Management of oesophageal varices

Lucy Dagher, David Patch, Andrew Burroughs

Beta-blockers are the treatment of choice to prevent the first episode of variceal bleeding and further rebleeding episodes. In acute bleeding all patients should receive pharmacological treatment with vasoconstrictors and endoscopic treatment. Failure of therapy should lead to consideration of transjugular intrahepatic portosystemic shunting.

Cirrhosis can be the end stage of any chronic liver disease. At the time of diagnosis of cirrhosis varices are present in about 60% of decompensated and 30% of compensated patients. The risk factors for the first episode of variceal bleeding in cirrhotic patients are the severity of liver dysfunction, large size of varices and the presence of endoscopic red colour signs but only a third of patients with variceal haemorrhage have the above risk factors.

Recent interest has been directed at identifying haemodynamic factors that may reflect the pathophysiological changes, which lead to variceal bleeding, e.g. it has been confirmed that no bleeding occurs if hepatic venous pressure gradient (HVPG) falls below 12 mmHg and bacterial infection may be a trigger for bleeding. Pharmacological treatment with β-blockers is safe, effective and is the standard long-term treatment for the prevention of recurrence of variceal bleeding. Combination of β-blockers with isosorbide-5-mononitrate needs further testing in randomized controlled trials.

The use of haemodynamic targets for reduction in HVPG response needs further study, and surrogate markers of pressure response need evaluation. If endoscopic treatment is chosen, variceal ligation is the modality of choice. The combination of simultaneous variceal ligation and sclerotherapy does not offer any benefit. However, the use of additional sclerotherapy for the complete eradication of small varices after variceal ligation needs to be evaluated. The results of current prospective randomized controlled trials comparing variceal ligation with pharmacological treatment are awaited with great interest.

Finally the use of transjugular intrahepatic portosystemic shunt (TIPS) for the secondary prevention of variceal bleeding is not substantiated by current data, as survival is not improved and because of its worse cost–benefit profile compared to other treatments. In contrast there still is a place for the selective surgical shunts in the modern management of portal hypertension. The ideal patients should be well-compensated cirrhotics, who have had troublesome bleeding, unsuccessful medical or surgical treqatment or live far from suitable medical services. Recently ligation has been compared with β-blockers for primary prophylaxis, but β-blockers would appear to be the recommended treatment.

NATURAL HISTORY AND PROGNOSIS OF VARICEAL BLEEDING

At the time of diagnosis of cirrhosis, varices are present in about 60% of decompensated and 30% of compensated patients. The minimal portal pressure gradient or its equivalent HVPG threshold for the development of varices is 10–12mmHg. In most patients, oesophageal varices enlarge over time, although regression of varices in a minority of patients has also been observed. The presence and size of oesophageal varices is associated with the severity of liver disease and continued alcohol abuse.

PRIMARY PROPHYLAXIS

Risk of first variceal bleeding

The incidence of variceal bleeding in unselected patients who have never previously bled is low (4.4/100/year). Risk factors are severity of liver disease, larger size and endoscopic red signs on varices (De Franchis, 1988; Grace et al, 1998).

Dr Lucy Dagher is Clinical Research Fellow, **Dr David Patch** is Consultant Physician and Hepatologist and **Dr Andrew Burroughs** is Consultant Physician and Hepatologist, Royal Free Hospital NHS Trust, London NW3 2QG

Correspondence to: Dr A Burroughs

However, mortality of the first bleeding episode is high (25–50%). It is important to identify those patients with varices that might bleed in order to offer effective prophylactic therapy to the critical cases especially if the therapy is invasive or costly.

RANDOMIZED CONTROLLED TRIALS FOR PREVENTING FIRST VARICEAL BLEEDING

The optimal prophylactic treatment should be easy to administer, have relatively few side-effects and be reasonably effective. Drug therapy potentially fulfils these criteria best. In addition, drug therapy has the potential to protect against bleeding from portal hypertensive gastropathy, which accounts for a sizeable proportion of first bleeding episodes.

Sclerotherapy compared with non-active treatment

There are 20 trials involving 1756 patients. The principal feature of these trials is the statistically significant heterogeneity ($P<0.001$) in the direction and size of the treatment effect for bleeding and death, so that the meta-analysis is not possible. The larger trials did not confirm benefit and indeed some trials have suggested that prophylactic sclerotherapy is deleterious. Two of the larger studies had to be stopped because there was a significant survival advantage for patients randomized to the control group.

Beta-blockers compared with non-active treatment

There are nine prophylactic trials in 996 cirrhotic patients with large varices: seven with propranolol, two with nadolol. There is a statistically significant bleeding risk reduction with β-blockers. The number of patients that need to be treated to prevent one bleeding episode is estimated to be 11. Mortality rate is reduced with β-blockers but not significantly so (odds ratio (OR)=0.75; 95% confidence interval (CI)=0.57–1.06).

Beta-blockers have been shown to be effective independent of cause and severity of cirrhosis, presence of ascites and variceal size in an analysis of individual patient data from four of the above trials. Bleeding, however, may occur when β-blockers are stopped, suggesting that therapy should be maintained life-long.

There are currently no adequate data to recommend alternative medication other than non-selective β-blockers for primary prophylaxis of variceal bleeding (Goulis and Burroughs, 1999). The addition of isosorbide-5-mononitrate to β-blockade has been evaluated in a single study in which the combination with nadolol was more effective in reducing bleeding, with only a small increase in side-effects. However, in a study of direct comparison between propranolol and isosorbide-5-mononitrate for the prevention of variceal bleeding, nitrates were associated with a higher long-term mortality in older patients. Vasodilators on their own should not be used until further data are published on their safety.

Beta-blockers compared with banding

There are three trials, comprising 229 patients. The OR showed that there was no significant difference between the two treatments (OR=2.4; 95% CI=1.04–5.4). These studies have shown that prophylaxis with banding is safe, but there are doubts whether it is better than β-blockers, and it is more expensive.

Variceal ligation compared with non-active treatment

There are six studies comprising 612 patients with only high-risk oesophageal varices. Variceal ligation significantly reduced the risk of first variceal bleeding (OR=4.26; 95% CI=2.85–6.37) and mortality (OR=2.44; 95% CI=1.7–3.51); no serious complications resulted from variceal ligation. However, as β-blockers are effective these trials do not contribute to clinical practice.

Variceal ligation compared with sclerotherapy

The efficacy of endoscopic ligation compared with endoscopic sclerotherapy for the primary prevention of variceal bleeding was evaluated in three small studies. The results are conflicting and the data cannot be evaluated as there is significant heterogeneity for bleeding ($P=0.045$). There is no significant difference in mortality (OR=0.84; 95% CI=0.35–2.05).

CLINICAL GUIDELINES BASED ON RANDOMIZED STUDIES

The data from prophylactic trials suggest that screening for varices in cirrhotics should be part of routine clinical practice and, if these are found, prophylactic treatment to prevent first variceal bleeding should be given (Vlachogiannakos et al, 2000). Currently the data suggest only patients with a high-risk of bleeding should be treated, but there is a case to treat all patients with varices (De Franchis, 1988).

The treatment of choice is prophylactic β-blocker therapy: it is cheap, easy to administer and is effective in preventing the first variceal

haemorrhage and bleeding from gastric mucosa. Primary prophylaxis with variceal ligation appears to be safe and may be a reasonable alternative for:

- Patients with contraindications to β-blockers
- Patients who can not tolerate or have no haemodynamic response to the drug therapy.

These hypotheses need to be proven in controlled trials. However, variceal ligation is unlikely to be a routine prophylactic treatment as it is much more expensive and less available than β-blockers and it will not also prevent gastric mucosal bleeding.

ACUTE VARICEAL BLEEDING

Presentation and diagnosis

Acute variceal bleeding is a life-threatening complication in patients with cirrhosis and portal hypertension, with a mortality from 30% to 50%. Overall survival may be improving, because of new therapeutic approaches, but mortality is still related to failure to control haemorrhage or early rebleeding, which occurs in as many as 50% of patients in the first days to 6 weeks after admission.

Effective resuscitation, accurate diagnosis and early treatment can reduce the high mortality. The aims should be to stop bleeding as soon as possible and prevent early rebleeding. Thus any treatment regimen should be carefully evaluated not only in terms of immediate cessation of haemorrhage, but also in terms of providing a bleed-free interval of at least 5 days.

DRUG THERAPY IN ACUTE VARICEAL BLEEDING

The rationale for drug therapy is based on the factors that influence pressure in a column of fluid: resistance and flow. Ohm's law states that pressure=flow x resistance. Thus, it is possible to reduce portal and consequently variceal pressure by reducing the portal collateral blood flow (by splanchnic vasoconstriction), and by decreasing the vascular resistance of the intrahepatic and portal circulation (by means of vasodilators) or a combination of the two.

Vasopressin

Its significant systemic vasoconstrictor effects have resulted in only occasional use, particularly as there is a question about its efficacy. Of 417 episodes of variceal bleeding treated with vasopressin in 15 randomized controlled clinical trials, control of haemorrhage was only seen in 50%, and side-effects were observed in 45%, which necessitated cessation of therapy in 25% of cases (Goulis and Burroughs, 1999).

Only four trials compared the efficacy of vasopressin with a placebo, and two of these studies used an intra-arterial route of administration. There was a significant reduction in failure to control bleeding (OR=0.22; 95% CI=0.12–0.43), with no benefit in terms of mortality. Three randomized controlled trials including 176 patients have compared vasopressin alone with vasopressin plus nitroglycerin. The combination was more effective for control of bleeding (OR=0.38; 95% CI=0.21–0.72) but no difference in mortality was demonstrated (OR=0.94; 95% CI=0.49–1.79). Adverse effects were significantly reduced with the combination treatment.

Terlipressin (triglycyl lysine vasopressin)

This is a synthetic analogue of vasopressin with intrinsic vasoconstrictor activity. It is slowly cleaved into vasopressin in vivo by enzymatic cleavage of the triglycyl residue. It has the advantage over vasopressin of a longer biological half-life, allowing administration as a 4-hourly bolus, and in five unblinded trials, had a significantly lower complication rate when compared with vasopressin alone and vasopressin and nitroglycerine.

Terlipressin is the only vasoconstrictor that has been shown to reduce mortality in placebo-controlled trials of acute variceal bleeding (OR=0.38; 95% CI=0.22–0.69). As a result of these studies, it is the only drug licensed in Europe for the management of acute variceal bleeding. Grade C patients given terlipressin before arrival to hospital show increased survival (Levacher et al, 1995).

Somatostatin

Somatostatin is a 14-amino acid peptide which has a great variability in the degree of portal pressure response ranging from none to 10–20% reduction. Bolus injections of somatostatin appear to have greater haemodynamic effects as compared with continuous infusion, and may be the preferred method of administration. The standard dose for a bolus injection is 250 μg and 250 μg/h is given as a continuous infusion.

Three placebo-controlled studies had divergent conclusions, which caused statistically significant heterogeneity in the meta-analysis of the six studies which compare somatostatin with placebo or inactive treatment (P=0.004). There was a trend in favour of somatostatin but the result was not statistically significant by the Der Simonian and Laird method (OR=0.6; 95% CI=0.2–1.65). There was no difference in mor-

tality between the two treatment groups (OR=1.20; 95% CI=0.65–1.66).

Somatostatin was compared with vasopressin in seven studies with a total of 301 patients and two recent studies have compared somatostatin with terlipressin. Both studies showed that the three drugs were similarly effective in preventing failure to control variceal bleeding and death. There was no difference in mortality between the three vasoactive agents (OR=0.93; 95% CI=0.57–1.5). However, a statistically significant reduction in complications was observed in the group receiving somatostatin.

Somatostatin was also shown to have no statistical difference in either efficacy or mortality when compared with balloon tamponade in two trials. Three trials, with a total of 197 patients, have compared the efficacy of somatostatin with sclerotherapy in the control of variceal haemorrhage. Evaluation of the efficacy of treatment was performed at the end of drug administration. Meta-analysis showed that there was no statistical difference in failure to control bleeding (OR=1.55; 95% CI=0.76–3.18) or death (OR=1.51; 95% CI=0.8–2.87), and many trials showed sclerotherapy to be more effective and popular. However, complications were statistically less frequent in patients treated with somatostatin (OR=0.41; 95% CI=0.2–0.86). A multicentre Spanish study, published recently, has shown that continuous somatostatin infusion for 5 days after the initial control of bleeding was as effective as sclerotherapy in the prevention of early variceal rebleeding. There was no difference in mortality between the two treatment groups. The safety of the somatostatin treatment was also confirmed in this study, as the rate of complications was significantly lower in the somatostatin group.

Finally, a recent large randomized, placebo-controlled trial that involved 205 patients investigated whether the early administration of somatostatin in combination with sclerotherapy was more effective than sclerotherapy alone. Treatment failure was statistically less frequent in the somatostatin plus sclerotherapy group (P=0.004). Deaths during infusion were less in the somatostatin plus sclerotherapy group, but the result was not statistically significant. There was no difference in the incidence of complications between the two treatment groups.

The results of these studies show that somatostatin can be safely used as adjuvant therapy to sclerotherapy during the critical 5-day period followed variceal bleeding. If these results are confirmed in future trials, the early administration of somatostatin before emergency endoscopy may mark an important development in the management of variceal bleeding.

Octreotide

Octreotide is a synthetic octapeptide analogue of somatostatin that shares four amino acids with the native compound, which are responsible for its biological activity and longer half-life, but again very variable haemodynamic responses have been reported. The recommended dose is as a continuous infusion 25–50 μg/h.

The efficacy of octreotide treatment for acute variceal bleeding has not been adequately evaluated. Octreotide was found to be comparable with balloon tamponade and vasopressin in one study and with glypressin plus nitoglycerin in another. However, the sample sizes were small and the end points not very clear, and these results should be interpreted with caution.

Five clinical trials, including 419 patients, have recently compared the efficacy of octreotide continuous infusion with sclerotherapy in acute variceal bleeding. There was a significant heterogeneity in the evaluation of failure to control bleeding as the results of three studies were in favour of octreotide and two in favour of sclerotherapy. The OR, using the Der Simonian and Laird method, showed that there was a trend in favour of sclerotherapy, but the results were not statistically significant (OR=1.72; 95% CI=0.7–4.4). Mortality (OR=1.30; 95% CI=0.8–2) and incidence of complications (OR=0.76; 95% CI=0.3–2.1) were not significantly different between the two treatment modalities.

Recently several clinical trials have used octreotide in combination with sclerotherapy and compared this treatment with sclerotherapy alone. One placebo-controlled study published as a peer-reviewed article and two unblinded studies (published only in abstract form) have shown that control of variceal bleeding was significantly better in patients receiving combination treatment compared with those treated with sclerotherapy alone. However, mortality was not different between the treatment groups in any of these studies. Finally, two recent studies used octreotide (100 μg 8-hourly subcutaneously) or placebo to prevent early rebleeding after the control of the initial bleeding episode. Both studies found no difference in early rebleeding or mortality between the two treatment groups.

Antibiotic therapy

Bacterial infections have been documented in 35–66% of patients with cirrhosis who have variceal bleeding. In the cirrhotic patient admitted for gastrointestinal bleeding who had not received antibiotic therapy in the previous 7 days. Bernard et al (1995) showed in a multivariate analysis that bacterial infections were a prediction of early rebleeding ($P<0.02$). Patients with bacterial infections had a risk of rebleeding 6–7 times higher than the remaining patients and a high Child–Pugh score as a predictive of death ($P<0.001$).

Moreover these results were recently confirmed in our institution: multivariate analysis showed that proven bacterial infection ($P<0.0001$), antibiotics ($P<0.001$), active bleeding at endoscopy ($P<0.001$) and Child–Pugh score ($P<0.02$) were independent prognostic factors of failure to control bleeding (Goulis et al, 1998, 1999).

A recent meta-analysis has demonstrated that antibiotic prophylaxis significantly increased the mean survival rate (9.1% mean improvement rate; 95% CI=2.9–15.3; $P=0.004$) and also increased the mean percentage of patients free of infection (32% mean improvement rate; 95% CI=22–42; $P<0.001$) (Bernard et al, 1999). All cirrhotics with upper gastrointestinal bleeding should now receive prophylactic antibiotics whether sepsis is suspected or not. The optimal regimen is yet to be decided but oral or intravenous quinolones have been used. The data on antibiotics and infection mean that all new studies on acute variceal bleeding will need to include information on therapeutic use of antibiotic and diagnosis of infection.

Emergency sclerotherapy

The best evidence for the value of sclerotherapy in the management of acute variceal bleeding has come from a recently published study by the Veterans Affairs Cooperative Variceal Sclerotherapy Group (Hartigan et al, 1999). In this study sclerotherapy, compared with sham sclerotherapy, stopped haemorrhage from actively bleeding oesophageal varices and significantly increased patient survival.

Today, it is generally accepted that sclerotherapy should be performed immediately at diagnostic endoscopy as there is evidence that this is beneficial compared with delayed injection.

Data have been evaluated recently from 33 randomized clinical trials: sclerotherapy combined with drugs was more effective than drugs alone (OR=2.59; CI=1.59–4.2) but there was no difference in mortality (OR=1.33; CI=0.78–2.27). Sclerotherapy when compared with drugs alone was significantly better than drugs in preventing failure to control bleeding (OR=1.68; 95% CI=1.07–2.63) and death (OR=1.38; 95% CI=1.0–1.9) with no significant difference in complications (OR=0.7; 95% CI=0.41–1.2). Sclerotherapy plus drugs was more effective than sclerotherapy alone (OR=0.42; 95% CI=0.29–0.6) but there was no difference in mortality (OR=1.02; 95% CI=0.63–1.64). There was no difference in efficacy in studies comparing sclerotherapy with variceal ligation (OR=0.66; 95% CI=0.36–1.18). Thus future studies still need to evaluate the role of the drugs adjunctive to sclerotherapy. If this regimen is significantly effective there should be a reduction in mortality compared with sclerotherapy alone, which has not been shown to date.

CLINICAL GUIDELINES BASED ON RANDOMIZED STUDIES

Terlipressin is the most effective drug in the management of acute variceal bleeding, and mortality is reduced, albeit in small trials. However, in comparative trials somatostatin has a directly comparable efficacy with terlipressin, with less side-effects. Furthermore trials of somatostatin combined with sclerotherapy show that they are more effective than sclerotherapy alone and are safe given over 5 days. The therapeutic strategy of combined drug and sclerotherapy appears to have a sound basis, so that somatostatin combined with sclerotherapy is also a regimen of first choice. Prophylactic antibiotics must be used in all cirrhotics with upper gastrointestinal bleeding.

RANDOMIZED CONTROLLED TRIALS FOR PREVENTING VARICEAL REBLEEDING

All studies of secondary prevention show that active treatment is better than no treatment, because the risk of rebleeding is high (70–80% without therapy). Thus the issue is which treatment is better.

Sclerotherapy compared with drugs

Eleven trials, involving 971 patients, compared sclerotherapy with drugs (propranolol in 10 and nadolol plus isosorbide mononitrate in 1) for the prevention of recurrent bleeding. The OR showed that there was no significant difference between the two treatment modalities (OR=0.88; 95% CI=0.58–1.32). More patients who were randomized to sclerotherapy survived but the result was not statistically significant (OR=0.95; 95% CI=0.58–1.32). Moreover, the number of

patients free of adverse events was significantly higher in the drug group compared with sclerotherapy group (OR=0.85; 95% CI=0.65–1.11). This means that if there are no contraindications, β-blockers are a first choice treatment for the prevention of variceal bleeding as they also prevent bleeding from portal hypertensive gastropathy. There are only two studies in abstract form comparing β-blockers with banding, both of which show equivalence.

Sclerotherapy plus drugs compared with sclerotherapy

There are 12 trials of sclerotherapy and drugs (propranolol in 8, nadolol in 3 and isosorbide-5-mononitrate in 1) *vs* sclerotherapy alone, comprising 853 patients. Theoretically, the drugs should prevent rebleeding before variceal obliteration. OR showed that there was significantly less rebleeding in the combined treatment arm (Der Simonian and Laird method: OR=0.54; 95% CI=0.34–0.86). However, there is significant heterogeneity in both direction and magnitude of treatment effect and the data are difficult to interpret. There was no statistically significant heterogeneity in the evaluation of survival which favoured the combined treatment arm (OR=0.65; 95% CI=0.43–0.97).

Sclerotherapy *vs* banding

There are 18 studies (n=1509 patients) comparing sclerotherapy with variceal ligation for the prevention of recurrent bleeding. Rebleeding is significantly less after ligation compared with sclerotherapy (OR=0.54; 95% CI=0.43–0.68). The number of patients needing treatment with variceal ligation rather than with sclerotherapy to prevent one rebleeding episode is 10 (95% CI=7–17). Variceal ligation was also associated with lower mortality when compared with sclerotherapy, but the result did not reach statistical significance (OR=0.78; 95% CI=0.59–1.02) (P=0.07).

Complications (in all studies except one) were also less common in patients treated with variceal ligation (OR=0.3; 95% CI=0.19–0.46). In addition, the number of treatment sessions needed to achieve variceal obliteration was less with ligation in all the studies (2.7–4.1 sessions with variceal ligation compared with 4–6.5 sessions with sclerotherapy). However, there was no difference between the endoscopic modalities in the number of patients with varices obliterated (OR=1.19; 95% CI=0.89–1.59), while the recurrence of varices was significantly more frequent in patients treated with variceal ligation (OR=1.48; 95% CI=1.03–2.12). However, rebleeding after initial eradication seems unusual especially if patients are in a regular endoscopic follow-up and varices which recur are re-obliterated.

Transjugular intrahepatic portosystemic shunt

Eleven randomized trials *vs* endoscopic therapy involving 811 patients have been analysed (Papatheodoridis et al, 1999). The median follow-up ranged from 10 to 32 months. Variceal bleeding was significantly more frequent in the patients treated with endoscopic treatment (47%) than with TIPS (19%) (OR=3.8; 95% CI=2.8–5.2) ($P < 0.001$), but there was no difference in mortality (OR=0.97; 95% CI=0.71–1.34). Post-treatment encephalopathy occurred significantly less often after endoscopic treatment (19%) than after TIPS, despite its occlusion (34%) (OR=0.43; 95% CI=0.3–0.6) (P<0.001). Thus TIPS has the same results as surgical shunting, in which very similar results were obtained in sclerotherapy *vs* distal splenorenal shunt studies, and can not be recommended as the first choice treatment for prevention of variceal bleeding, but should be reserved only for patients in whom secondary preventive treatment fails.

NEW MANAGEMENT SCHEMES

With drug therapy there is evidence that a target reduction in portal pressure (HVPG) of 12 mm Hg or less results in no bleeding. If HVPG is reduced to 20% from baseline, rebleeding is approximately 15% or less (Feu et al, 1995). However, timing of remeasurements needs further confirmation, as many patients rebleed very early and it is unclear whether these results are seen in practice. Combined drug therapy of β-blocker and isosorbide mononitrate may be better (Villanueva et al, 1996). The trials of combined banding and drug therapy, which may also reduce rebleeding, need to be evaluated.

Injection of adhesives may be more effective than banding, but randomized studies are needed, as well as studies of adhesive injection when other endoscopic techniques fail.

CLINICAL GUIDELINES FROM RESULTS OF RANDOMIZED STUDIES

The treatment of first choice is β-blockers and if there are contraindications or intolerance banding should be used. Failure of either therapy should lead to consideration of TIPS or if this is not available surgical shunting in well-compensated patients. The regular measurement of por-

tal pressure to assess degree of reduction requires further study to prove the link between target reduction and rebleeding. The use of adhesives by injection needs to be assessed in randomized studies. HM

Conflict of interest: none.

Bernard B, Cadranel J-F, Valla D et al (1995) Prognostic significance of bacterial infections in bleeding cirrhotic patients: a prospective study. *Gastroenterology* **108:** 1824–34

Bernard B, Nguyen KE, Nguyen KE, Opolon P, Poynard T (1999) Antibiotic prophylaxis (AbP) for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding (GB): a meta-analysis. *Hepatology* **29:** 1655–61

De Franchis R (1988) Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices- a prospective multicenter study. *N Engl J Med* **319:** 983–9

Feu F, Garcia–Pagan JC, Bosch J et al (1995) Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal hemorrhage in patients with cirrhosis. *Lancet* **346:** 1056–9

Goulis J, Burroughs AK (1999) Portal Hypertensive bleeding: prevention and treatment. In: McDonald JWD, Burroughs AK, Fegan BG, eds. *Evidence Based Gastroenterology and Hepatology*. BMJ Publishing Group, London: 389–426

Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burrough AK (1998) Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* **27**(5): 1207–12

Goulis J, Patch D, Burroughs AK (1999) Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* **353**: 139–42

Grace ND, Groszmann RJ, Garcia-Tsao G et al (1998) Portal hypertension and variceal bleeding: an AASLD single topic symposium. *Hepatology* **28**(3): 868–80

Hartigan PM, Gebhard RL, Gregory PBF (1999) For the veterans cooperative variceal sclerotherapy group, Sclerotherapy for actively bleeding esophageal varices in male alcoholics with cirrhosis. *Gastrointestinal Endosc* **46:** 1–7

Levacher S, Letoumelin O, Pateron D, Blaise M, Lapandry C, Pourriat JL (1995) Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* **346:** 865–8

Papatheodoridis GV, Goulis J, Leandro G, Patch D, Burroughs AK (1999) Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: a meta-analysis. *Hepatology* **30:** 612–22

Villanueva C, Balanzo J, Novella MT et al (1996) Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* **334:** 1624–9

Vlachogiannakos J, Goulis J, Patch D, Burroughs AK (2000) Review article: primary prophylaxis for portal hypertensive bleeding in cirrhosis. *Aliment Pharmacol Ther* **14(7):** 851–60

KEY POINTS

- Beta-blockers are the treatment of choice for prevention of first variceal bleeding.
- If there is a high risk of bleeding present and the patient is intolerant to β-blockers or isosorbide mononitrate, variceal banding might be considered.
- Pharmacological treatment with Terlipressin should be started immediately when variceal bleeding is suspected, endoscopic treatment should be performed at diagnostic endoscopy.
- Patients surviving a bleeding episode should be treated with non-selective β-blockers. Those intolerant or with contraindications to β-blockers should be treated with endoscopic therapy (variceal banding) until complete eradication of varices.
- Recurrent or uncontrolled bleeding should be considered for 'rescue therapy' with transjugular intrahepatic portosystemic shunt or shunt surgery and referral to a liver transplant centre for further evaluation.