

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

R Jalan, P C Hayes

## 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.

**Department of Internal Medicine, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK**  
R Jalan†  
P C Hayes

†Present address: Institute of Hepatology, RFUCLMS, 69–75 Chenies Mews, London WC1E 6HY, UK

Correspondence to:  
Dr R Jalan. Email:  
rjalan@ucl.ac.uk

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)

## 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; HVPG, hepatic venous pressure gradient; PCS, portacaval shunts; GOV, gastro-oesophageal varices; IGV, isolated gastric varices; B-RTO, balloon occluded retrograde transvenous obliteration.

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 malena 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.)

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

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

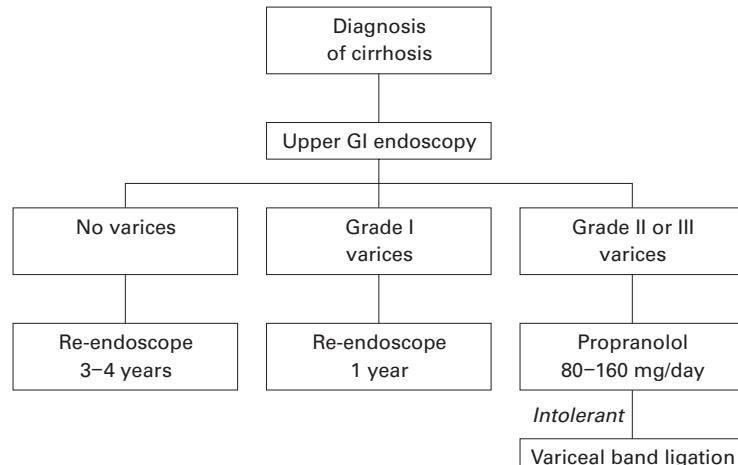


Figure 1 Proposed algorithm for surveillance for varices and primary prophylaxis.

## **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 CIRRHTIC 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*

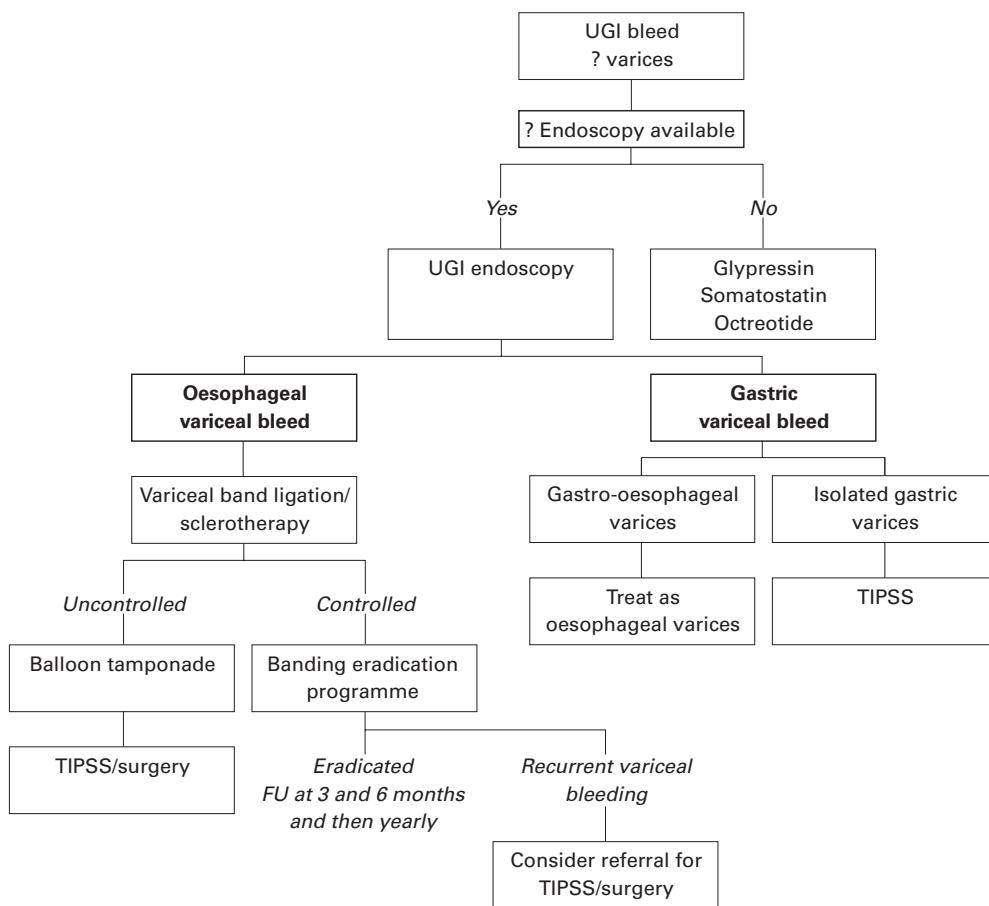
The addition of nitroglycerine enhances its effects on portal pressure and reduces cardiovascular side effects.<sup>80</sup> Three randomised trials compared vasopressin alone with vasopressin and nitroglycerine<sup>81-83</sup> and the pooled data from these showed that the combination was associated 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 stent 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>109-113</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 bucyrilate 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 TAMPOONADE

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 stent 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> Fluoroquinolines 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 fluoroquinolines and therefore the evidence dictates the use of a fluoroquinolone (ciprofloxacin) as the simplest measure at a dose of 1 g per day orally.

The authors gratefully acknowledge the contribution of the members of the Liver Section, British Society of Gastroenterology.

**9.0 References**

- Eccles M, Clapp Z, Grimshaw J, et al. North of England evidence based guidelines development project: methods of guideline development. *BMJ* 1996;312:760–2. **Grade: IV**
- Grimshaw J, Eccles M, Russel I, et al. Developing clinically valid practice guidelines. *J Evaluation Clin Pract* 1995;1:37–48. **Grade: IV**
- De Franchis R. Developing consensus in portal hypertension. *J Hepatol* 1996;25:390–4. **Grade: IV**
- Christensen E, Fauerholdt L, Schlichting P, et al. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. *Gastroenterology* 1981;81:944–52. **Grade: III**
- Cales P, Pascal JP. Natural history of esophageal varices in cirrhosis (from origin to rupture). *Gastroenterol Clin Biol* 1990;12:245–54. **Grade: III**
- Czaja AJ, Wolf AM, Summerskill WH. Development and early prognosis of esophageal varices in severe chronic active liver disease (CALD) treated with prednisolone. *Gastroenterology* 1979;77:629–33. **Grade: III**
- Baker LA, Smith C, Lieberman G. The natural history of esophageal varices. *Am J Med* 1959;26:228–37. **Grade: III**
- Dagradis A. The natural history of esophageal varices in patients with alcoholic liver disease. *Am J Gastroenterol* 1972;57:520–40. **Grade: III**
- MacDougall BR, Westaby D, Theodossi A, Dawson JL, Williams R. Increased long-term survival in variceal haemorrhage using injection sclerotherapy. Results of a controlled trial. *Lancet* 1982;1:124–7. **Grade: Ib**
- Dawson J, Gertsch P, Mosimann F, et al. Endoscopic variceal pressure measurements: Response to isosorbide dinitrate. *Gut* 1985;26:843–7. **Grade: IIb**
- Lebrec D, De Fleury P, Rueff B, et al. Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. *Gastroenterology* 1980;79:1139–44. **Grade: III**
- Garcia-Tsao G, Groszman RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985;5:419–24. **Grade: III**
- Groszman RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401–7. **Grade: Ib**
- Vinell JP, Cassingeul J, Levade M, et al. Assessment of short term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of porto-hepatic gradient. *Hepatology* 1986;6:116–17. **Grade: III**
- Palmer ED, Brick IB. Correlation between severity of esophageal varices in portal cirrhosis and their propensity toward hemorrhage. *Gastroenterology* 1956;30:85–90. **Grade: III**

**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.

- 16 Polio J, Groszmann RJ. Hemodynamic factors involved in the development and rupture of esophageal varices: A pathophysiologic approach to treatment. *Semin Liver Dis* 1986;6:318–31. **Grade: III**
- 17 Beppu K, Inokuchi K, Koyanagi N, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981;27:213–18. **Grade: III**
- 18 North Italian Endoscopic Club (NIEC) for the study and treatment of esophageal varices. Prediction of first variceal haemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med* 1988;319:983–9. **Grade: Ib**
- 19 Inokuchi K, Sugimachi K, Sato T, et al. Improved survival after prophylactic portal nondecompression surgery for esophageal varices: A randomized clinical trial. *Hepatology* 1990;12:1–6. **Grade: Ib**
- 20 Prada A, Bortoli A, Minoli G, Carnovali M, Colombo E, Sangiovanni A. Prediction of oesophageal variceal bleeding: Evaluation of the beppu and North Italian Endoscopic Club scores by an independent group. *Eur J Gastroenterol Hepatol* 1994;6:1009–13. **Grade: III**
- 21 De Franchis R, Primignani M, Arcidiacono PG, et al. Prophylactic sclerotherapy in high-risk cirrhotics selected by endoscopic criteria: A multicenter randomized controlled trial. *Gastroenterology* 1991;101:1087–93. **Grade: Ib**
- 22 Feu F, Del Arbol LR, Banares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. *Gastroenterology* 1996;111:1291–9. **Grade: Ib**
- 23 Merkel C, Bolognesi M, Bellon S, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. *Gastroenterology* 1992;102:973–9. **Grade: IIb**
- 24 Pascal JP, Cales P and Multicentre Study Group. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987;317:856–61. **Grade: Ib**
- 25 Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhosis: A prospective, randomized study. *Hepatology* 1988;8:6–9. **Grade: Ib**
- 26 Lebrec D, Poinard T, Capron JP, et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis. A randomized trial. *J Hepatol* 1988;7:118–25. **Grade: Ib**
- 27 Italian Multicenter Project for Propranolol in Prevention of Bleeding. Propranolol prevents first gastrointestinal bleeding in non-ascitic cirrhotic patients. Final report of a multicenter randomized trial. *J Hepatol* 1989;9:75–83. **Grade: Ib**
- 28 Conn HO, Grace ND, Bosch J, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized controlled clinical trial. *Hepatology* 1991;13:902–12. **Grade: Ib**
- 29 Lebrec D, Poinard T, Bernau J, et al. A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a final report. *Hepatology* 1984;4:355–8. **Grade: Ib**
- 30 Burroughs AK, Jenkins WJ, Sherlock S, et al. Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. *N Engl J Med* 1983;309:1539–42. **Grade: Ib**
- 31 Villeneuve JP, Pomier-Layrargues G, Infante-Rivard C, et al. Propranolol for the prevention of recurrent variceal haemorrhage: a controlled trial. *Hepatology* 1986;6:1239–43. **Grade: Ib**
- 32 Colombo M, De Franchis R, Tommasini M, Sangiovanni A, Dioguardi N. beta-Blockade prevents recurrent gastrointestinal bleeding in well-compensated patients with alcoholic cirrhosis: A multicenter randomized controlled trial. *Hepatology* 1989;9:433–8. **Grade: Ib**
- 33 Garden OJ, Mills PR, Birnie GG, Murray GD, Carter DC. Propranolol in the prevention of recurrent variceal hemorrhage in cirrhotic patients. A controlled trial. *Gastroenterology* 1990;98:185–90. **Grade: Ib**
- 34 Garden OJ, Motyl H, Gilmour WH, et al. Prediction of outcome following acute variceal haemorrhage. *Br J Surg* 1985;72:91–5. **Grade: III**
- 35 Christensen E, Krintel JJ, Hansen M, Krogh S, et al. Prognosis after the first episode of gastrointestinal bleeding or coma in cirrhosis. *Scand J Gastroenterol* 1989;24:999–1006. **Grade: III**
- 36 Cardin F, Gori G, McCormick PA, Burroughs AK. A predictive model for very early rebleeding from varices. *Gut* 1990;31:A1204 (abstract). **Grade: III**
- 37 Balzano J, Villanueva C, Espinosa J, et al. Predictive value of the endoscopic signs in variceal bleeding. *J Hepatol* 1991;13:(suppl 2):S93 (abstract). **Grade: III**
- 38 Siringo S, McCormick PA, Mistry P, Kaye G, McIntyre N, Burroughs AK. Prognostic significance of the white nipple sign in variceal bleeding. *Gastrointest Endos* 1991;37:51–5. **Grade: III**
- 39 Graham DY, Smith JL. The course of patients after variceal haemorrhage. *Gastroenterology* 1981;80:800–9. **Grade: III**
- 40 Burroughs AK, Mezzanote G, Phillips A, Aiden McCormick P, McIntyre N. Cirrhotics with variceal haemorrhage: The importance of the time interval between admission and the start of analysis for survival and rebleeding rates. *Hepatology* 1989;9:810–17. **Grade: II**
- 41 Pugh RNM, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–9. **Grade: III**
- 42 Conn HO, Lindenmuth WW, May CJ, Ramsby GR. Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. *N Engl J Med* 1965;272:1255–63. **Grade: II**
- 43 Jackson FC, Perrin EB, Smith AG, Dagrad AE, Nadal HM. A clinical investigation of the portacaval shunt. II. Survival analysis of the prophylactic operation. *Am J Surg* 1968;115:22–42. **Grade: III**
- 44 Resnick RH, Chalmers TC, Ishihara AM, et al. A controlled trial of the prophylactic portacaval shunt. A final report. *Ann Intern Med* 1969;70:675–88. **Grade: Ib**
- 45 D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: A meta-analytic review. *Hepatology* 1995;22:332–54. **Grade: Ia**
- 46 Andreani T, Poupon RE, Balkau BJ, et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: Results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. *Hepatology* 1990;12:1413–19. **Grade: Ib**
- 47 The PROVA Study Group. Prophylaxis of first hemorrhage from oesophageal varices by sclerotherapy, propranolol or both in cirrhotic patients. A randomised multicenter trial. *Hepatology* 1991;14:1016–24. **Grade: Ib**
- 48 Strauss E, de Sa MFG, Albano A, Lacet CMC, Leite MO, Maffei RA Jr. A randomised controlled trial for the prevention of the first upper gastrointestinal bleeding due to portal hypertension in cirrhosis: sclerotherapy or propranolol versus control groups. *Hepatology* 1988;8:1395 (abstract). **Grade: Ib**
- 49 Colman J, Jones P, Finch C, Dundley F. Propranolol in the prevention of variceal hemorrhage in alcoholic cirrhotic patients. *Hepatology* 1990;12:851 (abstract). **Grade: IIa**
- 50 Hayes PC, Davis JM, Lewis JA, Bouchier IAD. Meta-analysis of the value of propranolol in the prevention of variceal haemorrhage. *Lancet* 1990;336:153–6. **Grade: Ia**
- 51 Navasa M, Chesta J, Bosch J, Rodes J. Reduction of portal pressure by iso-sorbide-5-mononitrate in patients with cirrhosis. Effects upon splanchnic and systemic haemodynamics and liver function. *Gastroenterology* 1989;96:1110–18. **Grade: IIb**
- 52 Angelico M, Carli L, Piat C, et al. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993;104:1460–5. **Grade: Ib**
- 53 Merkel C, Marin R, Enzo E, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Gruppo Triveneto per l'ipertensione portale. *N Engl J Med* 1996;334:1624–9. **Grade: Ib**
- 54 Paquet KJ, Koussous P. Is there an indication of prophylactic endoscopic paravariceal injection sclerotherapy in patients with liver cirrhosis and portal hypertension? *Endoscopy* 1986;18:32–5. **Grade: IV**
- 55 Witzel L, Wolberg E, Merki H. Prophylactic endoscopic sclerotherapy of oesophageal varices. A prospective controlled study. *Lancet* 1985;1:773–5. **Grade: Ib**
- 56 Koch H, Henning H, Grimm H, Soehendra N. Prophylactic sclerosing of esophageal varices—Results of a prospective controlled study. *Endoscopy* 1986;18:40–3. **Grade: Ib**
- 57 Kobe E, Zipprich B, Schentke KU, Nilius R. Prophylactic endoscopic sclerotherapy of esophageal varices—A prospective randomized trial. *Endoscopy* 1990;22:245–8. **Grade: Ib**
- 58 Wordehoff D, Spech HJ. Prophylaktische Oosphagus-Varizenzklerosierung: Ergebnisse Einer Prospektiven, Randomisierten Langzeitstudie über 7 Jahre (Prophylactic sclerotherapy of esophageal varices: Results of a prospective, randomized long-term trial over seven years). *Deutsche Medizinische Wochenschrift* 1987;112:947–51. **Grade: Ib**

- 59 Santangelo WC, Dueno MI, Estes BL, Krejs GJ. Prophylactic sclerotherapy of large esophageal varices. *N Engl J Med* 1988;318:814-18. **Grade: Ib**
- 60 Sauerbruch T, Wotzka R, Kopcke W, et al. Prophylactic sclerotherapy before the first episode of variceal hemorrhage in patients with cirrhosis. *N Engl J Med* 1988;319:8-15. **Grade: Ib**
- 61 Piai G, Cipolletta L, Claar M, et al. Prophylactic sclerotherapy of high-risk esophageal varices: Results of a multicentric prospective controlled trial. *Hepatology* 1988; 8:1495-500. **Grade: Ib**
- 62 Potzi R, Bauer P, Reichel W, Kerstan E, Renner F, Gangl A. Prophylactic endoscopic sclerotherapy of oesophageal varices in liver cirrhosis. A multicentre prospective controlled randomised trial in Vienna. *Gut* 1989;30:873-9. **Grade: Ib**
- 63 Russo A, Giannone G, Magnano A, Passanisi G, Longo C. Prophylactic sclerotherapy in nonalcoholic liver cirrhosis: Preliminary results of a prospective controlled randomized trial. *World J Surg* 1989;13:149-53. **Grade: Ib**
- 64 Triger DR, Smart HL, Hosking SW, Johnson AG. Prophylactic sclerotherapy for esophageal varices: Long-term results of a single-center trial. *Hepatology* 1991;13: 117-23. **Grade: Ib**
- 65 VA Cooperative Variceal Sclerotherapy Group. Sclerotherapy for male alcoholic cirrhotic patients who have bled for esophageal varices: results of a randomized multicenter clinical trial. *Hepatology* 1994;20:618-25. **Grade: Ib**
- 66 Saggioro A, Pallini P, Vitalba A, et al. Complications of the endoscopic sclerotherapy of oesophageal varices: Comparison between different techniques. *Policlinico - Sezione Chirurgica* 1987;94:461-4. **Grade: IIa**
- 67 Fleig WE, Stance EF, Hunecke R, et al. Prevention of recurrent bleeding in cirrhotics with recent variceal hemorrhage: Prospective, randomized comparison of propranolol and sclerotherapy. *Hepatology* 1987;7:355-61. **Grade: Ib**
- 68 Planas R, Boix J, Dominguez M, et al. Prophylactic sclerosis of esophageal varices. Prospective trial. *J Hepatol* 1989;9 (suppl 1):S73 (abstract). **Grade: Ib**
- 69 Sarin SK, Guptan RKC, Jain AK, Sundaram KR. A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. *Eur J Gastroenterol Hepatol* 1996;8:337-42. **Grade: Ib**
- 70 Lay CS, Tsai YT, Teg CY, et al. Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. *Hepatology* 1997;25: 1346-50. **Grade: Ib**
- 71 Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988-93. **Grade: Ib**
- 72 Merigan TC, Plotkin GR, Davidson CS. Effect of intravenously administered posterior pituitary extract on hemorrhage from bleeding esophageal varices. *N Engl J Med* 1962;266:134-5. **Grade: IIb**
- 73 Conn HO, Ramsby GR, Storer EH, et al. Intraarterial vasopressin in the treatment of upper gastrointestinal hemorrhage: a prospective controlled clinical trial. *Gastroenterology* 1975;68:211-21. **Grade: IIa**
- 74 Mallory A, Schaefer JW, Cohen JR, Holt AS, Norton LW. Selective intra-arterial vasopressin infusion for upper gastrointestinal tract hemorrhage. A controlled trial. *Arch Surg* 1980;115:30-2. **Grade: Ib**
- 75 Fogel MR, Knauer CM, Andres LL, et al. Continuous intravenous vasopressin in active upper gastrointestinal bleeding. A placebo-controlled trial. *Ann Intern Med* 1982;96: 565-9. **Grade: Ib**
- 76 Soderlund C, Ihre T. Endoscopic sclerotherapy v. conservative management of bleeding esophageal varices. *Acta Chir Scand* 1986;151:449-56. **Grade: Ib**
- 77 Larson AW, Cohen H, Zwiebel BA, et al. Acute esophageal variceal sclerotherapy. *JAMA* 1986;255:497-500. **Grade: IV**
- 78 Alexandrino P, Alves MM, Fidalgo P, et al. Is sclerotherapy the first choice treatment for active variceal bleeding in cirrhotic patients? Final report of a randomised clinical trial. *J Hepatol* 1990;11(suppl):S1. **Grade: Ib**
- 79 Westaby D, Hayes PC, Gimson AES, Polson R, Williams R. Controlled clinical trial of injection sclerotherapy for active variceal bleeding. *Hepatology* 1989;9:274-7. **Grade: Ib**
- 80 Groszmann RJ, Kravetz D, Bosch J, et al. Nitroglycerin improves the hemodynamic response to vasopressin in portal hypertension. *Hepatology* 1982;2:757-62. **Grade: IIb**
- 81 Tsai YT, Lay CS, Lai KH, et al. Controlled trial of vasopressin plus nitroglycerin vs vasopressin alone in the treatment of bleeding esophageal varices. *Hepatology* 1986; 6:406-9. **Grade: Ib**
- 82 Gimson AES, Westaby D, Hegarty J, Alastair W, Williams R. A randomized trial of vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. *Hepatology* 1986;6: 410-13. **Grade: Ib**
- 83 Bosch J, Groszman RJ, Garcia-Pagan JC, et al. Association of transdermal nitroglycerin to vasopressin infusion in the treatment of variceal hemorrhage: a placebo-controlled clinical trial. *Hepatology* 1989;10:962-8. **Grade: Ib**
- 84 Freeman JG, Cobden MD, Record CO. Placebo-controlled trial of terlipressin (glypressin) in the management of acute variceal bleeding. *J Clin Gastroenterol* 1989;11:58-60. **Grade: Ib**
- 85 Soderlund C, Magnusson I, Torngren S, Lundell L. Terlipressin (triglycyl-lysine vasopressin) controls acute bleeding oesophageal varices. A double-blind, randomized, placebo-controlled trial. *Scand J Gastroenterol* 1990;25: 622-30. **Grade: Ib**
- 86 Levacher S, Blaise M, Paterson D, Letoumelin PH, Lepandry C, Pourriat JL. Early administration of terlipressin plus transdermal nitroglycerin of active upper gastrointestinal hemorrhage in cirrhotic patients. *J Hepatol* 1994;21:S46 (abstract). **Grade: Ib**
- 87 Desaint B, Florent C, Levy VG. A randomised trial of triglycyl-lysine vasopressin versus lysine vasopressin in active cirrhotic variceal hemorrhage. In: Lebrec D, Blei AT, eds. *Vasopressin analogs and portal hypertension*. Paris: John Libbey Eurotext, 1987:155-7. **Grade: Ib**
- 88 Chiu WK, Sheen IS, Liaw YR. A controlled study of glypressin versus vasopressin in the control of bleeding from esophageal varices. *J Gastroenterol Hepatol* 1990;5: 549-53. **Grade: Ib**
- 89 Lee YF, Tsay YT, Laid KH, et al. A randomised controlled study of triglycyl-vasopressin and vasopressin plus nitroglycerin in the control of acute esophageal variceal hemorrhage. *Chin J Gastroenterol* 1988;5:131-8. **Grade: Ib**
- 90 D'Amico G, Traina M, Vizzini G, et al. Terlipressin or vasopressin plus transdermal nitroglycerin in a treatment strategy for digestive bleeding in cirrhosis. A randomized clinical trial. *J Hepatol* 1994;20:206-12. **Grade: Ib**
- 91 Silvain C, Carpenterier S, Sautereau D, et al. Terlipressin plus transdermal nitroglycerin vs octreotide in the control of acute bleeding from esophageal varices: a multicenter randomized trial. *Hepatology* 1993;18:61-5. **Grade: Ib**
- 92 Walker S, Kreichgauer HP, Bode JC. Terlipressin vs somatostatin in bleeding esophageal varices: a controlled double blind study. *Hepatology* 1992;15:1023-30. **Grade: Ib**
- 93 Variceal Bleeding Study Group. Hospitals Clínic (Barcelona), Germans Trias (Badalona), Gregorio Marañon (Madrid), Ramón y Cajal (Madrid). Double blind comparison of somatostatin infusion vs glypressin injection in the treatment of acute variceal hemorrhage in patients with cirrhosis. *J Hepatol* 1993;18(suppl 1):S37 (abstract). **Grade: Ib**
- 94 Colin R, Giuli N, Czernichow P, Ducrotte P, Lerebours E. Prospective comparison of glypressin, tamponade and their association in the treatment of bleeding esophageal. In: Lebrec D, Blei AT, eds. *Vasopressin analogs and portal hypertension*. Paris: John Libbey Eurotext, 1987:149-53. **Grade: IV**
- 95 Fort E, Sautereau D, Silvaine C, Ingrand P, Pillegard B, Beauchant M. A randomised trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute vasopressin hemorrhage. *Hepatology* 1990;11:678-81. **Grade: Ib**
- 96 Bosch J, Kravetz D, Rodes J. Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver. Comparison with vasopressin. *Gastroenterology* 1981;80:518-25. **Grade: Ib**
- 97 Burroughs AK, McCormick PA, Hughes MD, Sprengers D, D'Heygere F, McIntyre N. Randomized, double-blind, placebo-controlled trial of somatostatin for variceal bleeding: Emergency control and prevention of early variceal rebleeding. *Gastroenterology* 1990;99:1388-95. **Grade: Ib**
- 98 Valenzuela JE, Schubert T, Fogel MR, et al. A multicenter, randomized, double-blind trial of somatostatin in the management of acute hemorrhage from esophageal varices. *Hepatology* 1989;10:958-61. **Grade: Ib**
- 99 Kravetz D, Bosch J, Teres J, et al. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. *Hepatology* 1984;4:442-6. **Grade: Ib**
- 100 Jenkins SA, Baxter JN, Corbett W, et al. A prospective randomised controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal haemorrhage. *BMJ* 1985;290:275-8. **Grade: Ib**

- 101 Bagarani M, Albertini V, Anza M, et al. Effect of somatostatin in controlling bleeding from esophageal varices. *Ital J Surg Sci* 1987;17:21-6. **Grade: III**
- 102 Cardona C, Vida F, Balanzo J, Cusso X, Farre A, Guarner C. Eficacia terapéutica de la somatostatina versus vasopressina mas nitroglicerina en la hemorragia activa por varices esofagogastrica. *Gastroenterol Hepatol* 1989;12:30-4. **Grade: Ib**
- 103 Hsia HC, Lee FY, Tsai YT, et al. Comparison of somatostatin and vasopressin in the control of acute esophageal vasopressin hemorrhage. A randomised controlled study. *Chin J Gastroenterol* 1990;7:71-8. **Grade: Ib**
- 104 Saari A, Kivilaakso E, Inberg M, et al. Comparison of somatostatin and vasopressin in bleeding esophageal varices. *Am J Gastroenterol* 1990;85:804-7. **Grade: Ib**
- 105 Rodriguez-Moreno F, Santolaria F, Glez-Reimers E, et al. A randomized trial of somatostatin vs vasopressin plus nitroglycerin in the treatment of acute vasopressin bleeding. *J Hepatol* 1991;13:S162 (abstract). **Grade: Ib**
- 106 McKee R. A study of octreotide in oesophageal varices. *Digestion* 1990;45:60-5. **Grade: III**
- 107 Jaramillo JL, de la Mata M, Mino G, Costan G, Gomez-Camacho F. Somatostatin versus Sengstaken balloon tamponade for primary haemostasis of bleeding esophageal varices. *J Hepatol* 1991;12:100-5. **Grade: IIa**
- 108 Avgerinos A, Armonis A, Manolopoulos S, et al. Endoscopic sclerotherapy versus varical ligation in the long-term management of patients with cirrhosis after variceal bleeding. A prospective randomized study. *J Hepatol* 1997;26:1034-41. **Grade: Ib**
- 109 Di Febo G, Sirringa S, Vacirca M, et al. Somatostatin and urgent sclerotherapy in active esophageal variceal bleeding. *Gastroenterology* 1990;98:A583 (abstract). **Grade: Ib**
- 110 Jenkins SA, Copeland G, Kingsnorth A, Shields R. A prospective randomized controlled trial comparing somatostatin (SMS) and injection sclerotherapy in the control of acute variceal haemorrhage: an interim report. *Gut* 1992;33:F221 (abstract). **Grade: Ib**
- 111 Shields R, Jenkins SA, Baxter JN, et al. A prospective randomised controlled trial comparing the efficacy of somatostatin with injection sclerotherapy in the control of bleeding oesophageal varices. *J Hepatol* 1992;16:128-37. **Grade: Ib**
- 112 Planas R, Quer JC, Boix J, et al. A prospective randomized trial comparing somatostatin and sclerotherapy in the treatment of acute variceal bleeding. *Hepatology* 1994;20:370-5. **Grade: Ib**
- 113 Sung JJ, Chung SCS, Lai CW, Chan FKL, Leung JW, Young MY. Octreotide infusion of emergency sclerotherapy for varical hemorrhage. *Lancet* 1993;342:637-41. **Grade: Ib**
- 114 Burroughs AK. Double blind randomised clinical trial of 5 day octreotide versus placebo associated sclerotherapy for treatment failures. *Hepatology* 1996;24:901 (abstract). **Grade: Ib**
- 115 Barsoum NS, Boulous FI, Ell-Robby A, et al. Tamponade and injection sclerotherapy in the management of bleeding oesophageal varices. *Br J Surg* 1982;69:76-8. **Grade: II**
- 116 The Copenhagen Esophageal Varices Sclerotherapy Project. Sclerotherapy after first variceal hemorrhage in cirrhosis. A randomized multicenter trial. *N Engl J Med* 1984;311:1594-600. **Grade: Ib**
- 117 Paquet KJ, Feusener H. Endoscopic sclerosis and esophageal balloon tamponade in acute hemorrhage from esophagogastric varices: a prospective randomised trial. *Hepatology* 1985;5:580-3. **Grade: Ib**
- 118 Moreto M, Zaballa M, Bernal M, et al. A randomised trial of tamponade or sclerotherapy as immediate treatment for bleeding esophageal varices. *Surg Gynecol Obstet* 1988;167:331-4. **Grade: Ib**
- 119 Cello JP, Crass R, Trunkey DD. Endoscopic sclerotherapy versus esophageal transection in Child's class C patients with variceal hemorrhage. Comparison with results of portacaval shunt. Preliminary report. *Surgery* 1982;91:333-8. **Grade: Ib**
- 120 Huizinga WKJ, Angorn PA, Baker WW. Oesophageal transection versus injection sclerotherapy in the management of bleeding oesophageal varices in patients at high risk. *Surg Gynecol Obstet* 1985;160:539-46. **Grade: Ib**
- 121 Teres J, Baroni R, Bordas JM, Vias J, Pera C, Rodes J. Randomized trial of portacaval shunt, stapling transection and endoscopic sclerotherapy in uncontrolled variceal bleeding. *J Hepatol* 1987;4:159-67. **Grade: Ib**
- 122 Burroughs AK, Hamilton G, Philips A, Mezzanotte G, McIntyre N, Hobbs KIEF. A comparison of sclerotherapy with staple transection of the esophagus for the emergency control of bleeding from esophageal varices. *N Engl J Med* 1989;321:857-62. **Grade: Ib**
- 123 Cello JP, Grendell JH, Crass RA, Weber TE, Trunkey D. Endoscopic sclerotherapy versus portacaval shunt in patients with severe cirrhosis and acute variceal hemorrhage. Long term follow-up. *N Engl J Med* 1987;316:11-15. **Grade: Ib**
- 124 Steigmann G, Goff GS. Endoscopic esophageal varix ligation: Preliminary clinical experience. *Gastrointest Endosc* 1988;34:113-17. **Grade: III**
- 125 Steigmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992;326:1527-32. **Grade: Ib**
- 126 Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology* 1995;22:466-71. **Grade: Ib**
- 127 Ramond M-J, Valla D, Mosnier J-F, et al. Successful endoscopic obturation of gastric varices with butyl cyanoacrylate. *Hepatology* 1989;10:488-93. **Grade: III**
- 128 Soehendra N, Grimm H, Nam V, et al. N-Butyl-2-cyanoacrylate: a supplement to endoscopic sclerotherapy. *Endoscopy* 1987;19:221-4. **Grade: III**
- 129 Panes J, Teres J, Bosch J, Rodes J. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. *Dig Dis Sci* 1988;33:454-9. **Grade: III**
- 130 McCormick PA, Dick R, Panagou EB, Chin JK, Greenslade L, Burroughs AK. Emergency transjugular intrahepatic portosystemic stent-shunt salvage treatment for uncontrolled variceal bleeding. *Br J Surg* 1994;81:1324-7. **Grade: III**
- 131 Jalan R, John TG, Redhead DN, Finlayson NDC, Garden OJ, Hayes PC. A comparative study of the transjugular intrahepatic portosystemic stent-shunt (TIPSS) and oesophageal transection in uncontrolled variceal haemorrhage. *Am J Gastroenterol* 1995;11:1932-6. **Grade: IIa**
- 132 Sanyal AJ, Freedman AM, Luketic VA, et al. Transjugular intrahepatic portosystemic stent shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology* 1996;111:138-46. **Grade: II**
- 133 Rosemurgy AS, Goode SE, Zwiebel BR, et al. A prospective trial of transjugular intrahepatic portasystemic stent shunt versus small-diameter prosthetic H-graft portal caval shunts in the treatment of bleeding varices. *Ann Surg* 1996;224:378-86. **Grade: Ib**
- 134 Gatta A, Merkel C, Sacerdoti D, et al. Nadolol for prevention of variceal rebleeding in cirrhosis: a controlled clinical trial. *Digestion* 1987;37:22-8. **Grade: Ib**
- 135 Queuinet AM, Czernichow P, Lerebours E, Ducrotte P, Tranvouez JL, Colin R. Etude contrôlée due propranolol dans la prévention des récidives hémorragiques chez les patients cirrhotiques. *Gastroenterol Clin Biol* 1987;11:41-7. **Grade: Ib**
- 136 Sheen IS, Chen TY, Liaw YF. Randomized controlled study of propranolol for the prevention of recurrent esophageal varices bleeding in patients with cirrhosis. *Liver* 1989;9:1-5. **Grade: Ib**
- 137 Rossi V, Cales P, Pascal B, et al. Prevention of recurrent variceal bleeding in alcoholic cirrhotic patients: a prospective controlled trial of propranolol and sclerotherapy. *J Hepatol* 1991;12:283-9. **Grade: Ib**
- 138 Cerbelaud P, Lavignolle A, Perrin D, et al. Propranolol et prévention des récidives de rupture de varice oesophagienne du cirrhotique. *Gastroenterol Clin Biol* 1986;18:A10. **Grade: III**
- 139 Terblanche J, Bornman PC, Kahn D, Jonker MA, Campbell JAH, Kirsch R. Failure of repeated injection sclerotherapy to improve long term survival after oesophageal variceal bleeding. A five-year prospective controlled clinical trial. *Lancet* 1983;2:1328-32. **Grade: Ib**
- 140 Westaby D, MacDougall R, William R. Improved survival following sclerotherapy for esophageal varices: final analysis of a controlled trial. *Hepatology* 1985;5:827-30. **Grade: Ib**
- 141 Korula J, Balart LA, Radvan G, et al. A prospective randomized controlled trial of chronic esophageal variceal sclerotherapy. *Hepatology* 1985;5:584-9. **Grade: Ib**
- 142 Burroughs AK, McCormick DA, Sirringa S, Phillips A, McIntyre N. Prospective randomized trial of long term sclerotherapy for variceal rebleeding, using the same protocol to treat rebleeding in all patients. Final report. *J Hepatol* 1989;9(suppl)S12. **Grade: Ib**
- 143 Gregory PB. Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease. A randomized, single-blind, multicenter clinical trial. *Ann Intern Med* 1991;115:73. **Grade: Ib**

- 144 Alexandrino PT, Martin Alves M, Pinto Correia J. Propranolol or endoscopic sclerotherapy in the prevention of recurrence of variceal bleeding. A prospective, randomized clinical trial. *J Hepatol* 1988;7:175-85. **Grade: Ib**
- 145 Dollet JM, Champigneulle B, Patris A, Bigard MA, Gaucher P. Sclerotherapy endoscopique contre propranolol après hémorragie par rupture de varices œsophagiennes chez le cirrhotique. *Gastric Enterol Clin Biol* 1988;12:234-7. **Grade: Ib**
- 146 Westaby D, Polson RJ, Gimson AES, Hayes PC, Hayllar K, Williams R. A controlled trial of oral propranolol compared with injection sclerotherapy for the long-term management of variceal bleeding. *Hepatology* 1990;11:353-9. **Grade: Ib**
- 147 Martin T, Taupignon A, Lavignolle A, Perrin D, LeBodic L. Prévention des récidives hémorragiques chez des malades atteints de cirrhose. Résultats d'une étude contrôlée comparant propranolol et sclérose endoscopique. *Gastroenterol Clin Biol* 1991;15:833-7. **Grade: Ib**
- 148 Dasarathy S, Dwivedi M, Bhargava DK, Sundaram KR, Ramachandran K. A prospective randomized trial comparing repeated endoscopic sclerotherapy and propranolol in decompensated (Child class B and C) cirrhotic patients. *Hepatology* 1992;16:889-94. **Grade: Ib**
- 149 Liu JD, Jeng YS, Chen PH, Siauw CP, Ko FT, Lin KY. Endoscopic injection sclerotherapy and propranolol in the prevention of recurrent variceal bleeding. 1990 *Gastroenterology World Congress Abstract Book*; GP 1181. **Grade: IIa**
- 150 Teres J, Bosch J, Garcia Pagan JC, Feu F, Cirera I, Rodes J. Propranolol vs sclerotherapy in the prevention of variceal rebleeding: a randomised controlled trial. *Gastroenterology* 1993;105:1508-14. **Grade: Ib**
- 151 Gimson AES, Ramage JK, Panos MZ, et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. *Lancet* 1993;342:391-4. **Grade: Ib**
- 152 Laine L, El-Newehi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993;119:1-7. **Grade: Ib**
- 153 Hou MC, Lin HC, Kuo BIT, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: A prospective randomized trial. *Hepatology* 1995;21:1517-22. **Grade: Ib**
- 154 Hashizume M, Ohta M, Ueno K, Tanoue K, Kitano S, Sugimachi K. Endoscopic ligation of oesophageal varices compared with injection sclerotherapy: A prospective randomised trial. *Gastrointest Endosc* 1993;39:123-6. **Grade: Ib**
- 155 Laine L. Ligation: Endoscopic treatment of choice for patients with bleeding oesophageal varices. *Hepatology* 1995;22:661-5. **Grade: IV**
- 156 Rossle M, Deibert P, Haag K, et al. Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. *Lancet* 1997;349:1043-9. **Grade: Ib**
- 157 Sanyal AJ, Freedman AM, Luketic VA, et al. Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage: A randomized, controlled trial. *Ann Intern Med* 1997;126:849-57. **Grade: Ib**
- 158 Cello JP, Ring EJ, Olcott EW, et al. Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portosystemic shunt after initial sclerotherapy in patients with acute variceal hemorrhage: A randomized, controlled trial. *Ann Intern Med* 1997;126:858-65. **Grade: Ib**
- 159 Cabrera J, Maynar M, Granados R, et al. Transjugular intrahepatic portosystemic shunt (TIPS) versus sclerotherapy in the elective treatment of variceal hemorrhage. *Gastroenterology* 1996;110:832-9. **Grade: Ib**
- 160 Sauer P, Theilmann L, Stremmel W, Benz C, Richter GM, Stiehl A. Transjugular intrahepatic portosystemic stent shunt versus sclerotherapy plus propranolol for variceal rebleeding. *Gastroenterology* 1997;113:1623-31. **Grade: Ib**
- 161 Merli M, Salerno F, Riggio O, et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: a randomised multicenter trial. Gruppo Italiano Studio TIPS (G.I.S.T.) *Hepatology* 1998;27:48-53. **Grade: Ib**
- 162 Garcia-Villareal L, Martinez-Lagares F, Sierra A, et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage. *Hepatology* 1999;29:27-32. **Grade: Ib**
- 163 Jalan R, Forrest EH, Stanley AJ, et al. A randomised trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from oesophageal varices. *Hepatology* 1997;26:1115-22. **Grade: Ib**
- 164 Garcia-Villareal L, Martinez-Lagares F, Sierra A, et al. TIPS vs sclerotherapy for the prevention of variceal rebleeding. Preliminary results of a randomised study. *Hepatology* 1996;24:208A (abstract). **Grade: Ib**
- 164a Papathodoridis GV, Goulis J, Leandro G, et al. Transjugular intrahepatic protosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding. *Hepatology* 1999;30:612-22. **Grade: Ib**
- 164b Russo MW, Zack SL, Sandler RS, Brown RS jr. Cost-effectiveness analysis of transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic therapy for prevention of esophageal variceal bleeding. *Hepatology* 2000;31:358-63. **Grade: Ib**
- 165 Jackson FC, Perrin EB, Felix RW, Smith AG. A clinical investigation of the portacaval shunt: survival analysis of the therapeutica operation. *Ann Surg* 1971;174:672-701. **Grade: III**
- 166 Resnick RH, Iber FL, Ishiara A, Chalmers TC, Zimmermann H, The Boston Inter-Hospital Liver Group. A controlled study of the therapeutic portacaval shunt. *Gastroenterology* 1974;67:843-57. **Grade: Ib**
- 167 Rueff B, Prandi D, Sicot J, et al. A controlled study of therapeutic portacaval shunt in alcoholic cirrhosis. *Lancet* 1976;2:655-9. **Grade: Ib**
- 168 Reynolds TB, Donovan AJ, Mikkelsen WP, Redeker AJ, Turril FL, Weiner JM. Results of a 12 year randomized trial of portacaval shunt in patients with alcoholic liver disease and bleeding varices. *Gastroenterology* 1981;80:1005-11. **Grade: Ib**
- 169 Reichle FA, Fahmy WF, Golsorkhi M. Prospective comparative clinical trial with distal splenorenal and mesocaval shunts. *Am J Surg* 1979;137:13-21. **Grade: Ib**
- 170 Fisher JE, Bower RH, Atanian S, Welling R. Comparison of distal and proximal splenorenal shunts. *Ann Surg* 1981;194:531-44. **Grade: IIa**
- 171 Langer B, Taylor R, Mackenzie DR. Further report of prospective randomized trial comparing distal splenorenal shunt with end-to-side portacaval shunt. *Gastroenterology* 1985;88:424-9. **Grade: Ib**
- 172 Millikan WJ, Warren WD, Henderson JM, et al. The Emory prospective randomized trial: selective versus non-selective shunt to control variceal bleeding. *Ann Surg* 1985;201:712-21. **Grade: Ib**
- 173 Harley HAJ, Moergan T, Redeker AG, et al. Results of a randomized trial of end-to-side portacaval shunt and distal splenorenal shunt in alcoholic liver disease and variceal bleeding. *Gastroenterology* 1986;91:802-9. **Grade: Ib**
- 174 Grace ND, Conn HO, Resnick RH, et al. Distal splenorenal vs portal-systemic shunts after hemorrhage from varices: a randomized controlled trial. *Hepatology* 1988;8:1475-81. **Grade: Ib**
- 175 Rijkers LF, Burnett DA, Valentine GD, Buchi KN, Cormier RA. Shunt surgery versus endoscopic sclerotherapy for long term treatment of variceal bleeding. Early results of a randomized trial. *Ann Surg* 1987;206:261-9. **Grade: Ib**
- 176 Teres J, Bordas JM, Bravo D, et al. Sclerotherapy vs distal splenorenal shunt in the elective treatment of variceal hemorrhage: a randomized controlled trial. *Hepatology* 1987;7:430-6. **Grade: Ib**
- 177 Henderson JM, Kutner MH, Millikan WJ, et al. Endoscopic variceal sclerosis compared with distal splenorenal shunt to prevent recurrent variceal bleeding in cirrhosis. A prospective randomized controlled trial. *Ann Intern Med* 1990;112:262-9. **Grade: Ib**
- 178 Spina GP, Santambrogio R, Opocher E, et al. Distal splenorenal shunt versus endoscopic sclerotherapy in the prevention of variceal rebleeding. First stage of a randomized, controlled trial. *Ann Surg* 1990;211:178-86. **Grade: Ib**
- 179 Korula J, Yellin A, Yamada S, Weiner J, Cohen H, Reynolds TB. A prospective randomized controlled comparison of chronic endoscopic variceal sclerotherapy and portosystemic shunt for variceal hemorrhage in Child Class A cirrhotics. *Hepatology* 1988;8:1242 (abstract). **Grade: Ib**
- 180 Planas R, Boix J, Broggi M, et al. Portacaval shunt versus endoscopic sclerotherapy in the elective treatment of variceal hemorrhage. *Gastroenterology* 1991;100:1078-86. **Grade: Ib**
- 181 Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-9. **Grade: III**

- 182 Merican I, Burroughs AK. Gastric varices. *Eur J Gastroenterol Hepatol* 1992;4:511-20. **Grade: IV**
- 183 Gimson AES, Westaby D, Williams R. Endoscopic sclerotherapy in the management of gastric variceal haemorrhage. *J Hepatol* 1991;13:274-8. **Grade: IIa**
- 184 Sarin SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven year experience. *Gastrointest Endosc* 1997;46:8-14. **Grade: III**
- 185 Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. *Gastrointest Endosc* 1986;32:264-8. **Grade: III**
- 186 Oho K, Iwao T, Sumino M, Toyonaga A, Tanikawa K. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a non randomized study. *Endoscopy* 1995;27:349-54. **Grade: IIa**
- 187 Williams SGJ, Peters RA, Westaby D. Thrombin—an effective treatment for gastric variceal haemorrhage. *Gut* 1994;35:1287-9. **Grade: III**
- 188 Minocha A, Richards RJ. Sengstaken-Blakemore tube for control of massive bleeding from gastric varices in hiatus hernia. *J Clin Gastroenterol* 1992;14:36-8. **Grade: III**
- 189 Harada T, Yoshida T, Shigemitsu T, Takeo Y, Tada M, Okita K. Therapeutic results of endoscopic variceal ligation for acute bleeding of oesophageal and gastric varices. *J Gastroenterol Hepatol* 1997;12:331-5. **Grade: III**
- 190 Takeuchi M, Nakai Y, Syu A, Okamoto E, Fujimoto J. Endoscopic ligation of gastric varices. *Lancet* 1996;348:1038. **Grade: III**
- 191 Greig JD, Garden OJ, Anderson JR, Carter DC. Management of gastric variceal haemorrhage. *Br J Surg* 1990;77:297-9. **Grade: IV**
- 192 Riemschneider T, Bermel RE, Hirner A. Results from devascularisation of esophago-gastric junction after recurrent bleeding of esophageal and gastric varices. *Zentralb Chir* 1994;119:291-7. **Grade: III**
- 193 Thomas PG, D'Cruz A J. Distal splenorenal shunting for bleeding gastric varices. *Br J Surg* 1994;81:241-4. **Grade: III**
- 194 Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. *J Gastroenterol Hepatol* 1996;11:51-8. **Grade: IIb**
- 195 Koito K, Namieno T, Nagakawa T, Morita K. Balloon-occluded retrograde transvenous obliteration for gastric varices with gastrorenal and gastrocaval collaterals. *Am J Roentgenol* 1996;167:1317-20. **Grade: IIb**
- 196 Kuradusenge P, Rousseau H, Vinel J-P, et al. Hemorrhage from ruptured gastric varices: treatment with transjugular intrahepatic portosystemic stent shunts. *Gastroenterol Clin Biol* 1993;17:431-4. **Grade: III**
- 197 Stanley AJ, Jalan R, Ireland HM, Redhead DN, Bouchier IAD, Hayes PC. A comparison between gastric and oesophageal variceal haemorrhage treated with transjugular intrahepatic portosystemic stent shunt (TIPSS). *Aliment Pharmacol Ther* 1997;11:171-6. **Grade: IIa**
- 198 Bleichner G, Boulanger R, Squara P, et al. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. *Br J Surg* 1986;73:724-6.
- 199 Pauwels A, Chami N, Guivarch P, et al. Facteurs prédictifs des infections survenues au décours des hémorragies digestives hautes (HDH) du cirrhotique (abstract). *Gastroenterol Clin Biol* 1990;14:A219.
- 200 Bernard B, Cadrel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology* 1995;108:1828-34.
- 201 Gouliis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998;27:1207-12.
- 202 Rimola A, Bory F, Teres J, et al. Oral, nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. *Hepatology* 1985;5:463-7.
- 203 Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal haemorrhage. *Gastroenterology* 1992;103:1267-72.
- 204 Blaise M, Pateron D, Trinchet JC P, et al. Systemic antibiotic therapy prevents bacterial infections in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1994;20:34-8.
- 205 Pauwels A, Mostefa-Kara N, Debenes B, Degoutte E, Florent C, Levy VG. Antimicrobial prophylaxis after gastrointestinal hemorrhage for cirrhotic patients with a high risk of infection. *Hepatology* 1996;24:802-6.
- 206 Hsieh WJ, Lin HC, Hwang SJ, et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. *Am J Gastroenterol* 1998;93:962-6.
- 207 Zacharof AK, Petrogiannopoulos C, Flevaris C, Deliousis A, Poulikakos J. Ciprofloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage (abstract). *J Hepatol* 1997;26(suppl 1):101.
- 208 Bernard B, Grangé J, Khac EN, Amiot X, Opolon P, Poinard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: A meta-analysis. *Hepatology* 1999;29:1655-61.