fatal within six months, and is an indication for urgent liver transplantation.

Table 3

Major Diagnostic Criteria of Hepatorenal Syndrome (International Ascites Club)

Hepatic failure and portal hypertension
Creatinine >133 nmol/L or glomerular filtration rate < 40 ml/min
Absence of shock, ongoing bacterial infection, nephrotoxic agents, or fluid losses
No improvement after diuretic withdrawal and IV saline infusion of 1.5 L
Proteinuria < 500 mg/d, absence of apparent cause for renal disease

The pathogenesis of HRS involves a decrease in effective arterial blood volume which has lead to treatment by simultaneously administering albumin with arterial vasoconstrictors such as terlipressin, dopamine, midodrine and noradrenaline. Therapeutic response to vasoconstrictors varies between 40% to 83%.[13-15] Controlled and randomized studies are required to streamline future treat-

ment recommendations for HRS. Although the results at this juncture are still conflicting, the tentative data suggests a dominant role for vasoconstrictors in the foreseeable future. TIPS may also be beneficial in the setting of HRS with cumulative data showing survival rates at six months of 44%.[16]

Medical management of HRS remains a stabilizing tactic rather than a long-term remedy for these patients and liver transplantation continues to be the only curative option.

Variceal Hemorrhage

Gastroesophageal variceal hemorrhage is the most lethal and dramatic complication of cirrhosis. Although varices exist in 50% of patients with cirrhosis, the lifetime risk for first hemorrhage is about 30%. The one-year risk of rebleeding after an index bleed is 70% and the associated mortality with each episode reaches 50%. Bleeding or rebleeding can be prevented in many patients either pharmacologically with a nonselective beta-blocker, or with endoscopic banding. Primary prophylaxis with banding is as effective as beta-blocker therapy and is being used increasingly if high-risk varices are seen at index endoscopy. Non-selective beta-blockers are the most widely studied prophylactic agents and have been shown to reduce the risk of bleeding but not the mortality rates.[17]

In the acute setting of a hemorrhage, splanchnic vasoconstrictors like terlipressin and somatostatin are highly effective. Control of an acute variceal hemorrhage is in the region of 75% to 80%. The hemostatic benefit of somatostatin (or its analogue, octreotide) and terlipressin given as intravenous infusions reaches rates similar to therapeutic endoscopy. Stabilizing blood pressure in the setting of an acute hemorrhage is a necessity, but overexpanding intravascular volume should be avoided as it may accelerate bleeding. Blood products should be transfused to achieve a target hematocrit of 25% to 30%. Because of a high risk of bacterial infections in cirrhotic patients with variceal hemorrhage it is now considered standard care to institute antibiotics (*i.e.*, norfloxacin 400 mg *bid* for one week) as a part of short-term prophylaxis.[18]

Emergent therapeutic endoscopy undertaken within 24 hours of presentation controls bleeding in almost 90% of cases. Combination with pharmacologic therapy is commonly undertaken but there is no evidence to support the efficacy of this practice. Injection of sclerosants or band-ligation of the varices is equally effective in achieving initial hemostasis. Variceal eradication is essential since rebleeding occurs in 80% of patients within two years of the initial bleed. Followup band-ligation to eradication is the endoscopic treatment of choice. Sclerotherapy has a greater incidence of complications and requires a higher number of sessions. Pharmacologic therapy with beta-blockers should be continued in the interim. TIPS and shunt surgery are helpful in cases of uncontrolled bleeding but should not be used as the primary modality of intervention due to a higher incidence of complications.[19]

Portosystemic Encephalopathy

Onset of encephalopathy is a clear sign of deteriorating liver function and is an indication for early assessment for liver transplantation. Portal hypertension occurring in non-cirrhotic individuals is rarely complicated by encephalopathy but 50% to 70% of patients with cirrhosis have subclinical or overt encephalopathy. Nearly half of the patients with partial splenic embolization (PSE) recover spontaneously while another 30% improve with institution of specific therapy.

The management of encephalopathy has remained simple. A precipitating cause can be identified and treated in most episodes. Stringent protein restriction is eschewed to avoid harmful

protein-calorie malnutrition. In the acute setting, restriction of protein to 40 g daily is adequate in reversing PSE followed by sequential increments to achieve daily intakes between 0.8 g/kg to 1 g/kg. Where adequate protein intake cannot be established due to recurrence of PSE, substitution with vegetable protein may be required since it is better tolerated in these patients.

Lactulose remains the mainstay of treatment for these patients. Dosage should be titrated to effect a stool frequency of two to four motions daily. Where oral administration is not possible, substituting with enema-preparations (300 ml of lactulose in 700 ml of water) achieves a similar response. Neomycin demonstrated a similar response rate but is no longer available for oral use. Other oral non-absorbed antibiotics like metronidazole, vancomycin *etc.* may be used sparingly for lactulose-intolerant patients. Various new modalities of treatment are considered experimental and do not add to the improvement rates achieved by lactulose.[20]

In summary, cirrhosis of the liver is complicated by a number of portal hypertension-related disorders, many of which are potentially life threatening. Aggressive intervention and evolving therapies have reduced the mortality rate in many of these diseases. However, due to the irreversibility of advanced cirrhosis, most of these therapies serve as a stabilizing bridge to the more definitive treatment of liver transplantation. As such, liver transplantation remains the ultimate treatment of decompensated cirrhosis. CME

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