Management of portal hypertension, Budd–Chiari syndrome and portal vein thrombosis

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Abstract

Portal hypertension is associated with many of the known complications of cirrhosis and has an enormous impact on patients' prognosis. Ascites and hepatic encephalopathy represent the most common complications of cirrhosis; both are associated with a significantly worse prognosis, with 50% survival over 1–2 years. Acute variceal bleeding is a life-threatening complication, and despite significant improvements in the management it remains a leading cause of death in patients with cirrhosis. Advances in variceal bleeding management, including empirical antibiotic use, vasoactive drugs, early endoscopy and therapies such as transjugular intrahepatic portosystemic shunt (TIPSS) in patients with refractory bleeding, have resulted in improved mortality rates, currently around 11–20% per episode. Secondary prophylaxis of variceal bleeding with a combination of non-selective β-adrenoceptor blockers and endoscopic variceal ligation has also improved survival. Budd–Chiari syndrome (BCS) is a life-threatening disorder resulting from hepatic venous outflow obstruction. Myeloproliferative neoplasms represent the most common cause of BCS, although a significant proportion of patients have more than one risk factor. Therapeutic anticoagulation remains the first-line treatment for both BCS and symptomatic portal vein thrombosis. TIPSS is increasingly used in the management of BCS and can reduce the need for liver transplantation.

Keywords Anticoagulation; ascites; balloon-occluded retrograde transvenous obliteration (BRTO); Budd–Chiari syndrome; hepatic encephalopathy; MRCP; portal hypertension; portal vein thrombosis; transjugular intrahepatic portosystemic shunt (TIPSS); variceal bleeding

Key points

- In the management of acute variceal bleeding (AVB), a conservative blood transfusion policy is standard, aiming for a target haemoglobin concentration of 70–80 g/litre. All patients should be given empirical antibiotics and vasoactive therapy
- Early endoscopy remains the cornerstone of management in AVB. Oesophageal varices are typically treated with variceal ligation ('banding'), and gastric varices with endoscopic injection therapy
- All patients with cirrhosis should be endoscopically screened for the presence of varices so primary prophylactic therapy (non-selective β-adrenoceptor blocker or variceal banding) can be given for varices at increased risk of bleeding. A combination of non-selective β-blocker therapy and endoscopic variceal ligation is now the standard of care for secondary prophylaxis of variceal bleeding
- Budd–Chiari syndrome is a rare but life-threatening condition resulting from hepatic venous outflow obstruction. Anticoagulation remains the first-line therapy. Transjugular intrahepatic portosystemic shunting is increasingly used as a management option and can reduce the need for liver transplantation

Introduction

Cirrhosis represents an advanced stage of progressive hepatic fibrosis resulting from any chronic insult to the liver. It is characterized by distortion of the hepatic architecture and formation of regenerative nodules. Cirrhosis is a serious condition that reduces both quality of life and life expectancy. The development of many of the complications associated with cirrhosis, and to a large extent the prognosis, relates to the degree of portal hypertension (PH).

Portal hypertension

Portal venous blood flow in humans is approximately 1000–1200 ml/minute, and in healthy subjects 100% of portal blood flow is recovered from the hepatic veins that drain the liver. PH is characterized by a pathological elevation of pressure in the veins that carry blood from the splanchnic organs (including the spleen) to the liver. This results in increased resistance to blood flow through the portal venous system and ultimately the development of a collateral circulation to carry portal blood into the systemic veins.

In developed countries, PH most commonly develops as a consequence of liver cirrhosis. In cirrhosis, increased intrahepatic resistance to portal flow means that significantly less portal blood flow reaches the hepatic veins; the remainder enters the portosystemic collateral channels, of which the most clinically significant are those from gastro-oesophageal varices. PH is further worsened in cirrhosis by the development of circulatory changes including splanchnic vasodilatation and a hyperdynamic circulation, which leads to increased cardiac output, increased portal flow and higher portal pressures.

Non-cirrhotic PH is also well described and can be caused by prehepatic (portal vein thrombosis (PVT), schistosomiasis) or post-hepatic (Budd–Chiari syndrome (BCS)) conditions.

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Schistosomiasis represents a particularly important cause of PH in developing countries.

PH is associated with many of the known complications of cirrhosis (Table 1). Clinically, PH can be defined as an elevation of the hepatic venous pressure gradient to >5 mmHg, although in practice this is rarely measured.[1]

Ascites, spontaneous bacterial peritonitis and hepatic encephalopathy

Ascites is defined as the accumulation of free fluid in the peritoneal cavity and represents the most common complication of cirrhosis. Hepatic encephalopathy is defined as a reversible impairment of neuropsychiatric function occurring in a patient with advanced liver disease. It is the second most common complication occurring in cirrhotic patients after ascites and is associated with a significantly reduced quality of life. These conditions, their diagnosis and their management are considered elsewhere in this issue (see Diagnosis and management of ascites and hepatorenal syndrome, pages 828–832 and Hepatic encephalopathy, pages 833–837).

Oesophageal and gastric varices

Acute variceal bleeding (AVB) is a life-threatening complication occurring in patients with PH and remains a leading cause of death in patients with cirrhosis. Variceal haemorrhage is associated with substantial mortality, traditionally quoted as 30–50%. With advances in care, more recent studies show an improved mortality rate of 11–20%.[1]

At the time of diagnosis, gastro-oesophageal varices are present in approximately 50% of patients with cirrhosis (30% in patients with compensated cirrhosis, rising to 60% prevalence in patients with decompensated cirrhosis). Around 5–10% of cirrhotic patients develop oesophageal varices each year, and in patients with established varices approximately 12% have a first variceal haemorrhage within 1 year; this risk increases with large varices, varices with high-risk stigmata and more advanced liver disease. Thus, the presence of varices is common in patients with cirrhosis, although bleeding ultimately occurs in only approximately one-third of patients. After an episode of AVB, 60% patients rebleed within 1 year.

Management of acute variceal bleeding: a management algorithm for AVB is shown in Figure 1. The initial management priority is haemodynamic resuscitation before urgent endoscopy. A conservative blood transfusion policy is now standard practice, aiming for a target haemoglobin concentration of 70–80 g/litre; excessive blood volume replacement can increase the risk of rebleeding.[1] Protection of the airway is paramount to prevent pulmonary aspiration, with intubation mandatory if there is any concern about the safety of the airway. All patients should be given prophylactic antibiotics, which have been shown to prevent infection and significantly improve survival.

Vasoactive medications to decrease portal blood flow are commonly commenced before endoscopy in patients with suspected AVB. Commonly used agents include the vasopressin analogue terlipressin (1–2 mg intravenously 4–6-hourly) and the somatostatin analogue octreotide (50 micrograms intravenous bolus followed by continuous infusion at a rate of 25–50 micrograms/hour). Vasoactive medications improve haemostasis and decrease transfusion requirements, length of stay and early mortality.[1]

The cornerstone of management in AVB is urgent endoscopic treatment, which results in control of bleeding in almost 90% of patients. Endoscopic variceal ligation (EVL) or 'banding' is the gold standard technique to control bleeding oesophageal varices. Gastric varices are usually treated with endoscopic injection therapy, using a variety of agents (cyanoacrylate, thrombin, fibrin glue). In patients whose bleeding cannot be controlled with endoscopic and pharmacological therapy, treatment options include the following.

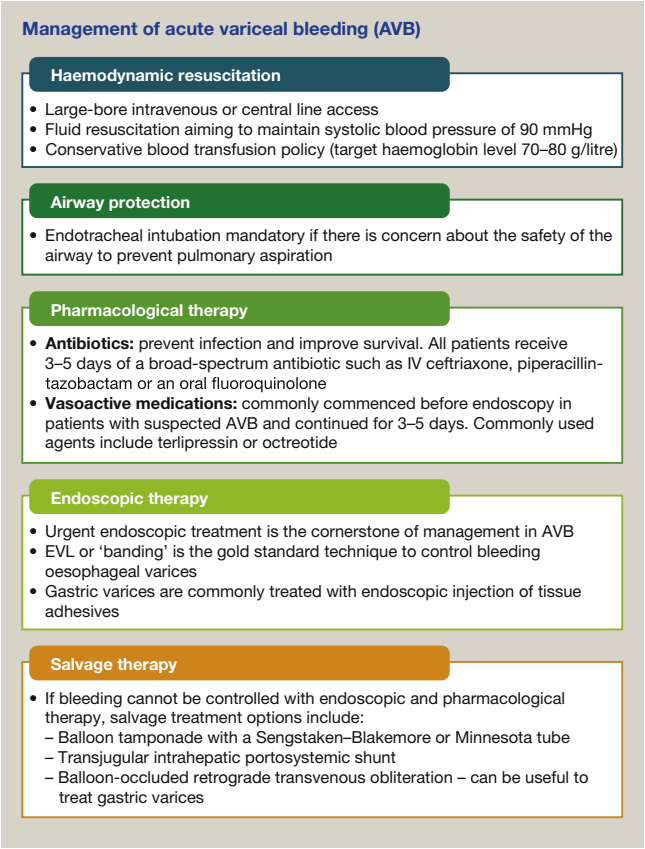

Figure 1

Complications of cirrhosis associated with portal hypertension

- Gastro-oesophageal varices
- Portal hypertensive gastropathy
- Ascites
- Spontaneous bacterial peritonitis
- Hepatic hydrothorax
- Hepatorenal syndrome
- Hepatic encephalopathy
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Cirrhotic cardiomyopathy

Table 1

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Balloon tamponade with a Sengstaken–Blakemore or Minnesota tube – a temporizing measure that pneumatically compresses the gastric fundus and lower oesophagus to achieve haemostasis. Patients should remain intubated and the tube should be deflated within 24 hours. Patients require further endoscopy immediately after deflation.

Transjugular intrahepatic portosystemic shunt (TIPSS) – a radiologically placed portosystemic shunt that achieves haemostasis in approximately 95% of patients with refractory variceal bleeding.[1] TIPSS is only available in specialized centres. The presence of a PVT is not an absolute contraindication but can make placement difficult. Hepatic encephalopathy is a recognized adverse effect.

Balloon-occluded retrograde transvenous obliteration (BRTO) – an advanced radiological procedure that is increasingly being used to treat gastric varices. Cardiofundal gastric varices usually have a unique vascular anatomy with splenorenal or gastrorenal shunts that flow into the systemic circulation. BRTO uses these shunts to access and obliterate gastric varices. It is highly efficacious but, unlike TIPSS, is not a decompressive procedure; therefore portal pressures can actually increase because of the diversion of blood flow into the portal circulation. Thus, although BRTO is not associated with hepatic encephalopathy, it can increase the risk of developing ascites and oesophageal varices.[1]

Primary prophylaxis: this encompasses strategies that aim to prevent the first episode of AVB in patients with cirrhosis and is recommended in patients with a high risk of bleeding. These include those with:

- medium or large varices
- small varices with high-risk stigmata ('red signs')
- decompensated cirrhosis (Child–Pugh B or C) regardless of variceal size.

Two main treatment strategies are currently widely employed: pharmacological reduction of portal pressures below pathological levels by the introduction of non-selective β-blockers (NSBBs), and direct variceal eradication through serial EVL procedures. Current expert consensus is that NSBBs and EVL have equivalent efficacy in preventing AVB.

Propranolol has traditionally been the β-adrenoceptor blocker most commonly used for primary prophylaxis. More recent studies have shown that carvedilol, an NSBB with intrinsic α_1-adrenergic activity, produces a greater decrease in portal pressure. Carvedilol should be considered as a first-line agent and may reduce the incidence of AVB more effectively than EVL. If propranolol is selected, the dose of β-adrenoceptor blocker is titrated to either the maximum dose, a reduction in resting heart rate of 25% from baseline or the development of adverse effects. With carvedilol, patients are commenced on 6.25 mg daily and the dose increased 1 week later to 12.5 mg if tolerated. Once treatment has been initiated, it is generally continued life-long as bleeding risk returns to baseline if the treatment is ceased.

If β-blockers are contraindicated because of co-morbidities such as reactive airway disease, congestive heart failure, bradycardia or heart block, EVL should be instituted. EVL involves serial episodes of variceal banding until oesophageal varices have been eradicated; this typically takes four to six procedures.

All patients with a new diagnosis of cirrhosis are recommended to undergo endoscopic screening to assess the presence and size of varices so that prophylactic therapy can be initiated for patients at increased risk of bleeding. They then undergo endoscopic variceal screening every 1–2 years, the timing being influenced by whether the liver injury is continuing. There is emerging evidence that some patients can undergo variceal risk stratification using non-invasive methods, which could for some obviate the need for endoscopy.

The probability of high-risk varices being present appears to be very low (<5%) in patients with compensated cirrhosis with a platelet count ≥150 x 10^9/litre and liver stiffness <20 kPa on transient elastography, although this is currently only well validated in patients with hepatitis C. In this patient cohort, one approach could be to perform annual platelet count and transient elastography scans, and perform endoscopic screening for varices if the platelet count drops to <150 x 10^9/litre or liver stiffness increases to ≥20 kPa[2]

Secondary prophylaxis: patients who recover from a variceal haemorrhage have a high risk of rebleeding (60% in the first year), with a mortality of up to 33%. Secondary prophylaxis should be considered mandatory and is ideally instituted before the patient is discharged from hospital. The standard of care for secondary prophylaxis is a combination of an NSBB and EVL. β-Adrenoceptor blocker therapy is the cornerstone of combination therapy as their benefit extends to other complications of PH.[2]

TIPSS is an alternative to combination therapy for secondary prophylaxis. TIPSS is associated with lower rebleeding rates than standard endoscopic and pharmacological therapy, but an increased risk of hepatic encephalopathy.[2] Guidelines now suggest that early TIPSS placement (within 72 hours) should be considered in any Child–Pugh class B patient who is actively bleeding at the time of endoscopy or any Child–Pugh C patient providing the Child–Pugh score is <14.

Budd–Chiari syndrome

BCS is the eponym used for a heterogeneous and life-threatening group of disorders resulting from hepatic venous outflow obstruction. Obstruction can occur at the level of the hepatic venules (hepatic veno-occlusive disease), the large hepatic veins or inferior vena cava (BCS), or the right atrium (congestive hepatopathy). Primary BCS is defined as thrombosis of the hepatic veins or the terminal portion of the inferior vena cava as a result of primary venous disease, whereas secondary BCS is related to compression or invasion from an external source (including hepatocellular or other malignancy, parasitic cysts, abscesses, haematoma or trauma). BCS is a rare disorder with an incidence of 0.8 per million per year.[3]

Aetiology

BCS should generally be regarded as a hepatic expression of underlying prothrombotic conditions, which are usually undiagnosed at the time of presentation. Common aetiological factors are listed in Table 2. Myeloproliferative neoplasms (MPNs) are the most common cause of primary BCS; other risk factors include acquired and congenital thrombophilias and oral contraceptives. Most patients presenting with BCS have at least one

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Causes of BCS

Hypercoagulable states

- Acquired
  - Myeloproliferative disorders
  - Antiphospholipid syndrome
  - Hyperhomocysteinaemia
  - Paroxysmal nocturnal haemoglobinuria
  - Malignancy
  - Pregnancy
  - Use of oral contraceptives
- Inherited
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency

Tumour invasion

- Hepatocellular carcinoma
- Renal cell carcinoma
- Adrenal carcinoma

Idiopathic

Other (uncommon causes)

- Behçet's syndrome
- Inferior vena caval webs
- Aspergillosis
- Hydatid disease
- Trauma
- Dacarbazine therapy
- Sarcoidosis

Table 2

identifiable prothrombotic condition, and the presence of multiple risk factors in the same patient has been found in 25–46% of patients.[3] All patients presenting with BCS should be screened for an underlying MPN and thrombophilia.

Screening for MPNs includes a full blood count and film, bone marrow biopsy and testing for molecular mutations. The most common of these is the *JAK2* V617F mutation, found in 95% of patients with polycythaemia rubra vera and 50% with essential thrombocytosis. In a recent meta-analysis of 1062 patients with BCS, 440 patients were investigated for MPN; the prevalence was reported to be 41%, of whom 80% were *JAK2* V617F-positive. Mutations in calreticulin and the *JAK2* exon 12 mutation are also increasingly being tested for.

Clinical presentation and diagnosis

There is a wide clinical spectrum, ranging from an asymptomatic presentation to fulminant hepatic failure, depending on:

- the location, extent and rapidity of the obstructive process
- whether the portal vein is thrombosed
- whether a venous collateral circulation has developed to decompress the liver sinusoids.

BCS can be classified as fulminant, acute, subacute or chronic. In the fulminant and acute forms, thrombosis of all major hepatic veins is usual.

The classic triad of presenting symptoms in BCS are ascites (typically exudative), hepatomegaly and abdominal pain. Any patient with this constellation of symptoms or an unexplained acute hepatitis should undergo urgent Doppler ultrasonography to ensure hepatic and portal vein patency. Serum alanine and aspartate aminotransferases can be greatly elevated (>5–10 times the upper limit of normal) in fulminant and acute BCS, indicative of hepatic necrosis.

Treatment

Acute BCS is life-threatening and should be managed in a transplant centre or a centre experienced in appropriate interventional radiological procedures. Initial management is therapeutic anticoagulation, initially with low-molecular-weight heparin (LMWH), shifting rapidly to warfarin with a target international normalized ratio (INR) of 2.5. Other therapeutic options have included thrombolysis, percutaneous transluminal angioplasty (PTA), TIPSS, surgical portosystemic shunting and liver transplantation. The choice and order of procedures can differ between centres depending on local expertise and experience, and there are no randomized controlled trials to guide treatment.

The European Network for Vascular Disorders of the Liver has advocated a stepwise management approach of anticoagulation followed by:

- consideration of recanalization strategies:
  - thrombolysis (rarely used and offers little benefit in clinical practice)
  - PTA or stenting (considered highly effective for short-length focal or segmental obstructions)
- TIPSS for those failing treatment
- liver transplant for those failing TIPSS.

This approach resulted in a 1-year survival and transplant-free survival of 88% and 85%, respectively; only 13% patients required liver transplantation.[4] In most patients requiring intervention, a TIPSS was inserted, consistent with other studies showing that TIPSS is increasingly used in BCS, with high success rates and a reduced need for liver transplantation.

Portal vein thrombosis

PVT is commonly encountered in patients with cirrhosis, especially in those with advanced or decompensated liver disease. Decreased velocity of portal vein flow appears to be the most important risk factor for thrombosis; other risk factors include the presence of an underlying thrombophilia or MPN, the presence of large collateral vessels and increased severity of the underlying liver disease.

Malignant PVT from hepatocellular carcinoma (HCC), pancreatic cancer, cholangiocarcinoma and other malignancies is also well described. PVT is an adverse prognostic factor in both cirrhosis and HCC. Among cirrhotic patients without HCC, 0.6–15.8% are found to have PVT on routine ultrasonography. Prevalence increases with severity of liver disease, from 1% in individuals with compensated cirrhosis to 8–25% in liver transplantation candidates.[5]

Clinical presentation and diagnosis

Cirrhotic patients with chronic PVT are commonly asymptomatic. Symptomatic patients tend to present with complications of the associated increased PH, such as variceal bleeding or

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increasing ascites. Rarely, if the PVT extends to the mesenteric veins, intestinal ischaemia or infarction can develop, with colicky abdominal pain, ascites or diarrhoea.

PVT is most commonly diagnosed by Doppler ultrasonography of the liver, which demonstrates absence of flow in the portal vein and hyperechoic material within the vein that can extend into the mesenteric or splenic veins. Splenomegaly is a common associated finding. Cross-sectional computed tomography or magnetic resonance imaging with contrast can also diagnose PVT, define the extent of thrombosis and look for associated malignancies.

Treatment

The management of acute, symptomatic PVT is therapeutic anticoagulation, usually with LMWH followed by warfarin if appropriate. The goal of anticoagulation is to prevent clot extension and enable recanalization so that intestinal infarction and PH do not develop.[5] Anticoagulation for acute PVT appears to be safe and beneficial in patients with cirrhosis. The optimal duration of anticoagulation is unclear; in the absence of a known hypercoagulable state, some centres recommend treating for 6 months.

The management of asymptomatic, chronic PVT in cirrhotic patients remains challenging as the risk of bleeding from anticoagulation needs to be balanced against the risk of life-threatening extension of thrombosis. A recent meta-analysis by Loffredo et al. and a large study by Pettinari et al. (see Further reading) both suggest that anticoagulation is safe even in patients with advanced liver disease. In these studies, anticoagulation was associated with improved survival rates, a low risk of bleeding complications and a recanalization rate of 53–57%. Before starting anticoagulation, all patients should be screened for oesophageal varices. In cirrhotic patients with an abnormal INR before initiation of therapy, it is probably safer to use LMWH.

There is a growing interest in the use of direct oral anticoagulants (DOACs) in PVT but clinical data in cirrhosis are scarce. From the small studies available, DOACs appear to be safe, with similar safety characteristics to LMWH or warfarin; however, cirrhotic patients have often been treated with lower than standard doses of DOACs.[5]

Primary prophylaxis

Few studies have looked at primary prophylaxis of PVT in cirrhotic patients, which is rarely ever done in practice. One study found that prophylactic enoxaparin in selected patients with Child–Pugh B cirrhosis (who did not have ascites, portal hypertensive bleeding, high-risk varices or a platelet count $<10{,}000/mm^3$) was associated with a significantly reduced incidence of PVT both during and after treatment. No bleeding complications were recorded. In addition, hepatic decompensation and death were significantly lower in the enoxaparin group. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 52-year-old man presented with frank haematemesis. He had a long history of heavy alcohol abuse.

On clinical examination, he smelt of alcohol, was confused and had multiple spider naevi on his chest. His blood pressure was 80/50 mmHg. The abdomen was soft with clinical evidence of shifting dullness.

Investigations

- Haemoglobin 89 g/litre (130–180)
- Platelets 90×10^9/litre (150–400)
- International normalized ratio 1.8 (<1.4)

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What is the best initial management of this patient?

A. Empirical antibiotic therapy
B. Urgent endoscopy
C. Blood transfusion
D. Vasoactive therapy with octreotide
E. Fluid resuscitation

Question 2

A 45-year-old man presented with haematemesis. At endoscopy, large oesophageal varices were found, which were ligated with achievement of haemostasis.

Upon discharge, what is the recommended first-line therapy to prevent a further variceal bleed?

A. A non-selective β-blocker (propranolol or carvedilol)
B. Repeated endoscopic ligation (banding)
C. A non-selective β-blocker (propranolol or carvedilol) and a nitrate
D. A transjugular intrahepatic portosystemic shunt
E. A non-selective β-blocker (propranolol or carvedilol) and repeat endoscopic ligation (banding)

Question 3

A 37-year-old woman presented acutely with abdominal pain, lethargy, anorexia and nausea. She had no relevant past medical history and was taking only the oral contraceptive pill. She had never smoked and did not drink or use illicit drugs. She had no family history of liver disease.

On examination, she had tender hepatomegaly with clinical evidence of shifting dullness.

Investigations

- Alanine aminotransferase 2183 U/litre (5—35)
- Aspartate aminotransferase 2437 U/litre (1—31).
- Alkaline phosphatase 210 U/litre (45—105)
- γ-Glutamyl transpeptidase 133 U/litre (4—35)
- Bilirubin 45 micromol/litre (1—22)
- An ascitic tap showed exudative fluid

Which is the best initial liver imaging modality for this patient?

A. MR scan with venogram
B. Quadruple-phase CT scan
C. Contrast-enhanced ultrasound (US) scan
D. Doppler US scan
E. Positron emission tomography-computed tomography scan

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