Management of the complications of chronic liver disease

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The complications of severe chronic liver disease result from hepatocellular failure, portal hypertension, or a combination of both. Acute variceal haemorrhage can be effectively managed by drugs, endoscopic techniques, balloon tamponade, and surgery. The advent of the transjugular intrahepatic portosystemic stent-shunt has offered a new therapeutic option. Prevention of re-bleeding also depends on endoscopic therapy or surgery. Beta-blockers have been shown to be useful, not only in preventing re-bleeding, but also in primary prophylaxis. Spontaneous bacterial peritonitis has proved to be preventable by antibiotic prophylaxis. Massive ascites can be satisfactorily treated by repeated large-volume paracentesis and albumin infusion. Hepatic encephalopathy responds to protein restriction and reduction of bowel ammonia production by classical and novel agents. Liver transplantation may be used for those with hepatorenal and hepatopulmonary syndromes and it is the ideal treatment of choice for all suitable patients with terminal chronic liver disease.

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Introduction

Severe chronic liver disease has a myriad of clinical problems, the main ones being the consequences of hepatocellular failure, portal hypertension, or the combined effects of both. While the underlying liver damage is usually irreversible, the goal of management is largely directed at preventing or treating the associated complications. The following discussion is selective rather than all-embracing in approach, owing to the extensive information accrued for each complication.

Variceal haemorrhage

When the portal venous pressure rises above 12 mmHg, oesophagogastric varices will form and subsequently bleed. About one third of patients with varices bleed at least once. The minimal risk of death is 20% to 30% in each haemorrhagic episode.[1] Despite the advances in medicine in the past few decades, less than 40% of patients will survive one year after the index bleed.[2]

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If varices have bled, the risk of re-bleeding is high over the next 10 to 20 days. For early re-bleeding, 40% occurs in the first 72 hours and 60% occurs within 10 days. The prognosis improves with time and by three months, it returns to baseline level. The risk of recurrent variceal haemorrhage is increased in patients with decompensated cirrhosis, large varices, renal failure, continued alcohol intake, and hepatocellular carcinoma. The risk of early re-bleeding is increased in patients older than 60 years, those with large varices, in renal failure, or who have severe initial bleeding.

Managing acute bleeding

Any patient presenting with haematemesis and/or melaena should be admitted to hospital and managed by a conjoint medical-surgical team with intensive nursing care. The severity of bleeding and hepatic dysfunction should be fully assessed. The correction of hypovolaemia is the most important initial therapy. Measures should be taken to prevent and treat hepatic encephalopathy and fluid retention and any suspected infection should be treated immediately. Vitamin K, 10 mg/day, should be given intravenously for three days. After resuscitation has been accomplished, endoscopy should then be performed with nasal oxygen supplementation and pulse oximetry monitoring. A

number of specific management measures can be performed.

Vasoactive drugs

Drug treatment is readily available and does not require sophisticated equipment or specialised training. Vasopressin, glypressin, and somatostatin have been found to be useful.

Vasopressin reduces blood flow to the splanchnic circulation. It is administered as an intravenous infusion at 0.4 units/min. In different studies, the efficacy of vasopressin varied between 33% to 74%.[3,4] The significant drawback of vasopressin is its haemodynamic adverse effects due to vasoconstriction of systemic regional circuits. Myocardial infarction, bowel gangrene, and skin necrosis have been reported. Nitroglycerin has been found to reduce the side effects of vasopressin[5] and should be used in combination with vasopressin, either administered via skin patches every 12 hours or by intravenous infusion (40 μg/min), maintaining a systolic blood pressure of 100 mmHg or more. Vasopressin is contraindicated in ischaemic heart disease and ECG monitoring is mandatory during therapy.

Glypressin is a synthetic analogue of vasopressin (triglycyl lysine vasopressin) that has a better therapeutic index and fewer side effects than vasopressin alone[6] or vasopressin combined with nitroglycerin.[7] Because of a long half-life, it can be administered by bolus intravenous injections of 2 mg every six hours. Nitroglycerin may still be necessary in combination with glypressin.

Somatostatin and its long-acting analogue, octreotide, are virtually free from haemodynamic side effects. They cause a reduction in splanchnic blood flow and a significant decrease in variceal pressure without inducing changes in the systemic vascular circulation.[8] Somatostatin is given as a 250 μg intravenous bolus followed by 250 μg/hour and octreotide is administered by intravenous infusion (50 μg/hour). Both drugs are as effective as[9] or more effective than[10] vasopressin and as effective as balloon tamponade[11] or sclerotherapy.[12]

Emergency endoscopic techniques

Endoscopic sclerotherapy (EST) is the treatment of choice and is the gold standard for emergency treatment of variceal haemorrhage. The sclerosant can be 5% ethanolamine oleate, 5% sodium morrhuate, and 1% sodium tetradecyl sulphate. The injection is made into and/or next to the variceal columns, 2 cm to 3 cm above the oesophagogastric junction and the volume should not exceed 4 ml in any one varix. In 71% to 88% of cases, the bleeding is controlled with a marked reduction in re-bleeding.[13] Failure to control bleeding after two injection sessions indicates the need for other forms of treatment. Minor complications are common (e.g. fever, retrosternal pain, oesophageal ulceration, pleural effusion), but major complications (e.g. oesophageal perforation, mediastinitis, portal vein thrombosis, venous embolisation of sclerosant) are rare.

Endoscopic variceal ligation (EVL) has been used recently to stop acute variceal bleeding. Prestretched rubber bands are placed on variceal columns, using a delivery cylinder mounted at the end of an endoscope. An overtube is needed for repeated intubation because the endoscope bears a single band, and six to eight bands may be required in each session. A delivery device that can apply several bands without reintubation has now been developed. Endoscopic variceal ligation may control bleeding in 88% of patients[14] with a low complication rate. Recurrent bleeding from the banding-related ulcers has been observed in 10% of cases. A comparison of EVL with EST in a recent study[15] shows that both can arrest active bleeding from oesophageal varices. However, EVL is more effective in decreasing re-bleeding, obliterating oesophageal varices more rapidly, and improving survival more significantly.[16] Major disadvantages of EVL include its being more time-consuming and requiring deeper sedation, and thus increasing the risk of airway aspiration. Use of the overtube can cause oesophageal trauma. The endoscopic field of view is reduced by the cylinder attachment, which also impedes the selective suction of blood or secretions. The technique is not suitable for treated varices embedded in a nonpliable mucosa that are difficult to aspirate into the cylinder attachment. The combination of EVL with EST, either synchronously or metachronously, may be superior to EST alone.[17] Combined treatment lengthens the time needed for treatment, however, although efficacy is improved and complications are reduced.[18] Endoscopic variceal ligation may be problematic in large fundal varices due to partial ligation. A modification of the technique by using a detachable snare has been described.[19]

The tissue adhesive, histoacryl (N-butyl-2-cyanocrylate), transforms from its native liquid to a solid state when added to a physiological medium like blood. Histoacryl should be diluted with the oily contrast agent lipiodol to prevent premature solidification, using a dilution ratio of 0.5 mL histoacryl to 0.8 mL lipiodol. Limiting injection aliquots to a maximum of 1.0 mL has been recommended. With

intravariceal injection, histoacryl polymerises instantly and hardens, thus plugging the varix lumen. Rapid haemostasis of an actively bleeding varix is then achieved. When combined with conventional sclerotherapy to eradicate smaller oesophageal varices that cannot be adequately treated with histoacryl injection, re-bleeding rates in the order of 10% have been reported. A randomised controlled trial from Egypt[20] comparing a combination of histoacryl and sclerotherapy with 5% ethanolamine oleate to sclerotherapy alone for the treatment of oesophageal and gastric varices showed that the immediate haemostasis rates were similar (100% vs 96%), but the former had a significantly lower re-bleeding rate (9% vs 25%).

Complications associated with the use of histoacryl are usually minor, including dysphagia without stenosis, bacteraemia, and pyrexia. However, cerebral,[21] pulmonary,[22] and portal vein embolisms[20] have been reported. The main advantages of this technique are the capacity to rapidly achieve haemostasis of actively bleeding varices and the effective treatment of gastric varices that have few non-surgical therapeutic options. The technique is complementary rather than competitive with conventional sclerotherapy.

Balloon tamponade

Variceal haemorrhage can be controlled with balloon tamponade in 40% to 90% of patients.[23,24] This technique is best used as a temporary measure to control variceal bleeding. It should be restricted to massive bleeding not controlled by initial therapy like EST and also used as an expedient to allow the safe transfer of a patient to a specialised centre. Balloon tamponade is used for 12 hours only in most cases (and no more than 24 hours), so as to minimise local mucosal ischaemic damage. Because of the high re-bleeding rate of about 50% within 24 hours of balloon deflation, a further procedure, e.g. EST or EVL, should be performed once the balloon has been removed. Balloon tamponade is associated with fatal complications in 6%[24] to 20% of cases.[25] These include large oesophageal ulcer, oesophageal stricture, aspiration pneumonia, and airway obstruction. Thus, this technique should only be used by skilled and experienced staff in an intensive care setting and airway intubation is a prerequisite for the procedure.

The transjugular intrahepatic portosystemic stent-shunt system

Transjugular intrahepatic portosystemic stent-shunt (TIPS) involves the establishment of portosystemic shunt by the transjugular insertion of an expandable metallic stent between the hepatic and portal veins through a balloon-dilated track under radiological monitoring. The diameter of the stent is commonly 10 mm or less, but can be more. This procedure is most useful for patients who have continued bleeding after endoscopic therapy or bleeding from gastric varices. Its use as a bridge to liver transplantation, because of its beneficial effects on ascites, renal function, and nutritional states, has been promising. A number of complications have been reported in association with TIPS placement. Procedural complications include liver capsule perforation, haemobilia, and intraperitoneal haemorrhage. Stent-induced complications include pulmonary embolisation and portal vein thrombosis. Systemic complications include renal failure, septic shock, and intravascular haemolysis. There are two significant post-shunt problems: hepatic encephalopathy and stent stenosis or occlusion. Encephalopathy occurs in 20% to 30% of cases, which is comparable to the rate in patients with surgical shunts. The rates of shunt stenosis or occlusion range from 16% to 50%.[26,27] Stenosis occurs because of pseudointimal hyperplasia. The role of emergency TIPS in the setting of active variceal bleeding is not well defined. Since one recent report[28] found a mortality rate of 56% for emergency TIPS compared with 5.5% for non-emergency TIPS, variceal haemorrhage should probably be stopped by other methods before TIPS is tried.

Surgery

Emergency surgery and non-surgical procedures have similar mortality rates, which are determined by the degree of liver failure.

Oesophageal transection, using a staple gun, is a rapid emergency salvage procedure for acute variceal haemorrhage. The early re-bleeding rate is less than that with EST, although late re-bleeding occurs in 50% of patients.

Emergency surgical shunts are virtually no longer used, but can be life-saving. The risk of ensuing thrombosis is high. Portocaval shunts alter vascular anatomy, making subsequent liver transplantation more difficult. After emergency shunts, 50% of patients develop portosystemic encephalopathy.[29]

Devascularisation (i.e. stripping of all venous collaterals from the oesophagus and stomach), combined with transection and/or splenectomy, may be required if there is portal, mesenteric, or splenic thrombosis. Splenectomy is the procedure of choice for isolated splenic vein thrombosis.

With the advent of TIPS, these procedures need to be re-evaluated.

Preventing re-bleeding

Long term endoscopic sclerotherapy or banding ligation

Repeated injections are performed at intervals of one to two weeks. The sclerosant causes obliteration of the varices of the lower oesophagus. Periodic follow up endoscopy is performed once every three weeks and varices are treated again when they reappear. A meta-analysis showed that EST significantly reduced re-bleeding and mortality.[30] Although EVL seems to be more convenient than EST, this needs to be confirmed by a longer follow up.

Pharmacological therapy

Non-selective β-blockers (e.g. propranolol) are used to decrease variceal pressure—they do this by reducing cardiac output (β_1-blockade), allowing unopposed vasoconstriction in the splanchnic bed (β_2-blockade), and by causing a marked reduction in collateral blood flow. Unfortunately, approximately 30% of patients with cirrhosis do not respond to β-blockade.[31] Alcoholics with well-compensated cirrhosis have better responses. The addition of other portal pressure-reducing drugs, such as isosorbide mononitrate, has been shown to change non-responders to responders. A recent meta-analysis shows that β-blockade decreases re-bleeding compared with placebo (44% vs 65%), but does not improve mortality.[32] Overall, β-blockade is inferior to or no better than long term sclerotherapy. As many patients are intolerant of β-blockers, they are used only in selected patients with well-compensated cirrhosis. The target is to reduce the resting pulse rate to 60 beats per minute (or by 25%), or to achieve a maximal tolerance in terms of hypotension and other side effects. It seems reasonable to combine sclerotherapy with β-blockers because this approach has been shown to be better than one using β-blockers alone.

The transjugular intrahepatic portosystemic stent-shunt system

The usefulness of TIPS in preventing re-bleeding over the long term has not been established. One recent randomised study suggests that TIPS is more effective than EST in the prevention of variceal bleeding in cirrhotic patients.[33]

Surgery

Compared with EST, shunt surgery markedly reduces re-bleeding, but chronic or recurrent portosystemic encephalopathy is increased.[34] There is no difference in mortality rates between the two treatments.[35]

Non-selective decompressive shunts are total shunts. Portal blood goes into the systemic circulation and the liver loses hepatotrophic substances and cannot detoxify the portal blood. This may result in liver function impairment and portosystemic encephalopathy. Survival is not increased, but re-bleeding is markedly reduced. The types of shunts include the end-to-side portocaval shunt, small-bore 8 mm interposition H graft portocaval shunt, mesocaval interposition shunt, mesocaval C graft, and proximal splenorenal shunt. Shunts, especially portocaval ones, make liver transplantation more complicated. Mesocaval shunts are total shunts of choice in candidates for liver transplantation.

An example of a selective shunt is the distal splenorenal shunt (DSRS). This shunt decompresses the varices, via the short gastric and splenic veins, into the renal vein. There are no significant differences in re-bleeding rates compared with non-selective shunts. The DSRS has slightly less encephalopathy and long term mortality associated with it.[36]

Devascularisation procedures have various forms. The simplest is oesophageal transection, which does not prevent re-bleeding in the long term. The most complicated is the Sugiura operation in which the collateral veins are stripped off the oesophagus and stomach and an oesophageal transection is performed together with a splenectomy. The re-bleeding rate is less than 10% in Japan,[37] but similar results have not been found in other countries. Devascularisation should be reserved for patients with failed non-operative treatment and who cannot undergo shunt surgery or TIPS.

Primary prophylaxis for variceal bleeding

Surgery and injection sclerotherapy

Both surgery and injection sclerotherapy are contra-indicated as they have been shown to increase mortality. Banding ligation has not been evaluated.

Pharmacological therapy

This is the prophylaxis of choice. A recent meta-analysis showed that patients given β-blockers had significantly lower rates of bleeding, fatal bleeding, and death from bleeding, with a trend towards a reduction in total mortality.[38] Cirrhotic patients should have their varices evaluated endoscopically. For those without contraindications and with varices at risk of

bleeding (e.g. large varices and cherry red spots over variceal surface), β-blockers should be given.

Ascites

Ascites is defined as the presence of fluid inside the peritoneal cavity. At least one to five litres of fluid must be accumulated before ascites can be clinically detected. Ultrasound can detect as little as 100 mL of fluid and is the most sensitive examination method. The 'overfill', 'underfill', and 'peripheral arterial vasodilatation' hypotheses have been proposed to explain the formation of ascites. Half of the patients whose cirrhosis is detected before decompensation have ascites in 10 years' time.[39]

Renal perfusion is improved by bed rest. Fluid intake should be restricted to 1500 mL per day until diuresis occurs. Although salt restriction is important, a diet with severe sodium restriction is unacceptable to patients. A 40 mmol per day sodium diet is more palatable and less restrictive.

Diuretics

Approximately 85% of ascitic patients respond to diuretics. Spironolactone is started at 100 mg to 200 mg per day and increased by 100 mg every three days. Elevation of the spironolactone dose is limited by the presence of hyperkalaemia, dehydration, and dyspepsia. Two controlled trials have shown that single-agent spironolactone is superior to single-agent furosemide.[40] If there is no response to spironolactone, furosemide can be added in 20 mg increments up to an arbitrary maximum of 120 mg. Since the process of increasing the spironolactone dose may lead to a long hospitalisation, it may be wise to start the combination of spironolactone and furosemide on the first day of treatment. Spironolactone can cause painful gynaecomastia and amiloride at 10 mg to 40 mg per day is a good alternative.

Overdiuresis may result in dehydration, hyponatraemia, and uraemia, and may precipitate hepatic encephalopathy, oliguria, and the hepatorenal syndrome. Weight loss is kept at 0.5 kg per day in the absence of peripheral oedema, and at 1 kg per day if peripheral oedema is present. This is a safe practice since ascitic fluid is reabsorbed at the rate of 700 mL to 900 mL per day, and the presence of oedematous fluid can prevent the shrinkage in plasma volume due to the rate of diuresis exceeding that of ascitic fluid reabsorption.

Paracentesis

A more rapid way to remove the ascitic fluid is therapeutic paracentesis followed by albumin infusion. The candidates for large-volume paracentesis are patients with massive and tense ascites. Ascitic fluid can be drained at a rate of 4 to 6 L per day or a total tap given, taking an average volume of 10 L. Paracentesis is usually performed with an 18-gauge needle (with additional side holes) connected to a low pressure suction device. A concomitant infusion of 6 g to 8 g of albumin is given for every litre of ascitic fluid removed. The safety of synthetic colloids in the long term is still under investigation. Most patients who have a total tap and comply with their sodium restriction return every two to three weeks for paracentesis. Diuretics are used at small maintenance doses.

Complications of ascites

Complications include spontaneous bacterial peritonitis (SBP) and refractory ascites. The former is bacterial peritonitis that occurs in patients with ascites in the absence of recognised secondary causes such as bowel perforation or intra-abdominal abscess. The pathogenesis is due to bacterial translocation from blood to the ascitic fluid. Only 50% to 60% of patients have symptoms, which include fever, abdominal pain, lethargy, and encephalopathy. Pseudo-obstruction of the bowel often occurs. The mortality rate has been high in the past. Currently, most studies show a mortality rate of about 30% to 40%.[41]

The classical criteria for SBP are polymorphonuclear leucocytes (PMN) >500/mm^3 in ascitic fluid or PMN>250/mm^3 with culture-positive fluid. Culture-negative ascites is common. The PMN count in ascitic fluid, however, is thought to be the single best predictor of SBP and if there are more than 500 PMNs/mm^3, antibiotic treatment is mandatory. An intravenous third generation cephalosporin (e.g. cefotaxime) is the drug of choice, as most of the isolates are Gram-negative organisms and streptococci (only 6% are anaerobes). A cure rate of at least 85% has been shown to occur with cefotaxime 2 g administered intravenously every eight hours.[42] Generally, five to seven days of cefotaxime therapy is recommended, with the requisite verification that the PMN count falls by 50% within 48 hours and <250/mm^3 at the completion of treatment. The probability of recurrence at one year is almost 70%. Antibiotic prophylaxis has been used to prevent recurrence. A double-blind, placebo-controlled study has shown that norfloxacin, 400 mg, once a day, is an effective preventive measure.[43]

Refractory ascites is ascites that cannot be mobilised or the early recurrence of which (i.e. after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. The term 'refractory ascites' includes

two different subtypes: 'diuretic-resistant ascites' and 'diuretic-intractable ascites'. Diuretic-resistant ascites is due to a lack of response to dietary sodium restriction and intensive diuretic treatment. Diuretic-intractable ascites results from the development of diuretic-induced complications that preclude the use of an effective diuretic dosage.

Patients with refractory ascites should be considered for liver transplantation after the following have been excluded: non-compliance to the drug regimen and low sodium diet, inadvertent dietary indiscretions, and hypokalaemia and alkalosis—both of which impair renal tubular sodium excretion. Those patients for whom liver transplantation is not indicated, may be treated by other means.

The side-to-side portocaval shunt is the most suitable shunt for treating ascites. The liver sinusoids and mesenteric capillaries are decompressed. Shunt surgery should only be performed in patients not suitable for liver transplantation and not in those with hepatic failure.

The extracorporeal ultrafiltration and reinfusion of ascitic fluid has experienced a recent resurgence of interest. New filter membranes are now being used to prevent fever and disseminated intravascular coagulation. Two small controlled trials have demonstrated a similar efficacy to large volume paracentesis.[44]

Peritoneovenous shunts have a one-way valve. Ascitic fluid flows from the peritoneal cavity to a central chest vein. Complications can be fatal. These include disseminated intravascular coagulation and sepsis. Thrombosis of the major veins and shunt blockage are common. Although a recent controlled trial showed equivalent efficacy[45] for peritoneovenous shunt and large-volume paracentesis, this treatment is currently seldom recommended.

Refractory ascites has been effectively treated by TIPS.[46] There is often a reduction or disappearance of the ascitic fluid. This procedure is also effective in controlling hepatic hydrothorax.[47]

Hepatic encephalopathy

The neuropsychiatric syndrome of hepatic encephalopathy may complicate nearly all types of liver disease. The encephalopathy can be episodic and reversible but it can also lead to coma and death. Latent hepatic encephalopathy was found in 71% of patients with cirrhosis in a study that used non-instrumental psychometric tests.[48] The mechanisms involved are poorly understood but the most widely held hypothesis is that liver failure results in the hepatic metabolism of gut-derived substances, which can cause neurotoxicity, directly or indirectly, or modulate neural function by enhancing its inhibition.

Patients with hepatic encephalopathy have an increased sensitivity to benzodiazepine agonists and have been shown to have elevated levels of endogenous benzodiazepine-like substances.[49] However, the benzodiazepine antagonist, flumazenil, has been reported to achieve only transient improvement or no effect in patients with hepatic encephalopathy.[50]

The mainstay treatments of hepatic encephalopathy include the correction of any precipitating causes, the reduction of protein in the diet, and the amelioration of ammonia production and absorption in the intestine.

Correctable precipitating factors include electrolyte abnormalities, sepsis, hypovolaemia, hypoxia, bleeding, constipation, and drugs (diuretics, sedatives, and opiate analgesics). Protein intake is stopped and then increased by 20 g per day until tolerance (usually every three days) of up to 50 g to 60 g per day is reached. Branched chain amino acids have shown favourable effects.[51] Their use remains controversial, however, since some other studies have revealed no advantage from this therapy. Bromocriptine is now almost completely abandoned. Non-absorbable carbohydrates, especially lactulose, are used to decrease ammonia absorption—by dint of their effect on the gut flora. Lactulose, at a daily dose of 30 mL, divided into three to five portions, is used to ensure that two soft bowel motions occur daily. A recent study showed that lactulose improved psychometric test results in 88% of patients with latent hepatic encephalopathy.[48] Lactitol, a more palatable nonabsorbable disaccharide, has been shown to be equally as effective as lactulose, with fewer side effects and a quicker onset of action.[52] Antibiotics are used to reduce the level of aerobic urea-splitting bacterial flora in the intestine in chronic hepatic encephalopathy. Neomycin (0.5 g to 1 g, 4 times a day) and metronidazole (0.2 g, 4 times a day) are the commonly used agents. A new antibiotic, rifaximin (200 mg per day), has been found to be as effective as lactulose in cirrhotic patients with hepatic encephalopathy.[53] It has a more rapid onset of action and significantly greater tolerability.

The hepatorenal syndrome

The hepatorenal syndrome (HRS) is defined as renal failure that occurs in patients with severe liver disease

in the absence of clinical, laboratory, or anatomical evidence of other known causes. Cirrhosis is usually present, but it is not necessary for the development of HRS. The pathogenesis remains uncertain. Mechanisms that lead to renal vasoconstriction and cortical hypoperfusion result in renal failure. Multiple factors, including the sympathetic nervous system, renin-angiotensin system, eicosanoids, renal kallikrein, endotoxaemia, nitric oxide, and endothelins, have been implicated in the pathogenesis.[54] Urinary sodium usually falls to 1 to 2 mmol/L and hyponatraemia, hypotension, and oliguria develop in the terminal phase. The prognosis is poor and more than 95% of these patients die within a few weeks of the onset of azotaemia.[55]

Treatment is unsatisfactory in most cases. Plasma expanders, vasoactive drugs, portosystemic shunts, the Le Veen shunt, paracentesis, haemofiltration, and dialysis all give disappointing results. The TIPS shunt has recently been used in patients with HRS. Results of a pilot study suggest that this procedure may be able to relieve ascites and improve renal function.[56] Liver transplantation is the only treatment associated with acceptable perioperative mortality and good long term survival in HRS[57] and should be considered in all suitable patients.

The hepatopulmonary syndrome

The hepatopulmonary syndrome (HPS) remains a challenging pulmonary vascular complication of liver disease. Pulmonary vascular dilatation and direct arteriovenous communications may develop as a consequence of the hepatic dysfunction. This syndrome is essentially the triad of liver disease, pulmonary vascular dilatation, and abnormal arterial oxygenation, which can result in severe hypoxaemia (PaO_2<6.65 kPa, normal range, 11-14 kPa). Retrospective data suggest an approximate 40% survival rate 2.5 years after the diagnosis of severe hypoxaemia.[58] Medical therapeutic interventions using almitrine bimesylate, prostaglandin inhibitors, somatostatin analogues, and plasmapheresis have shown no benefits. Other options, which employ interventional radiology, include coil embolotherapy of discrete arteriovenous communications[59] and TIPS.[60] These have achieved a limited correction of the hypoxaemia. Many centres consider that deteriorating oxygenation in patients with stable chronic liver disease may well be indicators for liver transplantation.[61] However, there are patients with HPS whose oxygenation status does not improve following liver transplantation[62] and their prognosis is grave.

Other complications of chronic liver disease

Other complications of chronic liver disease include hypersplenism, septicaemia, coagulopathy, hypogonadism, feminisation, hepatocellular carcinoma, hepatic spastic paraparesis, and the pruritus and osteodystrophy of chronic cholestasis. The treatment of each of these entities merits individual discussion on its own and will not be detailed here.

Liver transplantation

All patients with complications of chronic liver disease are potential candidates for liver transplantation, which is the definitive treatment. While psychological and other medical problems are important in the selection process, the main indicators for referral are based on the severity of liver disease. These include deteriorating nutritional state, unacceptable chronic fatigue, bleeding caused by portal hypertension associated with advanced liver disease (Child's Grade C), repeated variceal bleeding despite endoscopic and/or medical therapy, refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, recurrent acute-on-chronic encephalopathy, and hypoxaemia secondary to liver disease.

Conclusion

There are now various treatments available for the complications of chronic liver disease. These are only palliative, however, even if successful, and some produce controversial or disappointing results. Liver transplantation, despite its many restrictions, remains the ideal treatment of choice for end-stage chronic liver disease.

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