Variceal bleeding

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Approximately 90% of patients with cirrhosis will have developed gastro-oesophageal varices within 10 yr. Oesophageal variceal haemorrhage is a devastating complication of cirrhosis with mortality as high as 25–50%. Therefore, prophylactic measures before the first bleed are crucial. If patients survive a variceal bleed, there is approximately a 70% risk that they will have a further bleed within the following 2yr. Measures to minimize the risk of re-bleeding have been investigated and hospital mortality has decreased from 42% in 1980 to 14% in 2000. This review describes the factors involved in variceal haemorrhage, management of an acute bleed, and current opinions on appropriate prophylactic measures.

Pathophysiology

Portal hypertension

Portal hypertension develops as a consequence of increased intrahepatic vascular resistance and increased blood flow through the portal system. Hepatic stellate cells in the space of Disse (subendothelial space between the sinusoids and hepatocytes) are activated and produce collagen that replaces the normal matrix. Subendothelial fibrosis occurs and liver function deteriorates. Evidence now suggests that activated stellate cells are contractile and regulate sinusoidal blood flow. Contraction of activated stellate cells is promoted by their increased susceptibility to the vasoconstrictor endothelin and a reduction in the vasodilator nitric oxide within the liver. Therefore, intrahepatic resistance increases. In contrast to its intrahepatic levels, nitric oxide concentrations are elevated in the peripheral and splanchnic circulation. This results in decreased systemic and splanchnic vascular resistance, thus increasing portal blood flow. This is a major factor in both exacerbating and maintaining portal hypertension. As a result of these pathological changes, the porto-systemic gradient increases and venous collaterals develop in an attempt to decompress the portal system (Fig. 1). The collaterals predominantly occur at the gastro-oesophageal junction and the rectum.

The most common cause of portal hypertension is cirrhosis. Other causes include portal vein thrombosis and alcoholic hepatitis. Portal vein thrombosis may be due to pancreatitis, abdominal malignancy, trauma, and inherited prothrombotic conditions such as Factor V Leiden. Post-hepatic causes of portal hypertension include Budd–Chiari syndrome (hepatic vein occlusion) and constrictive pericarditis.

Predictors of variceal haemorrhage

Oesophageal varices develop when portal pressure exceeds 10 mm Hg, and rupture of varices requires portal pressures to be >12 mm Hg. Factors which predict variceal bleeding include red colour signs on varices (cherry red spots), size of the varix, infection, portal vein thrombosis, and a high wedged hepatic venous portal gradient (WHVPG). The WHVPG is the difference between the free and the wedged hepatic venous pressure, both of which are measured by catheterization of the hepatic vein under fluoroscopic guidance. Its normal value is <5.5 mm Hg. Other factors, which may increase the risk of variceal bleeding by increasing portal pressure, include increased portal blood flow after meals, increased intra-abdominal pressure, alcohol ingestion, and exercise.

Primary prophylaxis

Mortality from a variceal haemorrhage is high (25–50%). Prophylaxis against haemorrhage is crucial; therefore, patients with cirrhosis and varices should be prescribed a non-selective beta-adrenergic blocker (e.g. propranolol). This reduces both cardiac output and splanchnic arterial blood flow, thereby reducing portal pressure. Treatment aims to reduce the WHVPG to <12 mm Hg. The dose of beta-blocker is titrated to cause a 25% decrease in resting heart rate to a minimum rate of 55 beats min⁻¹. However, the use of beta-blockade can be problematic; 15% of patients experience side-effects and 15% have contraindications to their use. In a further 30%, portal pressure is not reduced to a level adequate to prevent bleeding.

Key points

Mortality from gastro-oesophageal variceal haemorrhage is high.
Primary prophylaxis with beta-blockers is crucial.
Band ligation is the endoscopic procedure of choice to treat an acute bleed.
Antibiotics during an acute episode reduce mortality.
Liver transplantation should be considered in all cases.

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Management of an acute variceal bleed

The management of an acute variceal bleed is summarized in Figure 2.

Resuscitation

In patients suspected of having a variceal haemorrhage, i.v. access should be established with two wide bore 16 G cannulae and a blood sample immediately obtained for full blood count, urea and electrolytes, liver function tests, and a coagulation profile. The patient should also be cross-matched for six units of blood. Volume replacement can initially be with either a crystalloid (e.g. isotonic saline) or a colloid. If the patient is haemodynamically stable with no evidence of ongoing bleeding, it is reasonable to wait for the haemoglobin result before instituting blood transfusion. However, in a patient with haemodynamic compromise with ongoing bleeding, transfusion should be instigated immediately. Evidence now suggests that the haemoglobin level should be maintained between 70 and 80 g litre\(^{-1}\) as over-transfusion increases portal pressure and is also detrimental to the clotting time.

Uncontrollable haemorrhage places the patient at high risk of airway compromise. Airway protection may be required to minimize the risk of aspiration and to improve tolerance of therapeutic measures such as a Sengstaken tube. Other causes of airway compromise include a depressed conscious level as a result of circulatory collapse or encephalopathy.

Pharmacotherapy

Vasoconstrictors

Vasopressin and somatostatin, and their analogues, are used to control acute variceal bleeding. Vasopressin, given as an infusion, decreases portal pressure. It also constricts the cardiac and mesenteric arterial supply; therefore, its use is often limited by side-effects. Terlipressin (synthetic analogue of vasopressin) has an improved side-effect profile and a longer half-life, thereby allowing administration as a bolus. Terlipressin reduces the hepatic venous pressure gradient, variceal pressure, and azygous blood flow. It has been shown to significantly reduce mortality and, when used as an adjunct to endoscopic therapy, improves haemostasis. Terlipressin 2 mg is given every 4 h for 48 h, reducing to 1 mg for days 3–5.

Somatostatin also reduces the hepatic venous pressure gradient, variceal pressure, and azygous blood flow. As with vasopressin, it needs to be given as an infusion due to its short half-life. Its analogue octreotide has a longer half-life but does not reduce variceal pressure.

Despite a number of randomized controlled trials, controversy still remains as to which of these agents is superior. In contrast to terlipressin, octreotide does not reduce mortality compared with placebo, although it may reduce the risk of failure to maintain haemostasis.

Antibiotics

Infection occurs in 35–66% of patients with cirrhosis and gastrointestinal bleeding. It is not fully understood why there is a high risk of infection; decreased complement levels, the performance of invasive procedures such as endoscopy, and increased intestinal bacterial translocation are postulated to be causative factors. In addition to the risk of sepsis, concurrent infection also impairs coagulation and is thought to contribute to elevated portal pressure, thereby increasing the risk of re-bleeding. Studies have now confirmed that antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding improves mortality and reduces the risk of further bleeding. Gram-negative bacteria have been most commonly isolated in these patients; therefore, antibiotics such as ciprofloxacin are appropriate.

Endoscopy

Endoscopy is performed in cases of variceal bleeding, primarily in an attempt to achieve haemostasis. Endoscopic findings are also
useful prognostic indicators of the risk of re-bleeding. The endoscopic techniques used achieve haemostasis by either interrupting the collateral blood flow by immediate occlusion, such as with band ligation or tissue glue, or by causing thrombosis with sclerotherapy.5

Sclerotherapy
Endoscopic sclerotherapy was the first endoscopic technique developed for the management of bleeding varices. Ethanolamine or sodium tetradecyl sulphate are used most commonly. The sclerosant is injected either into or around the site of the varix. Injection commences distally and progresses proximally. The amount injected depends on which sclerosant is used and also on the number and size of the varices. The sclerosant causes necrosis, fibrosis, and ultimately obliteration of the varices. Despite this, the incidence of re-bleeding is 30–40%. Sclerotherapy is also associated with a number of complications, including severe oesophagitis, oesophageal stricture formation, and oesophageal perforation.

Band ligation
This technique involves the strangulation of the varices by applying rubber bands. Band ligators (up to 12 bands) are attached to the end of the endoscope. Intubation is performed as with standard endoscopy and, once a varix is found, suction is applied and a band deployed. As banding acts more superficially than sclerotherapy, recurrence of varices is more common and repeated ligation is required. However, complications are less frequent and meta-analysis has confirmed that endoscopic band ligation is superior to sclerotherapy in achieving initial haemostasis and preventing recurrent bleeding. Banding-induced ulceration is a complication of this technique. For this reason, patients are often given omeprazole to reduce the risk of ulcer-related bleeding.

Glue
Gastric varices are present in approximately 20% of patients with portal hypertension. The risk of bleeding from gastric varices is lower than that from oesophageal varices, but when bleeding does occur, transfusion requirements and mortality are greater. A number of techniques have been used to treat bleeding gastric varices; currently, the most effective is injection of tissue glue. Cyanoacrylate glue is injected into the varices and has been found to achieve haemostasis in nearly 100% of cases. Re-bleeding rates have been documented to be as low as 2%. However, this technique requires technical expertise to avoid harming the patient, endoscopist, or equipment. Complications related to thrombosis have been reported, including coronary and pulmonary emboli and strokes.

Balloon tamponade
A Sengstenk Blakemore tube is effective in controlling variceal bleeding in approximately 90% of cases. It has two balloons and two aspiration ports (gastric and oesophageal) and can be passed orally or nasally. In the majority of cases, inflating the gastric balloon with approximately 200 ml of air and applying traction to the gastro-oesophageal junction will achieve haemostasis. If bleeding persists, the oesophageal balloon should also be inflated. The oesophageal balloon should be deflated and re-inflated every 12 h to prevent oesophageal necrosis. When the balloons are deflated, 50% of patients will re-bleed; therefore, balloon tamponade is used as a bridge to further intervention such as endoscopy or trans jugular intrahepatic porto-systemic shunt (TIPS), rather than as definitive treatment. Additionally, this form of treatment is associated with serious complications, including oesophageal ulceration, oesophageal perforation, and pulmonary aspiration. These complications are the reason why the oesophageal balloon is rarely inflated.

Transjugular intrahepatic porto-systemic shunt
TIPS involves the insertion of a stent to connect the hepatic and portal veins. The aim is to divert portal blood flow, thereby reducing portal pressure. It has been shown stop variceal bleeding in up to 90% of cases. The portal vein must be patent for the procedure to be possible; therefore, patients are initially assessed with an abdominal ultrasound scan. There is an increased risk of hepatic encephalopathy; other complications include occlusion of the shunt by thrombosis or stenosis.

Surgery
Surgical shunting involves end-to-side portocaval anastomosis or a distal splenorenal shunt. These procedures are associated with a low risk of variceal re-bleeding. However, as with TIPS, they are associated with a high risk of encephalopathy. The operative mortality increases with the severity of liver disease; patients with Child’s grade C cirrhosis have a very poor prognosis. Surgical shunting is now rarely performed as TIPS has become a more favourable option.

Complications of variceal bleeding
The complications of variceal bleeding are due to either the bleeding itself or the procedures used to control bleeding. Bleeding-related complications include vascular collapse and hypotension, encephalopathy, aspiration, and subacute bacterial peritonitis. Complications of the therapeutic procedures used to achieve haemostasis are described earlier. All of these complications may necessitate admission to the ICU. However, the most common reasons for ICU admission are hypotension, aspiration and airway protection, and encephalopathy.

Hepatic encephalopathy is a neuropsychiatric syndrome characterized by personality change and a depressed conscious level. It has a number of precipitants such as infection, dehydration, constipation, and gastrointestinal bleeding. The clinical spectrum of encephalopathy ranges from inappropriate behaviour and lethargy, to a comatose patient at risk of aspiration, requiring...
ICU admission and endotracheal intubation. Treatment involves the correction of precipitating factors, rehydration, antibiotics, and lactulose. Lactulose inhibits intestinal ammonia production and is commonly used at a dose of 20 ml three times daily.

**Prevention of recurrent variceal bleeding**

**Pharmacotherapy**

Patients who survive a variceal bleed should receive secondary prophylaxis as soon as possible after day 6 following the index bleed. Non-selective beta-blockers such as propranolol reduce the risk of re-bleeding by approximately 40%, and overall mortality by 20%. The dose is usually commenced at 40 mg twice daily and titrated, depending on tolerance, to achieve the parameters described in primary prophylaxis. It was previously reported that the addition of isosorbide mononitrate enhanced the effect of beta-blockers in reducing portal pressure, but this is not recommended in practice. Patients who have been on beta-blockers as primary prophylaxis, but who have a subsequent variceal bleed, should have endoscopy and band ligation performed.

**Endoscopy**

Variceal eradication by endoscopic procedures is also effective, with band ligation being the preferred method. Sclerotherapy may be performed when band ligation is not technically possible, although it is less effective in reducing the risk of re-bleeding. Endoscopic band ligation was initially performed as secondary prophylaxis when patients had bled, despite being on beta-blockers, or when beta-blockers were not tolerated or contraindicated. However, recent data suggest that combination therapy of band ligation and beta-blockers reduces the rate of variceal re-bleeding compared with either therapy alone.

**Transjugular intrahepatic porto-systemic shunt**

If secondary prophylaxis with beta-blockers or endoscopic band ligation (or both) does not prevent variceal bleeding, TIPS should be considered. It is effective in preventing re-bleeding, although it has not been found to improve survival. As previously mentioned, a high risk of hepatic encephalopathy is a serious complication of this procedure. Liver transplantation should be considered in all cases and TIPS can be used as a bridge to this.

**References**


Please see multiple choice questions 8–11