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 of which the most clinically significant are those from gastro- oesophageal varices (Fig. 15.22.3.1). Portal hypertension is fur- ther exacerbated in cirrhosis by the development of circulatory changes including splanchnic vasodilatation, which leads to plasma volume expansion resulting in a hyperdynamic circula- tion and increased cardiac output with increased portal flow and raised portal pressures. Noncirrhotic portal hypertension due to prehepatic (portal vein thrombosis, schistosomiasis) or posthepatic (Budd–Chiari syn- drome, right heart dysfunction, constrictive pericarditis) conditions are also well described. Schistosomiasis infection is a particularly common and important cause of portal hypertension in developing countries. The hepatic venous pressure gradient is a useful clinical

marker of portal pressure that has been shown to correlate well with portal pressure in both alcoholic cirrhosis and hepatitis C. It is defined as the gradient between the wedged hepatic venous pressure and the free hepatic venous pressure (the normal hepatic venous pressure gradient is <5 mmHg). A portal pressure greater than 10 mmHg is the baseline elevated pressure above which variceal formation and bleeding may occur, and the hepatic venous pressure gradient is predictive of both the risk of variceal bleeding and hepatic decom- pensation; it is also prognostic for survival. In all cases, higher hep- atic venous pressure gradient readings confer a poorer prognosis, although it is rarely measured in practice because of the invasiveness of the test. Clinical features Clinical manifestations of portal hypertension may include spleno- megaly, ascites, a venous hum over the xiphoid process or umbil- icus, and the development of abdominal wall veins such as caput medusae. Portal hypertension is associated with many of the known complications of cirrhosis (Box 15.22.31). The most common of these will be discussed in the following subsections. Ascites and hepatic encephalopathy Ascites is defined as the accumulation of free fluid in the peri- toneal cavity and is the most common complication of cirrhosis. (a) (b) Fig. 15.22.3.1 Gastro-oesophageal varices. (a) Corrosion cast showing gastro-oesophageal varices. (b) Postmortem radiograph study of the venous anatomy at the gastro-oesophageal junction in a normal subject. Used with permission of Vianna and colleagues. Box 15.22.3.1 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

 Hepatic encephalopathy is defined as a reversible impairment in neuropsychiatric function occurring in a patient with ad- vanced liver disease. It is the second most common complication occurring in cirrhotic patients after ascites. Both conditions are associated with significantly reduced quality of life and reduced survival. Ascites and hepatic encephalopathy are discussed in Chapters 15.22.2 and 15.22.4. Hepatorenal syndrome Hepatorenal syndrome is a life-threatening but potentially re- versible cause of renal dysfunction occurring in patients with advanced cirrhosis, ascites, and liver failure. It is characterized by functional renal impairment due to decreased renal perfu- sion in the setting of portal hypertension and splanchnic arterial vasodilatation. Two forms of hepatorenal syndrome are recognized: type 1 is characterized by an acute progressive decrease in kidney function with a median survival time of 2 weeks without treatment, whereas type 2 features more chronic and less severe kidney failure and longer survival compared with type 1. Liver transplantation is the only effective long-term therapy for hepatorenal syndrome. Management of hepatorenal syndrome involves identification and aggressive treatment of any precipitating factors such as infection. Pharmacological treatment with terlipressin (1–2 mg/4–6-hourly IV), a vasoconstrictor aiming to reverse splanchnic vasodilation, to- gether with albumin, is the first-line treatment for patients with type 1 hepatorenal syndrome. This combination is effective in reversing renal dysfunction in 40 to 50% of patients and improves survival in this group. Hepatopulmonary syndrome Hepatopulmonary syndrome is characterized by pathological vaso- dilatation of the pulmonary vasculature. It is defined by a clinical triad—occurring in the absence of coexisting cardiopulmonary disease—of (1) an arterial oxygenation deficit (Pao2 <80 mmHg), (2) intrapulmonary vasodilation, and (3) the presence of liver dis- ease with portal hypertension. The presence of hepatopulmonary syndrome should be con- sidered in all patients with liver disease who complain of dyspnoea, which is common in cirrhosis and present in at least 50% of pa- tients with this syndrome. Finger clubbing is very

common in hepatopulmonary syndrome, and one should always suspect hepatopulmonary syndrome in patients with chronic liver dis- ease and clubbing. Dyspnoea may be accompanied by pulmonary findings that are more specific for hepatopulmonary syndrome, including the following: • Platypnoea—dyspnoea that is induced by moving into an upright position and relieved by being supine. • Orthodeoxia—hypoxia that is worse when erect. Specifically, orthodeoxia refers to a decrease in arterial oxygen tension (by

> 4 mmHg) or arterial oxyhaemoglobin desaturation (by >5%) when the patient moves from a supine to an upright position, which is improved by returning to the recumbent position. The diagnosis of hepatopulmonary syndrome is made by esta blishing that impaired gas exchange in a patient with liver disease is due to pulmonary vascular dilatation. This is usually achieved by demonstrating the following: • Impaired oxygenation—arterial blood gases taken with the pa- tient sitting upright at rest show hypoxia (Pao2 <80 mmHg) and/ or an elevated alveolar–arterial (A–a) oxygen gradient, defined as ≥15 mmHg when breathing room air. • The presence of intrapulmonary shunting—most commonly shown with contrast-enhanced echocardiography, in which agitated saline microbubbles are used to differentiate between the normal situation (the bubbles opacify only the right heart chambers), a right-to-left intracardiac shunt (microbubbles ap- pear in the left heart within three heart beats after injection), and an intrapulmonary shunt (microbubbles appear in the left heart three to six heart beats after injection). Technetium-labelled macroaggregated albumin scanning is an alternative method of identifying pulmonary shunting and can determine the shunt fraction. There are no proven medical therapies for hepatopulmonary syn- drome and liver transplantation remains the primary treatment option. Long-term supplemental oxygen is the most frequently re- commended therapy for symptoms such as dyspnoea. Portopulmonary hypertension Portopulmonary hypertension refers to a rare pulmonary vascular disorder of pulmonary arterial hypertension coexisting with portal hypertension in a patient where alternative causes of pulmonary ar- terial hypertension have been excluded. It is a well-recognized com- plication of chronic liver disease and cirrhosis, but far less common than hepatopulmonary syndrome, although patients can rarely have features of both disorders. In portopulmonary hypertension, the pulmonary circulatory ab- normality is vasoconstriction with fibro-obliteration of the vascular bed, the opposite of the changes that occur in hepatopulmonary syn- drome. Patients may present with fatigue, dyspnoea, signs of right heart failure, chest pain, and syncope. The diagnosis may be sug- gested by echocardiography but is confirmed by right heart cath- eterization. Treatment tends to be as for other causes of pulmonary arterial hypertension. Patients with moderate to severe disease can be difficult to treat with medical therapy and perioperative mortality with liver transplantation is high. Cirrhotic cardiomyopathy Cirrhotic cardiomyopathy refers to cardiac dysfunction (including impaired cardiac contractility with systolic and diastolic dysfunc- tion, as well as electromechanical abnormalities such as prolonged QT syndrome)

> which occurs in patients with cirrhosis and portal hypertension in the absence of other known causes of cardiac dis- ease. Patients with cirrhotic cardiomyopathy usually have normal to increased cardiac output and contractility at rest but demonstrate a blunted response to pharmacological, physiological, or patho- logical stress, with unmasking of systolic incompetence. Cirrhotic cardiomyopathy has been associated with the development of heart failure following invasive procedures such as shunt insertion and liver transplantation. Current pharmacological treatment is nonspecific and directed towards left ventricular failure.

15.22.3 Portal hypertension and variceal bleeding 3071 Variceal bleeding In patients with portal hypertension, a combination of increased splanchnic blood flow and intrahepatic resistance to portal blood flow can lead to the development of portosystemic collaterals, of which the most clinically significant are those from gastro- oesophageal varices. Acute variceal bleeding is a common and life-threatening com- plication occurring in patients with portal hypertension and a leading cause of death in patients with cirrhosis. Variceal haem- orrhage continues to be associated with substantial mortality. Advances in care have seen the mortality rate associated with an episode of acute variceal bleeding significantly improve from 30 to 50% to 11 to 20% in more recent studies. This improvement in outcomes can be attributed to multiple factors, including recogni- tion of the importance of adequate resuscitation, early endoscopy, and accurate diagnosis. The therapeutic armamentarium has been significantly expanded and now includes endoscopic, adjunctive pharmacological and radiological therapies which have high efficacy at obtaining haemostasis. In addition, practice guidelines that outline optimal care for patients presenting with acute variceal bleeding have been developed. Definition Variceal haemorrhage is defined as bleeding from an oesophageal or gastric varix at the time of endoscopy or the presence of large oesophageal varices with blood in the stomach and no other recog- nizable cause of bleeding. Risk factors Gastro-oesophageal varices (Fig. 15.22.3.2) are present in approxi- mately 50% of patients with cirrhosis at the time of diagnosis. In patients with established varices, 12% will have a first variceal haem- orrhage within 1 year and approximately one-third will bleed at some point. Following an episode of acute variceal bleeding, 60% of patients will rebleed within 1 year. Many factors have been implicated in precipitating haemorrhage. The most significant risk factors for variceal bleeding include: (a) (c) (b) Fig. 15.22.3.2 (a) Grade 3 oesophageal varices.
(b) Oesophageal varices with high-risk stigmata (fibrin plugs at
7 o’clock and 11 o’clock). (c) Endoscopic variceal ligation of oesophageal varices. Pictures courtesy of Dr Ian Penman.

section 15 Gastroenterological disorders 3072 • large varices—for patients with nearly identical portal hyper- tension, the likelihood of acute variceal bleeding is markedly in- creased in patients with large varices • the presence of high-risk variceal stigmata collectively known as ‘red signs’—red wale, markings, cherry red spots, nipple sign, haematocystic spots • other endoscopic findings—blue varices, giant coiled varices, and panoesophageal varices • a portal venous pressure higher than 12 mmHg above inferior vena cava pressure Patients with severe liver disease (Child–Pugh score C) are also sig- nificantly more likely to experience acute variceal bleeding. Prognosis Several factors have been validated for the prediction of complica- tions such as early

rebleeding and mortality following an episode of variceal bleeding. Overwhelmingly, mortality is dictated by the severity of the underlying liver disease and hence scores such as the Model for End-Stage Liver Disease (MELD) score and the Child– Pugh (Child–Pugh–Turcotte) score, along with the presence of hep- atic encephalopathy, are predictive of outcome. Other risk factors which confer a poor prognosis are listed in Table 15.22.3.1. Reducing the portal pressure by at least 20% or to less than 12 mmHg following an acute variceal bleeding is associated with significant protection against further bleeding. Management of acute variceal bleeding Management of a patient with acute variceal bleeding incorporates both treatment and control of the active bleeding and the prevention of complications such as rebleeding, infections, and renal failure. Primary management goals include haemodynamic resuscitation, early endoscopic intervention aiming to control bleeding, and pre- vention and treatment of complications. A summary of acute vari- ceal bleeding management is shown in Fig. 15.22.3.3. Resuscitation Acute variceal bleeding is a life-threatening event and patients are often haemodynamically unstable or in haemorrhagic shock on presentation. Airway protection is paramount in order to prevent pulmonary aspiration, with endotracheal intubation mandatory if there is any concern about the safety of the airway. This should be considered at an early stage in encephalopathic patients, those with altered conscious state or a low Glasgow Coma Scale score, or those with severe uncontrolled bleeding. After attention (if required) to the airway, initial resuscitation is aimed at restoring haemodynamic stability and appropriate blood pressure. All patients with suspected acute variceal bleeding should receive immediate large-bore intravenous access, and blood volume replacement with plasma expanders should be initiated as soon as possible, aiming to maintain a systolic blood pressure of about 90 to 100 mmHg. It is imperative to avoid prolonged periods of hypoten- sion to prevent complications such as infection and renal failure, both of which are associated with increased risks of rebleeding and death. A restrictive blood transfusion strategy is now accepted as standard of care and is associated with significantly improved outcomes in patients with acute upper gastrointestinal bleeding. Patients should be transfused to maintain a target haemoglobin level between 70 and 80 g/L. Patients with rapid ongoing bleeding and those with underlying heart disease may benefit from a more liberal transfusion policy, which can be assessed on a case-by-case basis. Correction of coagulopathy and thrombocytopenia is widely practised with the use of both fresh frozen plasma and platelets, but there is no evidence to support this practice and endoscopy should not be delayed for this to occur. Recombinant activated factor VII has not shown any benefit in patients with acute variceal bleeding and is not recommended. Nutrition Malnutrition is prevalent among patients with chronic liver dis- ease and is associated with increased morbidity and mortality. Patients presenting with acute variceal bleeding are fasted to facili- tate treatment, but feeding should be resumed as soon as possible after haemostasis is achieved (practically this tends to be at least 24 h following control of bleeding). Enteral nutrition is preferable to parenteral nutrition due to lower cost and complications; if a naso- gastric tube is required, current guidelines recommend delaying in- sertion until at least 72 h after haemostasis and use of a fine bore tube. Administration of thiamine should also be given to alcoholic or malnourished patients to prevent Wernicke syndrome. Pharmacological management Prophylaxis and treatment of infection Infection is a strong prognostic indicator in acute variceal bleeding, associated with both early rebleeding and increased mortality. Gram-negative bacilli are the pathogens most commonly associated with upper gastrointestinal bleeding in cirrhotic patients. Empiric prophylactic antibiotics significantly reduce the incidence of infec- tion, resulting in a decreased risk of rebleeding, all-cause mortality, and hospital length of stay. All patients presenting with an episode of acute variceal bleeding should therefore receive prophylactic anti- biotic therapy on admission. Survival benefits are

observed independently of the antibiotic agent used and hence the choice of antibiotic should take into consideration local factors such as bacterial resistance profile and treatment cost. Oral quinolones (norfloxacin 400 mg twice daily or ciprofloxacin 500 mg twice daily for 7 days) have frequently been used due to their low cost and ease of administration, and these agents can also be given intravenously. Intravenous third-generation Table 15.22.3.1 Factors that confer a poor prognosis in patients presenting with acute variceal bleeding Advanced liver disease Child–Pugh C liver disease High MELD score Presence of hepatic encephalopathy Factors at presentation Shock Renal impairment Bacterial infection Characteristics and severity of the
variceal bleed Active bleeding at time of endoscopy High-risk stigmata on varices Red cell transfusion requirement Other Hepatocellular carcinoma Portal vein thrombosis Hepatic venous pressure gradient >20 mmHg

15.22.3 Portal hypertension and variceal bleeding 3073 cephalosporins such as ceftriaxone (1 g daily for 3–5 days) are also well studied and may be more efficacious in patients with advanced cirrhosis presenting with acute variceal bleeding. Other agents with broad Gram-negative cover such as piperacillin–tazobactam (Tazocin) are also used in many centres. Pre-endoscopic vasoactive therapy Vasoactive medications are commonly used in the management of acute variceal bleeding to acutely decrease splanchnic blood flow and portal pressures. Meta-analyses and treatment guidelines advocate that the combination of vasoactive drugs and endoscopic therapy is superior to either intervention alone. Medications include vasopressin and its analogue terlipressin, and somatostatin and its analogue octreotide. The use of vasoactive medications is associated with im- proved haemostasis, decreased 7-day mortality, decreased transfusion requirements, and shorter hospital length of stay, with terlipressin the only agent individually demonstrated to reduce mortality. Vasoactive therapy should be considered at the time of presenta- tion in all patients presenting with haematemesis who have known varices or are at risk for varices; it should not be delayed until the diagnosis is confirmed. Vasoactive therapy should be commenced prior to endoscopy if any delay is anticipated with endoscopic therapy. In situations where endoscopy is unavailable, vasoactive therapy should be considered as first-line therapy. Treatment is gen- erally continued for 3 to 5 days. • Vasopressin: administered by continuous intravenous infusion, but no longer recommended as a monotherapy in acute variceal bleeding due to the high risk of significant side effects including myocardial infarction and mesenteric ischaemia. Vasopressin ad- ministered in combination with nitrates (potent vasodilators) re- duces the side-effect profile and may lower portal pressures more effectively. • Terlipressin: a synthetic vasopressin analogue with a longer half-life and less adverse effects, and the vasoactive agent of choice in many • Endotracheal intubation mandatory to prevent pulmonary aspiration if there is any concern about airway safety (e.g. decreased GCS, encephalopathy) Airway protection • Large-bore central line or intravenous access • Fluid resuscitation aiming to maintain systolic blood pressure of
90 mmHg • Conservative blood transfusion policy (target haemoglobin level 7–8 g/dl) Haemodynamic resuscitation • Antibiotics: improve survival and prevent infection. All patients receive 3–5 days of a broad-spectrum antibiotic (IV ceftriaxone, piperacillin–tazobactam or oral fluoroquinolone) • Vasoactive medications: commonly commenced prior to endoscopy in patients with suspected acute variceal bleeding and continued for 3–5 days. Agents include terlipressin or octreotide. Pharmacological therapy • Urgent endoscopic treatment is the cornerstone of management • Endoscopic variceal ligation (EVL, ‘banding’) is the gold standard technique to control bleeding oesophageal varices • Gastric varices are treated with endoscopic injection of

tissue adhesives or thrombin Endoscopic therapy • If refractory ongoing bleeding despite endoscopic and pharmacological therapy, salvage treatment options include: • Balloon tamponade with a Sengstaken–Blakemore or Minnesota tube • Deployment of a self-expanding oesophageal stent • Transjugular intrahepatic portosystemic shunt (TIPS) Salvage therapy Fig. 15.22.3.3 Management algorithm for acute variceal bleeding. GCS, Glasgow Coma Score.

section 15 Gastroenterological disorders 3074 countries outside of the United States of America. It is administered as a 1- to 2-mg intravenous bolus every 4 to 6 h. Use of terlipressin in patients with acute variceal bleeding can achieve early haemostasis rates of 75 to 80% and a 34% relative risk reduction in mortality. Adverse events are uncommon, although terlipressin should not be used in patients with a history of ischaemic heart disease or periph- eral vascular disease due to a risk of inducing ischaemia. • Somatostatin: administered as an initial bolus of 250 µg followed by a 250- to 500-µg continuous infusion until a bleed-free period of 24 h is achieved. Somatostatin has shown superior haemostasis to vasopressin in studies and also has a superior safety profile with fewer side effects. Both somatostatin and octreotide have a good safety profile; side effects include hyperglycaemia and abdominal cramping. • Octreotide: a synthetic somatostatin analogue with a longer half- life and the most common agent used in the United States. It is ad- ministered as a 50-µg intravenous bolus, followed by a continuous infusion at a rate of 25 to 50 µg/h. Octreotide has been shown to be more effective than vasopressin and equivalent to other vasoactive treatments. Terlipressin and octreotide appear to be equivalent as an adjuvant therapy for control of acute variceal bleeding in con- junction with endoscopic variceal band ligation (EVL). Endoscopic management Urgent upper gastrointestinal endoscopy remains the gold standard for diagnosis and treatment of variceal haemorrhage; 80 to 90% of acute variceal bleeding episodes are successfully controlled by endo- scopic therapy. Emergency endoscopy should be performed as soon as safely possible after admission to confirm a variceal origin of the haemorrhage (which represents the leading cause of upper gastro- intestinal bleeding in cirrhotic patients) and to perform definitive haemostatic therapy. Delayed endoscopy (endoscopy >12–15 h after admission) is associated with increased rebleeding and mortality. The two principal methods for management of oesophageal varices are endoscopic injection sclerotherapy (EIS) and EVL. Both have been shown to be effective in the control of acute variceal bleeding. Endoscopic injection sclerotherapy EIS is a technique whereby a flexible catheter with a needle tip is passed through the accessory channel of the endoscope and used to inject a sclerosing agent either into the variceal lumen or adjacent to the varix. Sclerosing agents are oily or aqueous chemicals which in- duce thrombosis of the vessel and inflammation of the surrounding tissues. EIS achieves haemostasis by variceal thrombosis and/or ex- ternal compression of the varix by tissue oedema. EIS has a number of advantages: it is a low-cost and (relatively) easy-to-use technique, it can be quickly assembled, treatment of bleeding varices does not require a second oral intubation, and the sclerosants induce rapid thrombosis. The major disadvantage of EIS is the high rate of local and systemic complications associated with the procedure. Minor complications are extremely common and include fever, retrosternal chest discomfort, dysphagia, asymptom- atic pleural effusions, and nonspecific transient chest radiographic changes. These complications do not generally require treatment and resolve spontaneously. More significant complications are listed in Table 15.22.3.2. Bacteraemia, post-EIS oesophageal ulcer bleeding, and oesophageal strictures are the most frequent and significant ad- verse events encountered. These hazardous complications can be a consequence of incorrect injection technique, with either a large volume or a high concentration of sclerosant being injected and re- sulting in extensive wall necrosis. Mortality directly resulting from post-EIS complications is

around 2% and usually the result of re- current bleeding, perforation, sepsis, or severe respiratory disorders. EIS has been used to treat acute variceal bleeding for over 50 years. The technique was widely adopted in the 1970s which corresponded with the time of a significant improvement in survival of patients presenting with acute variceal bleeding. EIS is successful in control- ling active bleeding in at least 90% of patients and can reduce the frequency and severity of recurrent variceal bleeding. However, due to its high adverse event rate, EIS has now been superseded by EVL and should be used only in the circumstances or cases when band ligation is not available.
Endoscopic variceal ligation Ligation of oesophageal varices was introduced in the 1980s and evolved from the established treatment of banding haemorrhoids. EVL involves the sucking of a variceal column into a hollow plastic cylinder attached to the tip of the endoscope, followed by the place- ment of a rubber ring onto the column which ligates and ultimately strangulates the varix (Fig. 15.22.3.2). Following variceal banding, the tissue ligated by the rubber band undergoes ischaemic necrosis accompanied by variceal thrombosis. The ligated tissue, along with the band itself, generally falls off within a few days, leaving shallow oesophageal ulcers which are shallower, have a greater surface area, and heal more rapidly than those caused by EIS. Commercial multiband devices are available for EVL which are disposable and have between 4 and 10 preloaded bands, enabling multiple varices to be ligated in a single banding session.
Table 15.22.3.2 Complications of endoscopic injection sclerotherapy Category Complication Minor postprocedure Low-grade fever Retrosternal chest pain Transient dysphagia Nonspecific chest X-ray changes Local Injection-induced bleeding Oesophageal ulcers/mucosal ulceration Post-EIS ulcer bleeding Oesophageal strictures Perforation Cardiorespiratory Pleural effusions Adult respiratory distress syndrome Pericarditis Mediastinitis Broncho-oesophageal fistula Systemic/infectious Fever Bacteraemia Spontaneous bacterial peritonitis Distant embolism Distant abscess

 The most common side effects associated with EVL include chest discomfort and postbanding ulceration; rarer side effects in- clude oesophageal strictures and bleeding resulting from a band falling off. To minimize chest pain and band removal, patients are generally commenced on a liquid-only or soft diet for the first 12 h. The incidence of bacteraemia and infectious complications are significantly reduced with EVL compared to EIS. The incidence of bleeding from band-induced ulcers following EVL varies widely between studies, but is significantly more frequent in patients undergoing EVL for acute bleeding, as compared with elective EVL for primary or secondary prevention of variceal bleeding. Patients with more severe liver disease, as evidenced by a higher Child– Pugh score or impaired synthetic function (hypoalbuminaemia and/or coagulopathy) may be more likely to experience post-EVL bleeding. The incidence of bacterial infection is also higher in pa- tients experiencing post-EVL bleeding. Comparison of EIS and EVL Both EVL and EIS have been shown to be effective in the control of acute variceal bleeding. Multiple randomized control trials and meta-analyses have compared EVL and EIS. These studies demon- strate that EVL is superior to EIS for eradicating varices more rapidly, with significantly less recurrent bleeding, and is also associated with significantly fewer adverse events compared to EIS. Some (but not all) studies have also demonstrated a survival advantage in patients treated with EVL. Thus, EVL should be considered the gold standard endoscopic treatment for controlling an acute variceal haemorrhage, with EIS considered only in situations where EVL is not available. Rescue therapies in cases of refractory oesophageal
variceal bleeding Despite best practice management, 10 to 20% of patients with acute variceal bleeding will experience treatment failure or early rebleeding. Any bleeding that occurs more than

48 h after the ini- tial admission for variceal haemorrhage, provided there has been at least a 24-h period without bleeding, is considered to represent rebleeding. Approximately 40% of rebleeding episodes will occur within 5 days of the original variceal bleed. Mortality of patients in this group remains high (30–50%) and rebleeding remains a strong predictor of death from variceal bleeding. Treatment options in the setting of rebleeding include a second endoscopy, balloon tamponade, oesophageal stenting, and transjugular intrahepatic portosystemic shunting (TIPS) or surgical portosystemic shunting. Second endoscopy In the setting of failure of initial combined treatment (endoscopy and vasoactive therapy), it is reasonable to consider a second at- tempt at endoscopic therapy to obtain haemostasis. Second endos- copy can occur either before or after a period of balloon tamponade. Balloon tamponade Balloon tamponade with a Sengstaken–Blakemore or Minnesota tube (Fig. 15.22.3.4) is a temporizing measure that pneumatically compresses the gastric fundus and lower oesophagus to achieve haemostasis. It successfully achieves haemostasis in 60 to 90% of re- fractory variceal bleeds, and it may be life-saving in cases of massive bleeding where endoscopic treatment is unavailable. Generally, only the gastric balloon needs to be inflated with 250 to 300 ml of air. It is important that traction on the tube is maintained, usually using wooden spatulas attached around the tube at the mouth to prevent the traction slipping. Patients should remain intubated and the tube should be deflated within 24 h. Patients require further endoscopy (or other procedures such as TIPS) immediately after deflation as at least 50% will rebleed. Use of balloon tamponade is also associated with serious complications in 6 to 20% of patients, including aspiration, oesophageal ulceration, and oesophageal perforation, the latter being associated with extremely high mortality. Ideally, insertion of the bal- loon tamponade should be performed by someone experienced with the technique as this is associated with fewer complications. Self-expandable covered metal stents Case reports have documented the successful use of self-expandable covered metal stents in controlling refractory oesophageal vari- ceal bleeding. Stent insertion appears to be efficacious at stopping ongoing bleeding, although there is a high rebleeding rate with con- servative management following stent removal, hence it is likely to represent a temporizing measure to enable a definitive interven- tional or surgical procedure to lower portal pressures. Transjugular intrahepatic portosystemic shunt TIPS is a radiologically placed portosystemic shunt that achieves haemostasis in approximately 95% of patients with refractory vari- ceal bleeding. The procedure is only available in specialized centres and involves creation of a low-resistance channel between the hep- atic vein and the intrahepatic portion of the portal vein using angio- graphic techniques. TIPS does not require general anaesthesia or major surgery for placement. TIPS is a highly effective therapy in carefully selected patients. A good prognosis relies on the general condition of the patient, the value of the liver function reserve, associated comorbidities, and the timing of the procedure. The survival benefit of TIPS in patients with severe liver failure (defined as: Child–Pugh class C cirrhosis, MELD score >22, serum bilirubin >3 mg/dL) remains unclear. In patients with a Child–Pugh score greater than 13, early mortality after TIPS is almost inevitable. Chronic portal vein thrombosis does not absolutely preclude TIPS insertion but makes the pro- cedure technically challenging. Contraindications to TIPS are listed in Table 15.22.3.3. Treatment guidelines for acute variceal bleeding currently cat- egorize TIPS as a second-line treatment, applicable for patients in whom combined pharmacological and endoscopic therapy has failed to control bleeding. Its role as a salvage therapy stems from the fact that although TIPS is extremely effective in controlling variceal bleeding, two early meta-analyses demonstrated equivalent patient Fig. 15.22.3.4 A Sengstaken–Blakemore tube used to pneumatically tamponade varices.

section 15 Gastroenterological disorders 3076 survival to endoscopic therapy but with an increased risk of hepatic encephalopathy. More recently, the role of TIPS in acute variceal bleeding is being re-evaluated in the setting of technical advances and new studies. The introduction of extended polytetrafluoroethylene (PTFE) covered stents has significantly improved TIPS stent patency and reduced the incidence of encephalopathy when compared with bare stents. Carefully selected patients at high risk of bleeding-related mortality and/or rebleeding (hepatic venous pressure gradient ≥20 mmHg, Child–Pugh B patients with active bleeding at endoscopy or Child– Pugh C patients with a score <14) may benefit from early TIPS (within 3 days of admission) placement, with reduced treatment failure, hos- pital and intensive care unit length of stay, and in-hospital and 1-year mortality. In addition, a recent meta-analysis concluded that early TIPS in high-risk patients with acute variceal bleeding may improve survival with no significantly increased incidence of post-treatment hepatic en- cephalopathy Further studies are currently underway evaluating the benefits of early TIPS in high-risk patients with acute variceal bleeding. Surgical shunting procedures Following the introduction of TIPS, surgical shunting procedures are now rarely performed and they are no longer a first-line rescue therapy. Procedures included shunt operations (portacaval shunts, distal splenorenal shunts) and nonshunt operations (oesophageal transections or devascularization of the gastroesophageal junction). Portal decompressive surgery and oesophageal transection were highly effective in achieving haemostasis, although they are asso- ciated with significant mortality (approximately 45–75%). Similar to TIPS, shunt surgery also significantly increases the incidence of hepatic encephalopathy. Prophylaxis against variceal bleeding Primary prophylaxis All patients with a new diagnosis of cirrhosis are recommended to undergo endoscopic screening for the presence and size of varices so that prophylactic therapy can be given to those with varices that are at high risk of bleeding. Patients with compensated cirrhosis and no varices at index endoscopy should have endoscopy repeated every 2–3 years, with the timing influenced by whether the liver injury is ongoing. Patients with compensated cirrhosis and small varices with no high-risk stigmata may be considered for endoscopic vari- ceal surveillance annually to evaluate progression. There is emerging evidence that some patients with cirrhosis may be able to avoid screening endoscopy, with the risk of variceal bleeding assessed using noninvasive methods. The probability of high-risk varices being present appears to be very low (<5%) in pa- tients with compensated cirrhosis with a platelet count ≥150 000 and a liver stiffness of <20 kPa on transient elastography (TE), although currently this is only well validated in patients with hepatitis C. In this patient cohort, one approach may be to perform annual platelet count and TE scans, and perform endoscopic screening for varices if the platelet count drops to <150 000 and/or the LS increases to ≥20 kPa. More studies are required to validate this method. Primary prophylaxis of acute variceal bleeding, using either a nonselective β-blocker or EVL, is recommended in all patients with a high-risk of bleeding. These include: a) Patients with medium or large varices; b) Patients with small varices with high-risk stigmata (‘red signs’); c) Patients with decompensated cirrhosis (Child Pugh B or C) regardless of variceal size Both β-blockers and EVL display equivalent efficacy and survival and the choice of modality depends on factors such as comorbidities, compliance, and access to endoscopy. Propranolol has traditionally been the β-blocker most commonly prescribed for prophylaxis of variceal bleeding in cirrhotic patients. More recent studies have shown carvedilol, a nonselective β-blocker with intrinsic α1-adrenergic activity, to produce a greater decrease in portal pressure. Carvedilol (6.25 mg increasing to 12.5 mg oral daily) should be considered a first-line agent and may reduce the incidence of acute variceal bleeding more effectively than EVL. If propranolol is selected, the dose of β-blocker is titrated to either the maximum dose, a reduction in resting heart rate of 25% from baseline, or the develop- ment of side 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 is initiated, it is generally continued lifelong as bleeding risk returns to baseline if the treatment is ceased. If β-blockers are contraindicated due to comorbidities such as reactive airway disease, congestive heart failure, bradycardia, or heart block, EVL should be in- stituted. EVL involves serial episodes of variceal banding until oesopha- geal varices are eradicated; this typically takes four to six procedures. Secondary prophylaxis Following a variceal bleed, all patients should receive secondary prophylaxis with nonselective β-blockers and EVL, or TIPS. Non selective β-blockers and EVL both significantly decrease the risk of rebleeding and improve mortality; combination treatment is now re- commended as standard of care. β-blockers are an essential part of combination therapy, since their benefit extends to other complica- tions of portal hypertension. TIPS is associated with a lower rebleeding rate compared to endoscopic or pharmacological therapy, but at the expense of an increased risk of hepatic encephalopathy. TIPS is mainly considered in patients with recurrent acute variceal bleeding. Gastric varices Gastric variceal bleeding is significantly less common than oe- sophageal variceal bleeding but is another serious complication of portal hypertension. Gastric varices develop in approximately 20% Table 15.22.3.3 Absolute and relative contraindications to TIPS insertion Absolute contraindications Congestive cardiac failure Severe pulmonary hypertension Severe systemic sepsis Severe tricuspid regurgitation Unresolved biliary obstruction Relative contraindications Portal vein thrombosis Hepatocellular carcinoma Hepatic encephalopathy Severe coagulopathy Obstruction of all hepatic veins Polycystic liver disease (technically challenging with high risk of haemorrhagic complications) Adapted from Loffroy R, Estivalet L, Cherblanc V, et al. (2013). Transjugular intrahepatic portosystemic shunt for the management of acute variceal hemorrhage. World J Gastroenterol, 19, 6131–43.

15.22.3 Portal hypertension and variceal bleeding 3077 of patients with portal hypertension and represent 5 to 10% of all upper gastrointestinal bleeding episodes in cirrhotic patients. They are also commonly seen in patients with noncirrhotic portal hyper- tension and especially in patients with splenic vein thrombosis. The risk of first bleeding from gastric varices is lower than that for oe- sophageal varices, but bleeding is typically more severe and associ- ated with higher morbidity, transfusion requirements, and mortality than oesophageal varices. Gastric varices can be found alone or in combination with oesophageal varices (Fig. 15.22.3.5). Risk factors for gastric variceal bleeding appear in Table 15.22.3.4. Gastric varices are most commonly subtyped according to Sarin’s classification based on their location in the stomach and their relation- ship to oesophageal varices (Fig. 15.22.3.6). Type 1 gastro-oesophageal varices (GOV) represents the most common of all gastric varices (74%) and are also known as cardial varices. GOV2 and type 1 isolated gas- tric varices (IGV), at 21% and 7% of gastric varices respectively, are together referred to as fundal varices. Although less common than GOV1, fundal varices are much more likely to bleed and account for 80% of patients presenting with bleeding gastric varices. Diagnosis of gastric varices is made by endoscopy. Endoscopic ultrasonography can be used to clarify or further differentiate gastric varices if required (Fig. 15.22.3.5). If only IGV are present, exclusion (a) (b) (c)
Fig. 15.22.3.5 Endoscopic image of gastric varices. (a) Large gastric varices in the fundus of the stomach. (b) Endoscopic injection of thrombin into gastric varices. (c) Endoscopic ultrasonography with Doppler flow showing multiple collaterals extending into the gastric wall in a 56-year-old male with known segmental portal hypertension and gastric varices as a result of splenic vein thrombosis. Images courtesy of Dr Ian Penman. Table 15.22.3.4 Risk factors for gastric variceal bleeding Risk factor Explanation Location of gastric varices IGV1 >GOV2 >GOV1 (Fig. 15.22.3.5)

Size of gastric varices Large (>10 mm) >medium (5–10 mm)

> small (<5 mm) Severity of liver disease Child–Pugh class C >B >A MELD score ≥17 Concomitant hepatocellular carcinoma Presence of portal hypertensive gastropathy Presence of high-risk stigmata Red colour signs/red spots Adapted from Clinics in Liver Disease, Vol. 18, Sarin SK, Kumar A, Endoscopic treatment of gastric varices, Pages 809–27, Copyright © 2014, with permission from Elsevier.

section 15 Gastroenterological disorders 3078 of portal or splenic vein thrombosis as the underlying cause with Doppler ultrasonography is imperative. Management of acute gastric variceal bleeding The preliminary management of gastric variceal bleeding is identical to that for oesophageal bleeding: airway protection, fluid resuscita- tion, empiric antibiotic prophylaxis, and use of vasoactive agents. Evidence for the use of vasoactive drugs in acute gastric variceal bleeding is limited and efficacy is inferred from their effectiveness in controlling oesophageal variceal bleeding. Therapeutic options for acute gastric variceal bleeding include balloon tamponade, endo- scopic therapies, radiological therapies, or surgical procedures. Evidence in this area is scarce, with few randomized controlled trials and little consensus as to the gold standard treatment. Balloon tamponade Balloon tamponade with pneumatic compression of gastric varices is a temporizing measure or bridge to further definitive therapies. It can achieve haemostasis in up to 80% of patients with gastric vari- ceal bleeding, but rebleeding occurs frequently. Endoscopic management Endoscopic therapy remains the treatment of choice and all cir- rhotic patients presenting with upper gastrointestinal bleeding should be scoped as soon as possible. The endoscopic therapies util- ized for bleeding gastric varices often depend on availability and local expertise: • EIS: prior to the introduction of newer techniques, EIS with con- ventional sclerosants was used to control acute gastric variceal bleeding. EIS was less efficacious than when utilized for oesopha- geal varices, with larger volumes of sclerosant required and more side effects described. Overall, the success of EIS is questionable in the management of gastric variceal bleeding and it is not a pre- ferred haemostatic method. • EVL: EVL is also less effective for gastric varices. This is due to the fact that gastric varices are larger and located deep in the sub- mucosa, making ligation difficult. • Endoscopic variceal obturation (EVO): EVO is the endoscopic treatment of choice to gain haemostasis of gastric varices, su- perior to both EIS and EVL. Obturation is the term used for gas- tric varices treated by glue injection, because the varix can be visible after it has been effectively treated. EVO involves injecting tissue adhesives such as N-butyl-2-cyanoacrylate into the varix lumen. This rapidly undergoes exothermic polymerization on contact with water or blood, changing from a liquid to a hard brittle acrylic plastic and stemming the flow of blood from the varix. EVO can achieve haemostasis rates of over 90% in the man- agement of gastric variceal bleeding, and rebleeding rates vary from 15 to 30%. The most significant complication associated with cyanoacrylate injection relates to postprocedure thrombo- embolic phenomena including cerebral stroke, portal vein embol- ization, splenic infarction, renal, coronary, or spinal embolus, and pulmonary embolus, with rare deaths documented. Embolic and thrombotic phenomena are associated with larger volumes of glue injection. Other complications include the needle becoming stuck in the varix, gastric ulceration, retrogastric abscess, visceral fistula formation, and bacteraemia or sepsis. • Endoscopic thrombin injection: thrombin is a haemostatic agent first used

for the management of gastric varices in 1947. Bovine thrombin was used originally, but due to the increased risks of prion transmission has been superseded by human thrombin. Thrombin induces haemostasis by converting fibrinogen to a fibrin clot and also influences platelet aggregation. A 5-ml so- lution of thrombin containing 1000 units/ml of thrombin will clot a litre of blood in under 60 s. A standard gastroscope is Gastro-oesophageal varices (GOV) are associated with oesophageal varices which extend along the lesser curve of the stomach (GOV1), or along the fundus (GOV2) Isolated gastric varices (IGV) are gastric varices without any associated oesophageal varices; these can be localised to the fundus (IGV1) or at ectopic sites in the stomach or the first part of the duodenum (IGV2) GOV-1 GOV-2 IGV-1 IGV-2 Fig. 15.22.3.6 Sarin's classification of gastric varices. Adapted from Gastrointestinal Endoscopy, Vol. 46, Sarin SK, Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience, Pages 8–14, Copyright © 1997 American Society for Gastrointestinal Endoscopy, with permission from Elsevier.

15.22.3 Portal hypertension and variceal bleeding 3079 used for the procedure and no specific preparation is required. Thrombin injection is associated with high rates of haemostasis, low rebleeding rates, and minimal adverse effects. Rescue therapies in cases of refractory gastric variceal bleeding When patients with gastric variceal bleeding experience treatment failure with early rebleeding, a second endoscopic therapy should be attempted if possible. If endoscopic treatments fail to control bleeding, rescue therapy options include the following: • TIPS: as gastric variceal haemorrhage is uncommon, few studies (and no randomized trials) have investigated its efficacy in the setting of bleeding gastric varices. Despite this, TIPS with a PTFE-covered stent remains the treatment of choice for patients with acute gastric variceal bleeding who fail first-line medical and endoscopic therapy. • Balloon-occluded retrograde transvenous obliteration (BRTO): cardiofundal gastric varices usually have unique vascular anatomy, with spontaneous splenorenal or gastrorenal shunts that flow into the systemic circulation. BRTO is an advanced radiological pro-cedure that utilizes these shunts to access and obliterate gastric varices. With BRTO, venography is performed to identify gastric varices, gastrorenal shunts, and collateral veins; the veins draining gastric varices are subsequently embolized with microcoils and a sclerosant agent injected until all varices are obliterated. BRTO ap- pears to be highly efficacious in treating gastric varices however it is not a decompressive procedure and portal pressures may increase due to the diversion of blood flow into the portal circulation. Thus, while it is not associated with hepatic encephalopathy, it may in- crease the risk of developing oesophageal and ectopic varices. Ectopic varices Ectopic varices are defined as dilated portosystemic collateral veins occurring anywhere in the gastrointestinal tract other than the oesophagogastric region. They account for 2 to 5% of all variceal bleeds, but are the cause of bleeding in 20 to 30% of patients with extrahepatic portal hypertension. The most common sites for ec- topic varices include the duodenum, jejunum, ileum, colon, rectum, and enterostomy stoma. Bleeding from ectopic varices, while rare, can be massive and life-threatening. Ectopic varices should be considered in patients with portal hypertension who present with acute bleeding and have negative findings on upper endoscopy. Colonoscopy is the principal method for the diagnosis of colonic varices, although the diagnostic yield may be increased with endoscopic ultrasonography. Double-balloon enteroscopy or capsule endoscopy may be required to diagnose je- junal or ileal varices. Radiographic imaging is another common method of diagnosing ectopic varices. Management Bleeding ectopic varices are a difficult management problem and may require a multidisciplinary team of endoscopists, hepatologists, surgeons, and interventional radiologists. The diversity of their lo- cation, presentation, and complications increases the challenges of successful treatment and precludes development of standardized guidelines. The optimal therapeutic modality depends on a number of factors,

including the location of varices, the patient’s clinical condition, locally available expertise and facilities, and the cause of portal hypertension. Management incorporates urgent resuscitation, immediate workup to localize the site/source of bleeding, followed by application of a suitable treatment modality or transfer to a ter- tiary referral centre. As with other forms of variceal bleeding, vaso- active therapy and antibiotics are used, although there are no data specifically relating to ectopic variceal bleeding. Management options include the following: • Endoscopic therapy: EIS or EVO has the greatest body of evidence in the management of ectopic varices and is usually considered first-line therapy. Most ectopic varices are within the reach of a standard gastroscope or colonoscope, and injections using cyano- acrylate, thrombin, and other combination of sclerosants have successfully controlled bleeding from duodenal, jejunal, colonic, and rectal varices in case reports. • TIPS: TIPS has successfully been used to control bleeding ectopic varices, although there are multiple reports of ectopic varices rebleeding despite a reduction of the portosystemic pressure gra- dient to less than 12 mmHg and hence other treatment modal- ities such as embolization or endoscopic therapies may also be required. • Radiological embolization: a number of case reports have demon- strated successful haemostasis of ectopic varices with percutan- eous transhepatic obliteration, the goal of which is to occlude the feeding veins supplying the varix rather than occluding the varix itself. As embolization does not decompress the portal venous system, high rebleeding rates are noted with monotherapy, and thus combination therapy with TIPS is usually recommended. • Surgery: if endoscopic and/or interventional radiological proced- ures fail to control bleeding or are not feasible, surgery is a re- commended option if surgeons with appropriate expertise are available. Careful patient selection is important, based on an as- sessment of underlying liver function. FURTHER READING Al-Busafi SA, et al. (2012). Clinical manifestations of portal hyperten- sion. Int J Hepatol, 2012, 203794. Biecker E (2013). Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. World J Gastroenterol, 19, 5035–50. Bureau C, et al. (2004). Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a random- ized study. Gastroenterology, 126, 469–75. Cello JP (2005). Endoscopic treatment for bleeding esophageal varices. In: Sanyal AJ, Shah VH (eds) Clinical gastroenterology: portal hyper- tension, pp. 221–34. Humana Press, Totowa, NJ. Chavez-Tapia NC, et al. (2010). Antibiotic prophylaxis for cirrhotic pa- tients with upper gastrointestinal bleeding. Cochrane Database Syst Rev, 9, CD002907. Dai C, et al. (2015). Endoscopic variceal ligation compared with endo- scopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: a meta-analysis. World J Gastroenterol, 21, 2534–41. D’Amico M, Berzigotti A, Garcia-Pagan JC (2010). Refractory acute variceal bleeding: what to do next? Clin Liver Dis, 14, 297–305. Dechêne A, et al. (2012). Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stents. Digestion, 85, 185–91. De Franchis R (2015). Expanding consensus in portal hypertension: re- port of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol, 63, 743–52.

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