

# UK guidelines on the management of variceal haemorrhage in cirrhotic patients

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## 1.0 Introduction

These guidelines on the management of variceal haemorrhage were commissioned by the British Society of Gastroenterology under the auspices of the Liver Section. They were written in June 1998 and have been corrected and agreed upon by the members of the Liver Section. The nature of variceal haemorrhage in cirrhotic patients with its complex range of complications makes rigid guidelines inappropriate.

Over the past few years there have been numerous advances in the management of variceal haemorrhage in patients with cirrhosis. These have included better endoscopic techniques with the widespread availability of video endoscopy, establishment of variceal band ligation, availability of newer drugs such as somatostatin and vasopressin analogues, better surgical techniques, and finally the availability of transjugular intrahepatic portosystemic stent shunt (TIPSS).

These guidelines deal specifically with the management of varices in patients with cirrhosis and are not designed to address: (1) the management of the underlying liver disease; (2) the management of variceal haemorrhage in children; or (3) variceal haemorrhage from other aetiological conditions.

## 2.0 Validity and grading of recommendations

These guidelines have been produced to conform to the system proposed by the North of England evidence based guidelines development project.<sup>1 2</sup>

## 2.1 CATEGORIES OF EVIDENCE

These are graded as follows:

- Grade Ia: evidence obtained from meta-analysis of randomised trials.
- Grade Ib: evidence obtained from at least one randomised trial.
- Grade IIa: evidence obtained from at least one well designed controlled study without randomisation.
- Grade IIb: evidence obtained from at least one other type of well designed quasi experimental study.
- Grade III: evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case studies.
- Grade IV: evidence obtained from expert committee reports, or opinions or clinical experiences of respected authorities.

The evidence category is indicated after the citations in the reference section.

## 2.2 GRADING OF RECOMMENDATIONS

The strength of each recommendation is dependent upon the category of the evidence supporting it, and is graded according to the system shown in table 1.

## 3.0 Definitions

It is important to define the terms that should be used in the context of a variceal bleed. These are the consensus definitions.<sup>3</sup>

### 3.1 VARICEAL HAEMORRHAGE

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 recognisable cause of bleeding. An episode of bleeding is clinically significant when there is a transfusion requirement of 2 units of blood or more within 24 hours of the time zero, together with a systolic blood pressure of less than 100 mm Hg or a postural change of greater than 20 mm Hg and/or pulse rate greater than 100 beat/min at time zero (time zero is the time of admission to the first hospital the patient is taken to).

### 3.2 TIME FRAME OF ACUTE BLEEDING

The acute bleeding episode is represented by an interval of 48 hours from time zero with no evidence of clinically significant bleeding

**Abbreviations used in this paper:** TIPSS, transjugular intrahepatic portosystemic stent shunt; HVP, hepatic venous pressure gradient; PCS, portacaval shunts; GOV, gastro-oesophageal varices; IG, isolated gastric varices; B-RTO, balloon occluded retrograde transvenous obliteration.

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Table 1 Strength of recommendations

	A (the group feels this element of care should be strongly recommended)	B (a recommendation rated moderately important by the group)	C (rated as relatively unimportant by the group, although may be considered in some cases)
I (well designed RCTs, meta-analyses, or systematic reviews)	AI (strong recommendation based on strong evidence)	BI (strong evidence but has impact on quality of care)	CI (recommendations in this category are unlikely)
II (well designed cohort or case controlled studies)	AII (moderate evidence, but the group feels the issue is very important)	BII (moderate evidence, but moderately important)	CII (moderate evidence, but the group feels the issue is not particularly important)
III (uncontrolled studies)	AIII (a rare grading, with no good experimental evidence, but the group feel it is very important, for example, splenectomy recommended for ruptured spleen)	BIII (limited level of evidence, but the group feels moderately strongly)	CIII (limited level of evidence, but might be considered in some cases)

between 24 and 48 hours. Evidence of any bleeding after 48 hours is the first rebleeding episode.

### 3.3 VARICEAL REBLEEDING

Variceal rebleeding is defined as the occurrence of new haematemesis or melena after a period of 24 hours or more from the 24 hour point of stable vital signs and haematocrit/haemoglobin following an episode of acute bleeding. All bleeding episodes regardless of severity should be counted in evaluating rebleeding.

### 3.4 FAILURE TO CONTROL ACTIVE BLEEDING

The definition of failure to control active bleeding is divided into two time frames:

#### (i) Failure to control bleeding acute bleeding within six hours:

- Transfusion requirement of 4 units or more and inability to achieve an increase in systolic blood pressure by 20 mm Hg or to 70 mm Hg or more, and/or inability to achieve a pulse rate reduction to less than 100 beat/min or a reduction of 20 beat/min from baseline pulse rate.

#### (ii) Failure to control bleeding after six hours: any of the following factors

- Occurrence of haematemesis from the six hour point.
- Reduction in blood pressure of more than 20 mm Hg from the six hour point and/or increase in pulse rate of more than 20 beat/min from the six hour point on two consecutive readings an hour apart, transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the haematocrit to above 27%, or haemoglobin to above 9 g/l.

### 3.5 EARLY MORTALITY

Death within six weeks of the initial episode of bleeding.

## 4.0 Natural history of varices in cirrhosis

### 4.1 DEVELOPMENT OF VARICES

The rise in portal pressure is associated with the development of collateral circulation which allows the portal blood to be diverted into the systemic circulation. These spontaneous shunts occur: (a) at the cardia through the intrinsic and extrinsic gastro-oesophageal veins; (b) in the anal canal where the superior haemorrhoidal vein belonging to the portal system anastomoses with the middle and inferior haemorrhoidal veins which belong to the caval system; (c) in the falciform ligament of the liver through the para-umbilical veins which are the remains of the umbilical circulation of the fetus; (d) in the abdominal wall and the retroperitoneal tissues, from the liver to the diaphragm, veins in the lienorenal ligament, in the omentum and lumbar veins; and (e) blood diversion from the diaphragm, gastric, pancreatic, splenic, and adrenal which may drain into the left renal vein.

Numerous lines of evidence suggest that varices develop and enlarge with time. Christensen and colleagues<sup>4</sup> followed a cohort of 532

patients with cirrhosis and showed that the cumulative incidence of patients with varices increased from 12% to 90% over 12 years. In a study involving 80 patients followed for 16 months, Cales and Pascal<sup>5</sup> showed that 20% of patients who did not have varices developed new varices and 42% of patients with small varices showed definite enlargement. Czaja and colleagues<sup>6</sup> also showed that the prevalence of varices increased from 8% to 13% over five years in a cohort of patients with chronic active hepatitis even though they were treated with prednisolone.

The two factors that appear to determine the development of varices are continued hepatic injury and the degree of portosystemic shunting. Evidence for the former is derived from studies in which varices were shown to regress with time. Baker and colleagues<sup>7</sup> followed a cohort of 112 patients with oesophageal varices and showed that varices had disappeared in nine patients, regressed in seven, and remained unchanged in six. They concluded that the disappearance and regression of varices may be related to abstinence from alcohol. This observation was confirmed in a study by Dagradi and colleagues<sup>8</sup> who followed a cohort of patients with alcoholic cirrhosis over three years and showed a reduction in variceal size in 12 of the 15 patients with alcoholic cirrhosis who stopped drinking and an enlargement in variceal size in 17 patients who continued to drink. On the other hand, Cales and Pascal<sup>5</sup> showed that regression of varices occurred in 16% of patients with alcoholic cirrhosis who continued to imbibe alcohol. This may be related to the development of large portosystemic collaterals which decompress the portal system.

### 4.2 RISK FACTORS FOR FIRST VARICEAL BLEEDING

The factors that predispose to and precipitate variceal haemorrhage are still not clear. The suggestion that oesophagitis may precipitate variceal haemorrhage has been discarded.<sup>9</sup> Presently, the most important factors that have been held responsible include: (i) pressure within the varix, (ii) variceal size, (iii) tension on the variceal wall, and (iv) severity of the liver disease.

#### 4.2.1 Portal pressure

In most cases, portal pressure reflects intra-variceal pressure<sup>10</sup> and a hepatic venous pressure gradient greater than 12 mm Hg is necessary for the development of and bleeding from oesophageal varices but there is no linear relationship between the severity of portal hypertension and the risk of variceal haemorrhage.<sup>11 12</sup> However, the hepatic venous pressure gradient (HVPG) tends to be higher in bleeders as well as in patients with larger varices. In a prospective study comparing propranolol with placebo for the prevention of first variceal haemorrhage, Groszmann and colleagues<sup>13</sup> showed that bleeding from varices did not occur if the portal pressure gradient could be reduced to less than 12 mm Hg. This pressure has since been accepted as the aim of pharmacological therapy of portal hypertension.

#### 4.2.2 Variceal size

This is best assessed endoscopically. Variable results in the literature are because of the lack of a definition regarding the distinction between large and small varices. Numerous studies<sup>11–14</sup> have shown that the risk of variceal haemorrhage increases with the size of varices.<sup>15</sup>

#### 4.2.3 Variceal wall and tension

Polio and Groszmann<sup>16</sup> using an *in vitro* model showed that rupture of varices was related to the tension on the variceal wall. The tension depends on the radius of the varix. In this model, increasing the size of the varix and decreasing the thickness of the variceal wall caused variceal rupture.

Endoscopic features such as “red spots” and “wale” markings were first described by Dagradi.<sup>8</sup> They have been described as being important in the prediction of variceal haemorrhage. These features represent changes in variceal wall structure and tension associated with the development of microtelangiectasias. In a retrospective study by the Japanese Research Society for Portal Hypertension, Beppu and colleagues<sup>17</sup> showed that 80% of patients who had blue varices or cherry red spots bled from varices, suggesting that this was an important predictor of variceal haemorrhage in cirrhosis.

#### 4.2.4 Severity of liver disease and bleeding indices

Two independent groups prospectively assessed factors predicting first variceal haemorrhage in cirrhosis prospectively. The North Italian Endoscopic Club (NIEC)<sup>18</sup> reported their findings in 1988, followed in 1990 by data from the Japanese.<sup>19</sup> Both of these studies showed that the risk of bleeding was based on three factors: severity of liver disease as measured by Child class, variceal size, and red wale markings. The NIEC study showed a wide range for the risk of bleeding of 6–76% depending on the presence or absence of the different factors. This index was prospectively validated in a study by Prada and colleagues.<sup>20</sup> Using the same variables the NIEC index was simplified by De Franchis and colleagues<sup>21</sup> and shown to correlate with the original index. Further studies showed that the HVPG and intravariceal pressure were also independent predictors of first variceal haemorrhage when analysed in conjunction with the NIEC index.<sup>22–23</sup>

In summary, the two most important factors that determine the risk of variceal haemorrhage are the severity of liver disease and the size of varices. Measurement of HVPG is a useful guide for selection of patients for treatment and their response to therapy.

#### 4.3 RISK OF FIRST VARICEAL BLEED

Data describing the overall risk of bleeding from varices must be viewed with caution and have some pitfalls in interpretation. The natural history of patients who have varices that are diagnosed as part of their work up is different from patients who have complications of liver disease. Patients in trials may represent a

different population to patients who have had documented varices and not bled during follow up. Most studies do not comment on either the severity of liver disease or whether patients with alcoholic cirrhosis are continuing to drink. Both these factors have a significant effect on the risk of variceal haemorrhage.

Most studies report bleeding from varices in about 20–50% of patients with cirrhosis during the period of follow up. Baker and colleagues<sup>7</sup> reported variceal bleeding in 33 of 115 patients that they followed for a mean of 3.3 years, with a mortality of 48% from first variceal haemorrhage. These data were confirmed by Christensen and colleagues.<sup>4</sup> About 70% of episodes of bleeding occur within two years of diagnosis.

Analysis of the non-active treatment arms in the primary prophylaxis trials comparing propranolol with placebo show results similar to those of the primary prophylaxis shunt trials, with most of the episodes of bleeding occurring within the first two years of follow up. In these studies the rate of first variceal haemorrhage ranged from 22% to 61%.<sup>24–28</sup> This large difference in the rate of first bleed relates almost certainly to the number of patients with severe liver disease included in the study (Pascal, Child C—46%, bleeding—61%; IMPP, Child C—6%, bleeding—32%; Conn, Child C—6%, bleeding—22%). Mortality varied from 24% to 49% over two years (Pascal, mortality—49%; IMPP, mortality—24%; Conn, mortality—24%).

#### 4.4 PROGNOSIS OF ACUTE VARICEAL HAEMORRHAGE

The average mortality of the first episode of variceal bleeding in most studies is 50%. As discussed, this mortality from variceal haemorrhage is related closely to the severity of liver disease.<sup>29–33</sup> Over a mean follow up of one year, the average mortality from subsequent variceal haemorrhage is 5% in Child class A patients, 25% in Child class B patients, and 50% in Child class C patients. Although serum creatinine has been shown in some studies to predict overall survival,<sup>34–35</sup> Child class is superior to any other predictive factor in determining mortality within six weeks or 30 days of the initial haemorrhage (see box 1).

Vinel and colleagues<sup>14</sup> showed that HVPG was predictive of survival when this was measured at two weeks after the acute bleed. However, it is unclear if this was independent of the severity of liver disease. Whether active bleeding at the time of endoscopy predicts mortality is not clear. Although Cardin and colleagues<sup>36</sup> found that this was an important factor, Balanzo and colleagues<sup>37</sup> could not confirm this finding. Active bleeding at the time of endoscopy does however predict early rebleeding.<sup>38</sup> Risk of death decreases quickly after admission such that the risk of death becomes virtually constant about six weeks after bleeding.<sup>39–40</sup>

#### 4.5 PRIMARY PROPHYLAXIS

Since 30–50% of patients with portal hypertension will bleed from varices and about 50% will die from the effects of the first bleed, it

### Box 1—Recommendations

#### SEVERITY OF CIRRHOSIS

Severity of cirrhosis is best described using the Child-Pugh score.<sup>41</sup> This form of scoring is the sum of severity scores for the variables shown in table 2.

Table 2 Severity scores used for calculating the Child-Pugh score

Category	1	2	3
Encephalopathy	0	I/II	III/IV
Ascites	Absent	Mild-moderate	Severe
Bilirubin ( $\mu\text{mol/l}$ )	<34	34–51	>51
Albumin (g/l)	>35	28–35	<28
INR	<1.3	1.3–1.5	>1.5

Child-Pugh class A represents a score of 6 or less, class B a score of 7–9, and class C, 10 or greater.

Patients in class A are least likely to die from the effects of a variceal bleed whereas patients with Child class C disease are most likely to die. (Strength of recommendation grade AI.)

#### GRADING OF VARICES

Although numerous methods have been described for grading varices, the simplest method is to divide them into three grades:

Grade 1: varices that collapse to inflation of the oesophagus with air.

Grade 2: varices between grades 1 and 3.

Grade 3: varices which are large enough to occlude the lumen. (Strength of recommendation grade CII.)

seems rational to develop prophylactic regimens to prevent the development of, and bleeding from, these varices. However, most of the published trials do not have sufficient power to identify favourable treatment effects. Based on the expected bleeding and death rates in the control group, the minimum number of patients needed to detect a 50% reduction in bleeding would be 270 patients, and 850 patients in each arm to detect the same reduction in mortality. A proposed algorithm for surveillance and prophylaxis of varices is shown in fig 1.

#### 4.5.1 Surgery

*Portacaval shunts.* There are four trials in the literature which have randomised a total of 302 patients<sup>42–44</sup> either to prophylactic shunt surgery or to non-active treatment. A meta-analysis of these studies showed a significant

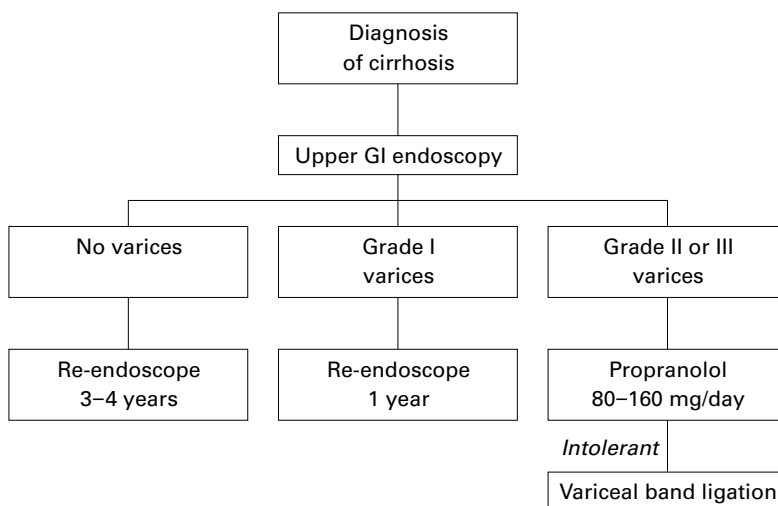


Figure 1 Proposed algorithm for surveillance for varices and primary prophylaxis.

benefit in the reduction of variceal bleeding (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.17–0.56) but also a significantly greater risk of hepatic encephalopathy (OR 2, 95% CI 1.2–3.1) and of mortality (OR 1.6, 95% CI 1.02–2.57) in patients treated with shunt surgery.<sup>45</sup>

*Devascularisation procedures.* Inokuchi and colleagues<sup>19</sup> showed that there was a significant reduction in variceal bleeding and in mortality in patients treated with a variety of devascularisation procedures. There are, however, numerous problems with the interpretation of this study because of the use of different procedures in each of the 22 centres. These results require confirmation.

#### 4.5.2 Pharmacological therapy

*Propranolol.* The mainstay of the pharmacological approach to the primary prophylaxis of variceal haemorrhage has been propranolol, which has been shown to reduce the portal pressure gradient, reduce azygos blood flow, and also variceal pressure. It achieves this by causing splanchnic vasoconstriction and reducing cardiac output.

There are nine randomised trials assessing its effectiveness: seven are published papers and two are in abstract form.<sup>24–28 46–49</sup> The risk of variceal bleeding was lower in seven studies,<sup>24–28 46 48</sup> significantly lower in four studies,<sup>25 27 28 46</sup> and unchanged in one study.<sup>47</sup> There was a higher incidence of bleeding in the propranolol group in one study. This was a small study and unbalanced randomisation is likely because of a very low bleeding rate in the control group.<sup>49</sup> Mortality was reduced in seven trials,<sup>24 25 27 28 46–48</sup> significantly in one,<sup>24</sup> and unchanged in two.<sup>26 27</sup> A meta-analysis showed that the risk of rebleeding was significantly lower (OR 0.54, 95% CI 0.39–0.74) but only borderline significance was detected for differences in mortality (OR 0.75, 95% CI 0.57–1.06).<sup>50</sup>

*Isosorbide mononitrate.* Interest in the use of vasodilators such as isosorbide mononitrate has grown since the demonstration that it reduces portal pressure as effectively<sup>51</sup> as propranolol. A trial comparing isosorbide mononitrate with propranolol showed no significant difference between these agents.<sup>52</sup>

*$\beta$  Blocker and isosorbide mononitrate.* The combination of nadolol and isosorbide mononitrate has been compared with nadolol in a randomised controlled trial. The combination therapy reduced the frequency of bleeding significantly but no significant differences were detected in mortality.<sup>53</sup>

#### 4.5.3 Endoscopic therapy

*Sclerotherapy.* There are 19 trials comparing endoscopic variceal sclerotherapy with no treatment, of which four are in abstract form.<sup>21 46–48 54–68</sup> These trials include 1630 patients and the studies are significantly heterogeneous. Ten of the trials included only patients with large varices; the other nine include patients with varices of any size. Various sclerosants were used at different doses and injected intra or paravariceally. The results

**Box 2—Recommendations: primary prophylaxis of variceal bleeding in cirrhosis**

## WHAT IS THE BEST METHOD FOR PRIMARY PROPHYLAXIS?

- Pharmacological therapy with *propranolol* is the best available modality at present. (Recommendation grade AI.)
- *Aim of therapy with propranolol*: Reduction in hepatic venous pressure gradient to less than 12 mm Hg. (Recommendation grade AI.)
- *Dose*: Starting dose 40 mg twice daily, increasing to 80 mg twice daily if necessary. Long acting propranolol at either 80 or 160 mg can be used to improve compliance. (Recommendation grade AI.)
- In case of contraindications or intolerance to propranolol, variceal band ligation is the treatment of choice. (Recommendation grade AI.)
- In difficult situations where neither propranolol nor variceal band ligation can be used, isosorbide mononitrate is the treatment of first choice (20 mg twice daily). (Recommendation grade BI.)

## WHO SHOULD HAVE SURVEILLANCE FOR VARICEAL BLEEDING

- All patients with cirrhosis should be endoscoped at the time of diagnosis. (Recommendation grade CI.)

## HOW OFTEN SHOULD CIRRHOTIC PATIENTS BE ENDOSCOPED?

- If at the time of first endoscopy no varices are observed, patients with cirrhosis should be endoscoped at three year intervals. (Recommendation grade AII.)
- If small varices are diagnosed, patients should be endoscoped at yearly intervals. (Recommendation grade AII.)

## WHICH PATIENTS WITH CIRRHOSIS SHOULD HAVE PRIMARY PROPHYLAXIS

- If grade 3 varices are diagnosed, patients should have primary prophylaxis irrespective of the severity of the liver disease. (Recommendation grade AI.)
- If patients have grade 2 varices and Child class B or C disease, they should have primary prophylaxis. (Recommendation grade BI.)

of these trials are variable with two studies showing a significant reduction in both bleeding and mortality,<sup>54 55</sup> one study showing a reduction in mortality but no difference in rebleeding,<sup>62</sup> one study showing a significant increase in the risk of bleeding,<sup>59</sup> and another significantly greater mortality.<sup>65</sup> Due to the marked heterogeneity between these studies a meta-analysis is clinically inappropriate. At the present time sclerotherapy cannot be recommended for prophylaxis of variceal haemorrhage in patients with cirrhosis.

*Variceal band ligation.* Sarin and colleagues<sup>69</sup> compared variceal band ligation with no active treatment in a randomised study and showed that there was a significant reduction in variceal bleeding in patients treated with band ligation. No significant effect on mortality was found. This observation has been confirmed in a recent study involving about 120 patients.<sup>70</sup> Variceal band ligation has been compared with propranolol in a randomised controlled trial and shown to reduce the frequency of first bleed significantly without affecting mortality.<sup>71</sup>

Recommendations for the primary prophylaxis of variceal bleeding in cirrhosis are given in box 2.

**5.0 Management of active variceal haemorrhage**

The most important step in the management of acute variceal haemorrhage is the initial resuscitation and protection of the airway to prevent aspiration. Early endoscopy allows examination of the upper gastrointestinal tract enabling accurate diagnosis of the bleeding site and

decision regarding management (fig 2). The following measures of controlling the bleeding are presently available.

**5.1 PHARMACOLOGICAL THERAPY**

The two major classes of drugs that have been used in the control of acute variceal bleeding are vasopressin or its analogues (either alone or in combination with nitroglycerine) and somatostatin or its analogues.

**5.1.1 Vasopressin**

Vasopressin reduces portal blood flow, portal systemic collateral blood flow, and variceal pressure. It does however have significant systemic side effects such as an increase in peripheral resistance, and reduction in cardiac output, heart rate, and coronary blood flow. In comparison with no active treatment, the pooled results of four randomised trials<sup>72-75</sup> showed that it reduced failure to control variceal bleeding although mortality was unaffected. Trials comparing sclerotherapy with vasopressin<sup>76-79</sup> have shown no significant effect on reduction in the failure to control the variceal bleed, except in one study<sup>78</sup> where rebleeding was significantly lower in patients treated with sclerotherapy.

**5.1.2 Vasopressin with nitroglycerine**

The addition of nitroglycerine enhances its effects on portal pressure and reduces cardiovascular side effects.<sup>80</sup> Three randomised trials compared vasopressin alone with vasopressin and nitroglycerine<sup>81-83</sup> and the pooled data from these showed that the combination was associated with a significant reduction in failure to control bleeding although no survival benefit was demonstrated.

**5.1.3 Glypressin with or without nitroglycerine**

Glypressin is a synthetic analogue of vasopressin which has an immediate systemic vasoconstrictor action followed by portal haemodynamic effects due to slow conversion to vasopressin. Its efficacy has been assessed in three placebo controlled trials and shown to significantly reduce failure to control bleeding and also to improve survival.<sup>84-86</sup> Five randomised trials compared its efficacy against vasopressin alone in three<sup>84 87 88</sup> and two in combination with nitroglycerine.<sup>89 90</sup> Glypressin significantly reduced failure to control bleeding compared with vasopressin alone and was as good as the combination of vasopressin and nitroglycerine. Three trials compared it with somatostatin and found it to be equally effective.<sup>91-93</sup> Two trials compared its efficacy against balloon tamponade and found it to be equally effective.<sup>94 95</sup>

**5.1.4 Somatostatin and octreotide**

Somatostatin causes selective splanchnic vasoconstriction and reduces portal pressure and portal blood flow.<sup>96</sup> It was shown to significantly reduce the failure to control bleeding in one trial<sup>97</sup> and did not show any significant differences against placebo in another.<sup>98</sup> Seven trials<sup>99-105</sup> compared its efficacy with

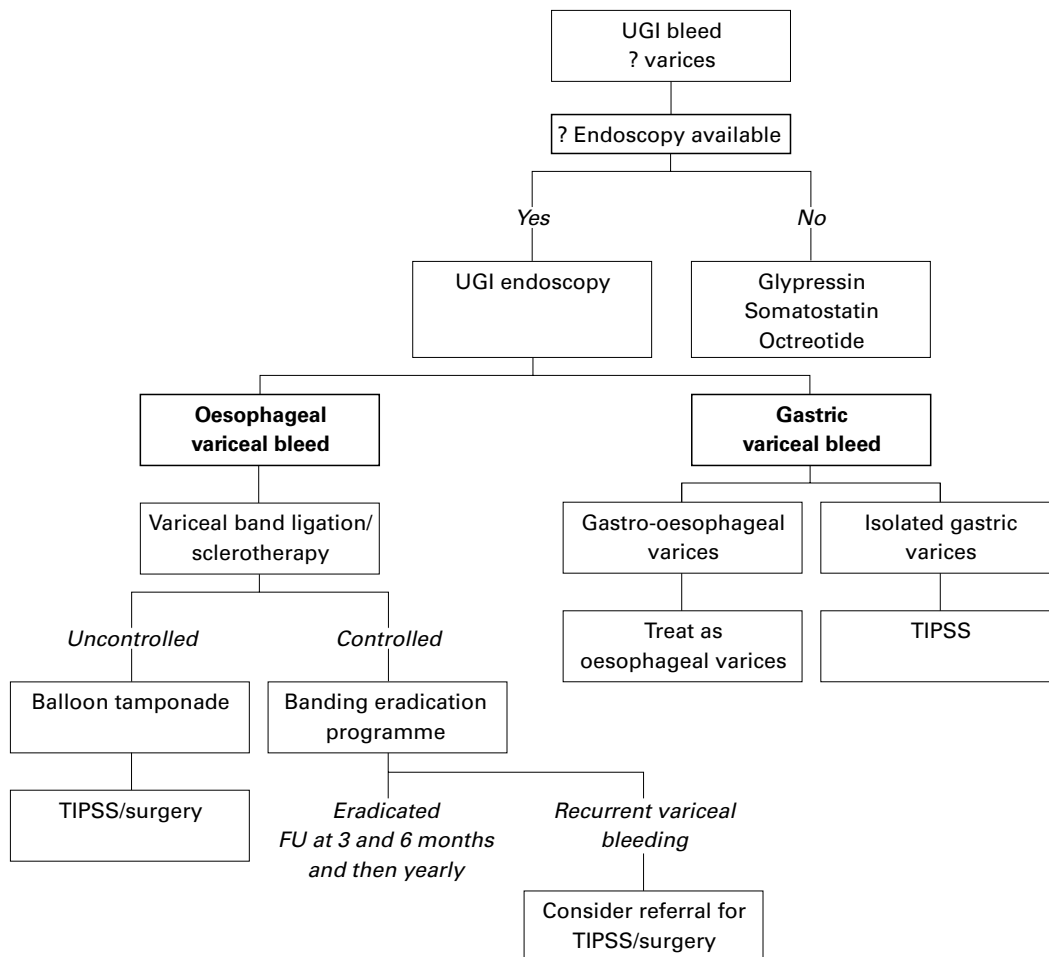


Figure 2 Algorithm for the management of variceal haemorrhage. UGI, upper gastrointestinal; FU, follow up; TIPSS, transjugular intrahepatic portosystemic shunt.

vasopressin and showed that somatostatin reduced the failure to control bleeding and was associated with significantly less side effects.

Three trials compared somatostatin with balloon tamponade and showed that these were equally effective in reducing the failure to control variceal bleeding.<sup>106-108</sup> Five trials have compared somatostatin or its analogue with sclerotherapy<sup>109-115</sup> and have shown no significant differences in failure to control bleeding, rebleeding, or mortality.

Data from a large randomised trial comparing octreotide with placebo was presented and showed conclusively that there was no significant difference between the two groups in terms of reduction in the failure to control bleeding, amount of blood transfused, or mortality at 42 or 90 days.<sup>114</sup>

## 5.2 ENDOSCOPIC THERAPY

### 5.2.1 Sclerotherapy

Endoscopic variceal sclerotherapy is based on the concept that bleeding from varices is stopped by thrombosis of the bleeding varix secondary to either intravariceal or paravariceal injection of a sclerosant. In trials of sclerotherapy in acute bleeding there is enormous variation in the type of sclerosant used, the experience of the operator, whether intravariceal or paravariceal injections are used, and the schedule of follow up. Furthermore, interpretation of the results of trials comparing

injection sclerotherapy with non-invasive therapy is complicated by inclusion of patients who were not actively bleeding at the time of randomisation.<sup>76 77</sup>

Four trials have compared sclerotherapy with balloon tamponade<sup>115-118</sup> and two of these showed significantly higher control of bleeding in patients treated with sclerotherapy.<sup>117 118</sup> The results of control of bleeding in the sclerotherapy patients are exceptional, at 95% and 100%, respectively.

Sclerotherapy has been compared with oesophageal transection in four randomised trials<sup>119-122</sup> and with portacaval shunt in one<sup>123</sup> in patients who had variceal haemorrhage that was uncontrolled. Although all studies showed a reduction in failure to control bleeding in patients treated with surgical therapy, this reached statistical significance in only one.<sup>122</sup> Rebleeding was also significantly higher in the sclerotherapy group. There were no differences in mortality but the rate of development of encephalopathy was significantly higher in patients treated with the surgical shunt.

### 5.2.2 Variceal band ligation

This technique is a modification of that used for the elastic band ligation of internal haemorrhoids. Its use in humans was first described in 1988<sup>124</sup> and a subsequent randomised clinical trial comparing banding with sclerotherapy showed a significant reduction in the rate of

**Box 3—Recommendations: control of active variceal bleeding in cirrhosis**

*Ideally patients with variceal bleeding should be treated in a unit where the personnel are familiar with the management of such patients and where routine therapeutic interventions can be undertaken. (Recommendation grade CII.)*

**(1) RESUSCITATION**

- **Site:** Where haemodynamic monitoring is possible. (Recommendation grade BIII.)

**● Methods:**

- 16 gauge peripheral cannulae, at least 2.
- Cross match 6 units of blood.
- Correct prothrombin time, platelet count.
- Central venous access.
- Protection of the airway by elective intubation:
  - (i) severe uncontrolled variceal bleeding;
  - (ii) severe encephalopathy;
  - (iii) inability to maintain oxygen saturation above 90%;
  - (iv) aspiration pneumonia. (Recommendation grade BIII.)

**(2) TIMING OF UPPER GASTROINTESTINAL ENDOSCOPY**

- As soon as the patient is haemodynamically stable. (Recommendation grade BIII.)

**(3) CONTROL OF BLEEDING**

- Variceal band ligation is the method of first choice. (Recommendation grade AI.)
- If banding is difficult because of continued bleeding or this technique is not available, endoscopic variceal sclerotherapy should be performed. (Recommendation grade AI.)
- If endoscopy is unavailable, vasoconstrictors such as octreotide (unlicensed) or glypressin, or a Sengstaken tube inserted (with adequate provision for airways protection) may be used while more definitive therapy is arranged. (Recommendation grade AI.)

**(4) FAILURE TO CONTROL ACTIVE BLEEDING**

- In case of bleeding that is difficult to control, a Sengstaken tube should be inserted until further endoscopic treatment, TIPSS, or surgical treatment. (Recommendation grade BI.)
- Specialist help should be sought at this time and transfer to a specialist centre should be considered. (Recommendation grade BII.)
- The mode of treatment—that is, surgical intervention such as oesophageal transection or TIPSS—is decided by which of these techniques is routinely used by the centre in which this patient is being managed. (Recommendation grade BII.)

complications and improvement in survival.<sup>125</sup> Another trial confirmed that banding controls active variceal haemorrhage and no significant differences were found between control of active bleeding between banding and sclerotherapy. Lo and colleagues<sup>126</sup> showed that active bleeding was controlled more readily with ligation (94%) compared with sclerotherapy (80%).

**5.2.3 Other endoscopic measures**

Control of bleeding using tissue adhesives such as cyanoacrylate or bucrylate has been reported in about 90% of cases.<sup>127 128</sup> There were however similar rates of rebleeding as with sclerotherapy, and there were significant complications in the form of cerebrovascular accidents related to injection of the tissue adhesives and to the risk of damage to the instrument.

**5.3 BALLOON TAMPONADE**

This form of treatment is highly effective and controls acute bleeding in up to 90% of patients although about 50% rebleed when the balloon is deflated.<sup>129</sup> It is, however, associated

with serious complications such as oesophageal ulceration and aspiration pneumonia in up to 15–20% of patients. Despite this, it may be a life saving treatment in cases of massive uncontrolled variceal haemorrhage pending other forms of treatment.

**5.4 TIPSS**

Three studies have specifically addressed the role of TIPSS in the management of uncontrolled variceal haemorrhage.<sup>130–132</sup> They show that TIPSS can be performed successfully in this situation and is associated with rapid control of bleeding. None of these studies was randomised but one study suggested that patients were likely to have a survival benefit if TIPSS was used in the situation of uncontrolled variceal haemorrhage in patients with cirrhosis compared with a historical control group treated with oesophageal transection. A recent study has compared TIPSS with H-graft portacaval shunts in patients who failed non-operative management and suggested that H-grafts were a useful method of reducing portal pressure and had a significantly lower failure rate ( $p < 0.02$ ). Before wider application, more data are needed.<sup>133</sup>

**5.5 LIVER TRANSPLANTATION**

This is probably only appropriate for patients who bleed while awaiting liver transplantation although studies using variceal band ligation or comparison with the transjugular intrahepatic portal-systemic shunt in this situation need to be done. Liver transplantation is however an exceedingly rare option for the vast majority of patients, both because it is not commonly available and because of shortages and delays in organ procurement. No controlled trials of liver transplantation in uncontrolled/active bleeding are available.

Recommendations for the control of variceal bleeding in cirrhosis are given in box 3.

**6.0 Secondary prophylaxis of variceal haemorrhage**

This form of treatment is aimed at preventing recurrence of variceal bleeding.

**6.1  $\beta$  BLOCKERS**

A total of 755 patients were randomised in 11 trials comparing propranolol or nadolol<sup>134</sup> with no active treatment.<sup>29 30–33 49 134–138</sup> Significant reduction in rebleeding was seen in four trials and a meta-analysis showed significant overall reduction (OR 0.4, 95% CI 0.3–0.54). Eight trials showed significant reduction in mortality, as did the overall analysis.

**6.2 ENDOSCOPIC THERAPY**

A total of 1111 patients have been randomised to either sclerotherapy or no active treatment in eight trials.<sup>76 116 137 139–143</sup> Rebleeding was significantly reduced in two studies.<sup>140 141</sup> Overall there was also a significant reduction in rebleeding (OR 0.63, 95% CI 0.49–0.79). Mortality was significantly reduced in one study.<sup>140</sup> Overall there was a significant reduction in mortality (OR 0.77, 95% CI 0.61–0.98).

Sclerotherapy has been compared with  $\beta$  blockers in nine trials which have randomised a total of 787 patients.<sup>67 137 144–150</sup> Significant reduction in rebleeding was found in the sclerotherapy group in two studies<sup>148 149</sup> and an increase was noted in three studies<sup>137 145 147</sup> which was not statistically significant. The remainder of the studies showed a reduction in rebleeding which was not statistically significant.

No significant differences were detected in a meta-analysis of 10 trials comparing sclerotherapy with sclerotherapy and  $\beta$  blockers.<sup>45</sup> Two trials comparing sclerotherapy and  $\beta$  blockers with  $\beta$  blockers alone showed that the combined therapy significantly reduced rebleeding and mortality.

There are now at least seven published randomised trials in the literature comparing sclerotherapy with variceal band ligation which have been combined in a meta-analysis.<sup>125 126 151–155</sup> This included 547 patients and concluded that variceal band ligation carried a significantly lower rate of rebleeding (OR 0.52, 95% CI 0.37–0.74), mortality (OR 0.67, 95% CI 0.46–0.98) and complications such as oesophageal stricture (OR 0.10, 95% CI 0.03–0.29). These studies comparing the two best available modalities of treatment have shown that variceal band ligation reduces rebleeding, mortality, and local complications.

### 6.3 TIPSS

Transjugular intrahepatic portosystemic shunt (TIPSS) has been compared with sclerotherapy in eight randomised trials<sup>156–162</sup> and with band ligation in one.<sup>163</sup> All except one study<sup>157</sup> comparing TIPSS with sclerotherapy showed a significant reduction in rebleeding in patients treated with TIPSS. One study showed decreased survival<sup>157</sup> and one study showed improved survival in patients treated with TIPSS.<sup>164</sup> The other studies showed no significant differences in mortality. The study comparing TIPSS with variceal band ligation plus “TIPSS rescue” showed that patients treated with variceal band ligation had significantly more rebleeding although there was no significant difference in mortality between the groups. A recent meta-analysis comparing TIPSS with endoscopic treatment confirmed that TIPSS reduces rebleeding and is associated with an increased risk of encephalopathy. No differences in survival were observed between patients treated with TIPSS or endoscopic therapy.<sup>164a</sup> Despite the problem of shunt insufficiency and the cost of shunt surveillance, TIPSS has been shown to be more cost effective than endoscopic therapy.<sup>164b</sup>

### 6.4 SURGERY

#### 6.4.1 Portacaval shunts

Portacaval shunts (PCS) may be either non-selective or selective. Non-selective PCS refer to diversion of portal blood flow into the systemic circulation thereby reducing liver blood flow. Selective shunts (distal splenorenal shunts) refer to drainage of the varices into the

systemic circulation without affecting liver blood flow.

Four trials have compared non-selective shunts with no active treatment<sup>165–168</sup> and all showed a significant reduction in rebleeding; mortality was reduced in three<sup>165 166 168</sup> and increased in one.<sup>167</sup> This difference was thought to be related to the randomisation procedure.

Six trials compared non-selective shunts with the distal splenorenal shunt<sup>169–174</sup> and included a total of 336 patients. No difference in rebleeding or encephalopathy was observed in any of the studies. Mortality was not significantly different in five of the trials although it was significantly reduced in one.<sup>170</sup>

Distal splenorenal shunt has been compared with sclerotherapy in four randomised trials<sup>175–178</sup> and with PCS<sup>123 179 180</sup> in three trials. Shunt surgery was associated with significantly lower rebleeding in five of the trials<sup>175–178 180</sup> and also in a meta-analysis (OR 0.18, 95% CI 0.12–0.28). The incidence of hepatic encephalopathy after shunt surgery was also significantly greater than sclerotherapy in four<sup>175–177 180</sup> studies and remained unchanged in two.<sup>123 178</sup> Mortality was increased significantly in the PCS group in one study but overall there were no significant differences.

Recommendations for the secondary prophylaxis of variceal bleeding in cirrhosis are given in box 4 and fig 2.

## 7.0 Gastric varices

### 7.1 NATURAL HISTORY

Gastric varices can be detected at the first endoscopy in 20% of patients with all types of portal hypertension (primary). Within the first two years of eradication of oesophageal varices a further 10% of patients develop gastric varices (secondary). Primary gastric varices are more commonly observed in patients with portal hypertension due to extrahepatic portal vein obstruction compared with cirrhosis.<sup>181 182</sup>

Gastric varices can be classified on the basis of their location in the stomach and relationship with oesophageal varices. This classification has implications for management. These varices can be divided into: (a) gastro-oesophageal varices (GOV), which are associated with oesophageal varices; and (b) isolated gastric varices (IGV), which occur independent of oesophageal varices. Type 1 GOV are continuous with oesophageal varices and extend for 2–5 cm below the gastro-oesophageal junction along the lesser curvature of the stomach. Type 2 GOV extend beyond the gastro-oesophageal junction into the fundus of the stomach. Type 1 IGV refers to varices that occur in the fundus of the stomach and type 2 describes varices anywhere in the stomach including the body, antrum, pylorus, and duodenum.<sup>181</sup> The most common type of varices seen in cirrhosis is GOV type 1. Patients who bleed from IGV are at a significantly higher risk of dying from an episode of variceal bleeding compared with patients bleeding from GOV.<sup>183</sup>

**Box 4—Recommendations: secondary prophylaxis of variceal bleeding in cirrhosis**

## (1) VARICEAL BAND LIGATION

- Following control of active variceal bleeding the varices should be eradicated using endoscopic methods. The method of first choice is variceal band ligation. (Recommendation grade AI.)
- It is recommended that each varix is banded with a single band at weekly intervals until variceal eradication. (Recommendation grade BII.)
- The use of the over tube should be avoided because this is associated with increased complications. (Recommendation grade BII.)
- Following successful eradication of the varices, patients should be endoscoped at three months and six monthly thereafter. In case of recurrence of varices they should be treated with variceal eradication. (Recommendation grade AII.)

## (2) ENDOSCOPIC VARICEAL SCLEROTHERAPY

- If banding is not available, sclerotherapy should be used. (Recommendation grade BI.)
- The sclerosant used may vary between institutions.
- The interval between treatments should be the same as those outlined above for banding. (Recommendation grade AII.)

(3) NON-SELECTIVE  $\beta$  BLOCKER WITH OR WITHOUT ENDOSCOPIC THERAPY

- Either combination treatment of sclerotherapy and non-selective  $\beta$  blocker or non-selective  $\beta$  blocker alone may be used. If the latter strategy is used then it is recommended that patients should have the hepatic venous pressure gradient measured to confirm that this has been successfully reduced to less than 12 mm Hg. (Recommendation grade AII.)

## (4) TIPSS

- TIPSS is more effective than endoscopic treatment in reducing variceal rebleeding but does not improve survival and is associated with more encephalopathy. It is a treatment option that may be used in certain centres with particular expertise. (Recommendation grade AI.)

## 7.2 MANAGEMENT

The options for management of gastric variceal haemorrhage are endoscopic methods, surgery, TIPSS, and other radiological methods. Pharmacological methods have no place in the current management of patients with gastric variceal bleeding.

## 7.2.1 Endoscopic therapy

*Endoscopic sclerotherapy.* Sclerotherapy as described for oesophageal variceal bleeding has been shown to be effective in controlling active bleeding from all types of gastric varices in about 70–80% of patients with gastric variceal bleeding.<sup>184 185</sup> However, active bleeding was arrested with sclerotherapy in only 26% of patients with IGV<sup>151</sup>. In addition, rebleeding after endoscopic sclerotherapy occurred in 60–90% of patients in the different studies.<sup>151 184 185</sup> Episodes of rebleeding are more common in patients with IGVs.<sup>151 184 185</sup>

*Endoscopic injection therapy with “super glue”.* Several studies have used cyanoacrylate for the treatment of oesophagogastric varices. Soehendra and colleagues<sup>128</sup> used it successfully to eradicate gastric varices. Ramond and colleagues<sup>127</sup> used cyanoacrylate to treat gastric varices in 27 patients and reported successful control of active bleeding in 90% of patients who were actively bleeding but 50% rebled. In a controlled but non-randomised study comparing butyl cyanoacrylate with sclerotherapy, Oho and colleagues<sup>186</sup> showed that the rate of

initial control of bleeding was significantly higher in patients treated with cyanoacrylate. Survival was significantly greater in patients treated with cyanoacrylate compared with sclerotherapy. Complications were not significantly different between groups.

*Endoscopic injection of thrombin.* Injection of bovine thrombin (1000 U/ml) for bleeding from gastric varices has been used in 11 patients with cirrhosis, bleeding from IGV1 in nine and from GOV1 in two patients. Control of bleeding was observed in all and varices were eradicated in all patients after a mean of two injections. Rebleeding, over a follow up of nine months, occurred in one patient.<sup>187</sup>

*Use of Sengstaken tube.* Several investigators have shown that immediate control of bleeding can be observed from all types of gastric varices except IGV2, using the Sengstaken-Blakemore tube with the gastric balloon, held under moderate traction. However, rebleeding is almost universal if another modality of treatment is not instituted.<sup>129 181 183 184 188</sup>

*Endoscopic band ligation.* Gastric variceal band ligation using “O” rings and detachable snares have been shown to control active bleeding from gastric varices but is followed almost invariably by recurrence of bleeding.<sup>189 190</sup> No controlled data are available on the use of this treatment approach. However, given the anatomy of gastric varices it may be dangerous to band them.

## 7.2.2 Surgery

Under running of gastric varices<sup>191</sup> has been shown to control active bleeding but is followed by recurrence of bleeding in 50% of patients and is associated with a perioperative mortality of greater than 40%. Complete devascularisation of the cardia, stomach, and distal oesophagus for bleeding from gastric varices is associated with good control of bleeding but is followed by rebleeding in over 40% of patients and early mortality in about 50%.<sup>192</sup> The use of distal splenorenal shunting for bleeding from gastric varices in patients with cirrhosis has been poorly studied and its use has been reported in six patients with Child class A or B cirrhosis. Although good control of bleeding was attained, two patients died in the postoperative period.<sup>193</sup>

## 7.2.3 Radiology

The use of “balloon occluded retrograde transvenous obliteration” (B-RTO) for the treatment of bleeding gastric varices has been pioneered by the Japanese.<sup>194 195</sup> This procedure involves insertion of a balloon catheter into an outflow shunt (gastric-renal or gastric-inferior vena caval) via the femoral or internal jugular vein. Blood flow is blocked by inflation of the balloon and then 5% ethanolamine oleate iopamidol is injected in a retrograde manner. The use of this technique has been described in about 60 patients. Good control of bleeding was observed in all patients and recurrence of varices occurred in about 10%. However, no controlled data for the use of this technique are available.

**Box 5—Recommendations**

## CLASSIFICATION OF GASTRIC VARICES

*Primary*

- Gastric varices that can be detected at the first endoscopy.

*Secondary*

- Those gastric varices that occur within two years of eradication of oesophageal varices.

*Types of gastric varices*

- Gastro-oesophageal varices types 1 and 2 (GOV): those gastric varices that are continuous with oesophageal varices and occur along the lesser curvature or the fundus, respectively.
- Isolated gastric varices types 1 and 2 (IGV): those gastric varices that are discontinuous from the oesophageal varices and occur either in the fundus of the stomach or anywhere else in the stomach, including the body, antrum, pylorus, and duodenum, respectively. (Recommendation grade BII.)

## MANAGEMENT OF ACTIVE BLEEDING FROM GASTRIC VARICES

*Gastro-oesophageal varices*

- Treat as for oesophageal varices. (Recommendation grade BII.)

*Isolated gastric varices*

- Initial therapy: injection sclerotherapy with either sclerosants, butyl-cyanoacrylate, or thrombin. (Recommendation grade BII.)
- In case of failure to control bleeding: balloon tamponade with Sengstaken-Blakemore tube. (Recommendation grade BII.)
- For long term control of variceal bleeding: TIPSS or shunt surgery. (Recommendation grade BII.)

**7.2.4 TIPSS**

TIPSS has been shown to control active bleeding from gastric varices in almost all patients in whom the shunt can be performed successfully.<sup>132 196 197</sup> Procedure related mortality is about 1% and rebleeding occurs with shunt insufficiency in about 15% of patients.<sup>197</sup> In a comparative study, evaluating the clinical outcome of patients treated with TIPSS for variceal bleeding from oesophageal and gastric varices, no significant differences were detected in the rate of control of bleeding, rebleeding, or survival.<sup>197</sup> TIPSS appears to be an effective method of treating gastric variceal bleeding. However, no randomised clinical trials comparing TIPSS with any other form of therapy are available.

Recommendations for the management of gastric varices are given in box 5.

**8.0 Antibiotics in variceal bleeding**

Bacterial infections occur in about 20% of patients with cirrhosis with upper gastrointestinal bleeding within 48 hours of admission<sup>198</sup> and the incidence increases to 35–66% within two weeks.<sup>199–201</sup> Prognosis both in terms of rebleeding, failure to control bleeding, and inhospital outcome are closely related to bacterial infections.<sup>199–201</sup> Six randomised controlled trials have compared antibiotic prophylaxis with no treatment.<sup>202–207</sup> Five of the fully published papers were combined in a

meta-analysis.<sup>202–206, 208</sup> Fluoroquinolones were used in four of the trials<sup>203–206</sup> combined with amoxycillin and clavulanic acid in two,<sup>204, 205</sup> and oral non-absorbable antibiotics in one.<sup>202</sup> The results show that antibiotic prophylaxis was associated with a significantly lower rate of infection, bacteraemia, and spontaneous bacterial peritonitis. Antibiotic prophylaxis was associated with significantly improved short term survival (mean improvement rate 9.1% (95% CI 2.9–15.3);  $p < 0.004$ ). The above would suggest that patients with cirrhosis and upper gastrointestinal bleeding should have antibiotic prophylaxis. The choice of the antibiotic and its dose is debatable and should be decided upon by the policy of the unit where the patient is being treated. However, most of the present studies have used fluoroquinolones and therefore the evidence dictates the use of a fluoroquinolone (ciprofloxacin) as the simplest measure at a dose of 1 g per day orally.

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**Box 6—Recommendations**

- Infection is common after upper gastrointestinal bleeding in cirrhotic patients and a major cause of morbidity and mortality.
- All patients presenting with an episode of variceal bleed should have antibiotic prophylaxis.
- It is suggested that they be treated with ciprofloxacin 1g/day for seven days.

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