ANNALS OF GASTROENTEROLOGY 2001, 14(3):178-186

Optimal treatment in acute variceal bleeding

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SUMMARY

Different treatment strategies have been used to control variceal haemorrhage including drugs, oesophageal tambonade, endoscopie sclerotherapy or ligation, TIPS, and surgery. Optimal therapy should stop bleeding and prevent early rebleeding. The initial resuscitation of patients is as important as the other specific measures to promote haemostasis. Balloon tambonade is a highly effective treatment to achieve a temporary control of bleeding but it carries a very high risk of complications. Pharmacologie treatment has the theoretical advantage of allowing specific therapy without requiring any complicated equipment and experienced personnel. Drugs currently used in the treatment include vasopressin, terlipressin and somatostatin or its analogues octreotide and vapreotide. In clinical studies somatostatin was more effective than vasopressin and as effective as terlipressin but with improved safety profile. Endoscopie treatments (sclerotherapy and ligation) are highly effective in achieving haemostasis but they are largely depended on the experience of the endoscopist. The association of endoscopie with pharmacologie therapy (preferably somatostatin), used as soon as the diagnosis is suspected (before the endoscopy) and continued for five days, currently appears to be the best approach to treatment. TIPS is indicated in patients in whom bleeding cannot be controlled or recurs after two sessions of endoscopie treatment.

Keywords: Portal hypertension, bleeding oesophageal varices, cirrhosis, sclerotherapy, lipation, vasoactive drugs.

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Variceal bleeding in cirrhotics is a common and serious complication of portal hypertension. Despite the advances in therapy, the mortality following the index haemorrhage has commonly been as high as 50%, with a 30% hospital mortality in subsequent bleeds. The severity of liver disease is accepted as the main risk factor for both early rebleeding and short-term survival. Other risks factors include active bleeding (spurting or oozing) at emergency endoscopy, presence of infection or renal dysfunction, presence of cardio respiratory disease and increased portal pressure (HVPG > 16 mmHg).[1]

The optimal management of patients with variceal bleeding requires a multidisciplinary approach by a team that includes endoscopists, interventional radiologists and surgeons. Goals in the management of active bleeding should be hemodynamic resuscitation, control of bleeding and prevention of complications associated with bleeding. The aim of this review is to provide an updated, practical strategy for the general management of cirrhotics patients with variceal haemorrhage.

RESUSCITATIVE MEASURES IN ACUTE VARICEAL HAEMORRHAGE

The initial resuscitation of patients with acute variceal haemorrhage is as important as the other specific measures to promote haemostasis. Haemodynamic resuscitation requires administration of blood products and crystalloids. Care must be taken to avoid over-transfusion, because rebound portal hypertension can lead to early rebleeding. Blood should be replaced to a modest target hematocrit at the level of 25-30% and the right atrial pressure at 4 to 8 mmHg.[2]

Clotting factors often need to be determined as well. Large volume transfusions may sometimes lead to thrombocytopenia and impaired haemostasis with prolongation of the prothrombin and partial thromboplastin times.[3] These complications of massive transfusion are related to multiple factors, including disseminated intra-

vascular coagulation and hemodilution.[4] A practical approach is to give 2 units of FFP after 4 units of blood when the PT is more than 20 seconds. Platelet transfusions are reserved for counts below 50,000/mL in an actively bleeding patient.

Massive transfusions, which may be necessary in some patients, may also result in other significant complications such as hypocalcemia, hypothermia and pulmonary microembolism. Thus the use of filters should be considered for large volume transfusions. However rapid transfusions cannot be administered with these, limiting their application.

Complications related to bleeding or its treatment can substantially increase the risk of death in each bleeding episode.[5] Lung aspiration of gastric contents and blood is a significant risk factor, especially for the encephalopathic patients and those with massive hematemesis. Patients with this particular risk need to be considered for endotracheal intubation before endoscopy or other invasive measures.[6]

Bacterial infections occur in up to 70% of cirrhotic patients with variceal bleeding[1]. Recently it has been shown[8,9] that the presence of bacterial infection on admission is an independent prognostic factor of failure to control bleeding or early rebleeding. Moreover, it was found that antibiotic prophylaxis significantly increases the mean survival rate and the percentage of patients free of infection. Therefore the use of antibiotic prophylaxis in the setting of acute variceal haemorrhage is mandatory, irrespectively of the presence of sepsis or not. Antibiotics that have been used are oral or IV quinolones and IV cephalosporins. Although the best possible regimen is yet to be defined, recently it was suggested that the antibiotic of choice should be norfloxacin administered orally at a dose of 400 mgr twice a day for 7 days.[10] In most cases this is possible by mouth or through a nasogastric tube. Otherwise it should be given intravenously.

Recently it was suggested[11] (figure 1) that the early HVPG measurement in patients with acute bleeding, offers significant prognostic information regarding control of bleeding and survival. In this study an HVPG greater than 20 mmHg, measured within 48 hours of admission, was associated with a significantly higher risk of failure to control the acute haemorrhage or of experiencing early rebleeding. Additionally, pressures above 20 mmHg, was related to a higher one-year mortality (63 vs. 20%). The results of this and others previously published studies,[12,13] suggest that the HVPG monitoring should be used early in the course of variceal bleeding as its height may help to select patients who will require more aggressive treatment and are possibly transplant candidates.

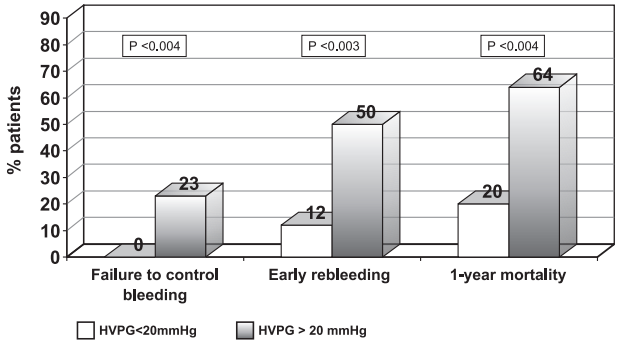

Figure 1. Summary of the results of the study (11) evaluating the outcome of patients with variceal haemorrhage according to HVPG on admission.

DRUG THERAPY IN ACUTE VARICEAL BLEEDING

Pharmacological treatment is aimed at arresting hemorrhage by decreasing pressure and blood flow within the oesophageal varices, thus allowing haemostasis at the bleeding point. From a theoretical point of view, the optimal drug treatment should be safe, effective and easy to administer, not only in the emergency room but also while the patient is being transferred to the hospital. Two major categories of drugs have been used in the control of acute variceal bleeding. Vasopressin or its analogues, alone or in combination with nitroglycerine, and somatostatin or its analogues.

• *Vasopressin*

Vasopressin therapy directly constricts mesenteric arterioles and decreases portal inflow, thus decreasing portal pressure and controlling as many as 60% to 75% of variceal bleeding episodes. However, it does not increase the survival rate and may actually increase the mortality rate because of the vasoconstrictive effects on other organs (e.g., heart, intestine).[14] Trials comparing sclerotherapy with vasopressin[15,16,17] have shown no significant differences in the control of bleeding and survival except in one study[18] where rebleeding was significantly lower in patients treated with sclerotherapy.

• *Vasopressin with nitroglycerine*

Nitroglycerine given concomitantly enhances the effect of vasopressin on portal pressure and reduces cardi-

ovascular side-effects; a meta-analysis[19] of three randomised controlled trials including 176 patients has shown that this combination is better than vasopressin alone for controlling acute bleeding.

• *Terlipressin (Glypressin) with or without nitroglycerine*

This synthetic vasopressin analogue has an immediate systemic vasoconstrictor action. After intravenous administration it is slowly converted to vasopressin by enzymatic cleavage. Blood levels are low because of the slow release of the active agent, thus side effects are less frequent.

Its efficacy has been assessed favourably against placebo in three controlled trials.[20-22] In the last of them (figure 2), in which terlipressin together with a nitrate patch was administered at a pre-hospital stage, a significant difference in favour of terlipressin regarding control of bleeding and mortality was observed, but only in child C class patients. However, the results of this trial have been criticised,[23] since despite the significant differences between the two groups regarding control of bleeding and mortality, the mean blood products units transfused during the study were similar.

Three randomised trials[20,24,25] compared the efficacy of terlipressin against vasopressin alone and two[26,27] in combination with nitroglycerine. The results of these trials suggested that the administration of terlipressin is superior to vasopressin alone in the control of bleeding, but equally effective when the vasopressin is combined with nitroglycerine. Two[28,29] trials compared its efficacy with balloon tambonade and three trials[30-32] with somatostatin and found it to be equally effective. However in the last of them the incidence of side effects was significantly higher for terlipressin compared to somatostatin. Moreover terlipressin is contraindicated in patients with a history of cardiovascular disease such as myocardial infraction, heart failure, atrioventricular block and arterial hypertension.

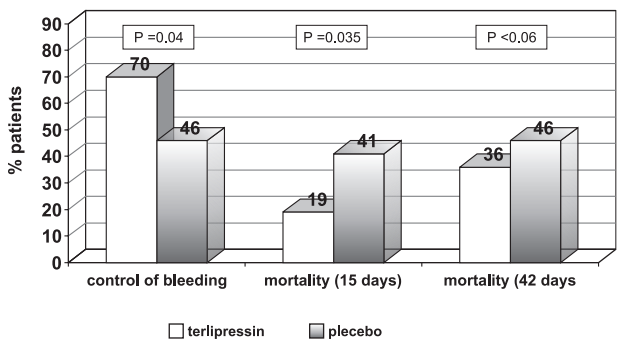

Figure 2. Summary of the results of the study (22) evaluating terlipressin in cirrhotic patients with upper gastrointestinal bleeding. The trial drug and initial resuscitative methods were administered within 60min and endoscopy and sclerotherapy were performed simultaneously within 24 hours of inclusion.

In a recently published multicenter study[33] with 219 patients, terlipressin was compared with sclerotherapy. Failure to control bleeding or early rebleeding (within 5 days) was 37% with terlipressin and 32% with sclerotherapy. No significant differences were observed in mortality, transfusion requirements and need for alternative treatments. Moreover terlipressin injections were associated with less frequent side effects than sclerotherapy. Therefore, terlipressin was found to be equally effective with sclerotherapy in acute variceal bleeding and the authors suggest that terlipressin may represent a first line treatment, especially in hospitals where a skilled endoscopist is not available 24 hours a day.

• *Somatostatin*

Somatostatin is a natural peptide that was introduced in the treatment of acute variceal haemorrhage because of its capacity to reduce splanchnic blood flow and portal and oesophageal pressure without the adverse effects of vasopressin on systemic circulation. Indeed the results of two studies showed that HVPG[34] and intravariceal pressure[35] decreased significantly after 30min continuous infusion of 250 μgr/h SMS or bolus injection of 250 μgr SMS respectively. Furthermore the decreased in HVPG caused by 500 μgr/h infusion rate (unlike the 250 μgr/h) was also associated with a marked and significant decrease in azygous blood flow.

• *Somatostatin vs Placebo*

Three double-blind, placebo controlled trials[36-38] have been published with 84, 120 and 94 patients respectively. None of them found a beneficial effect on survival and only the largest (second one) in the control of bleeding. Indeed, in the largest and most well designed[37] a 5 days continuous administration of somatostatin (250 μgr/h) was associated with a significant decrease in bleeding control failure (36% vs 59%, p=0.036) and transfusion requirements. The unusually high placebo responses rates observed in the others two studies[36,38] (83% - the highest reported in the literature - and 70% respectively) may explain their negative results. Furthermore, in contrast with the 120h continuous administration in the Burroughs trial, SMS was administered for a shorter period in the others studies (only 30 h and 24 h respectively).

• *Somatostatin vs vasopressin*

Two metanalytic studies[39,40] of the seven randomized controlled studies (349 patients in total) comparing somatostatin with vasopressin alone or in combination with nitroglycerine, showed an important reduction in failure to control bleeding with somatostatin but without any difference in mortality. In all the trials, the median treatment-related complications was significantly higher with vasopressin (46% vs 6.5%).

• *Somatostatin vs balloon tambonade*

Somatostatin has been compared to balloon tambonade in two trials.[41,42] No differences were found in the control of bleeding, early rebleeding and mortality. However the use of the balloon tambonade was associated with a significantly higher complication rate. Thus its use nowadays should be restricted to only the initial control of a massive and persistent (despite other conservative treatments) variceal bleeding episode. It should be used only by experienced teams, for a period of time not exceeding 24h, and must always be followed by more definitive therapy.[43]

• *Somatostatin vs endoscopic sclerotherapy*

There are five trials[44-48] comparing somatostatin with sclerotherapy. No significant differences were found in failure to control bleeding, rebleeding and survival. Complications were significantly less frequent and severe with somatostatin.

• *Somatostatin analogues: octreotide and vapreotide*

Octreotide is a cyclic synthetic octapeptide analogue of somatostatin. It has longer half-life than natural somatostatin and can be administered subcutaneously. A recent meta-analysis[49] suggested that octreotide is favoured over vasopressin/terlipressin for both efficacy and safety in patients with acute oesophageal variceal bleeding. It was also found that the use of octreotide is an effective adjunctive therapy after initial variceal sclerotherapy or ligation. No clear benefit was found in the use of octreotide alone vs immediate sclerotherapy for the control of bleeding, early rebleeding and survival.

In another study[50] octreotide was directly compared with somatostatin after initial haemostasis with sclerotherapy. Although both drugs were found to be equally effective in the control of bleeding, a significantly higher transfusion requirement was observed in patients receiving octreotide.

It has been shown[51] that octreotide produces a sharp decrease in portal pressure and azygos blood flow. However, it appears that the portal hemodynamic effects are short – lived and cannot be reproduced by either a continuous infusion of octreotide or repeated boluses of the drug administered intravenously.[52] These findings may perhaps explain the different effects achieved with octreotide infusions in acute variceal bleeding.

ENDOSCOPIC TREATMENT OF ACUTE VARICEAL BLEEDING

• *Sclerotherapy*

During the last 20 years endoscopic injection sclerotherapy has become the method of choice in the control of acute variceal bleeding and in the prevention of early rebleeding. A variety of techniques and sclerosants have been used. Sclerosants include ethanolamine (5%), sodium tetradecyl sulfate (3%), polidocanol (1%), sodium morrhuate (5%) and ethanol. Although a number of comparative studies have been published, they do not allow conclusions about the most effective sclerosant, as most of these agents have been documented to be effective in clinical trials.[53-59] The intravariceal injection of the sclerosant seems to be more effective and safe than the paravariceal. In addition the eradication of the varices may be achieved with fewer treatment sessions. However 35-45% of the injections that are meant to be intravariceal are actually paravariceal.[60]

Endoscopic sclerotherapy has been shown to be highly effective both in controlling active haemorrhage and in preventing early rebleeding. It has become the gold standard in the management of acute variceal haemorrhage, as it stops bleeding from varices in 80-100% of the patients.[61] A meta analysis of five studies[62] comparing sclerotherapy with sham, balloon tambonade and/or vasopressin in patients with documented active variceal bleeding revealed significant benefits of sclerotherapy in terms of cessation of acute bleeding, rebleeding and mortality. The best evidence for the value of sclerotherapy was observed in a recently published study.[63] In this trial sclerotherapy compared to sham therapy, stopped haemorrhage from active bleeding varices (91 vs 60%, $p<0.001$) and significantly increased hospital survival (75% vs 51%, $p=0.04$).

• *Ligation*

Endoscopic ligation of esophageal varices (an adaptation of the technique of band ligation for hemorrhoids) was developed with the hope of providing an alternative endoscopic treatment at least as effective as sclerother-

apy but with a lower incidence of complications.

According to a recent meta analysis, sclerotherapy and ligation appear to be equally effective in the emergency situation.[64] There is only one randomised controlled trial[65] specifically designed to compare sclerotherapy with variceal ligation for the control of an active bleeding episode. In this study only patients with actively bleeding varices were included and a significantly better primary haemostasis with ligation than with sclerotherapy (97 vs 76%) was found. In addition complications were less frequent after ligation.

However in the presence of active bleeding, ligation is sometimes very difficult to accomplish in patients with large amounts of blood in the oesophagous. The outer cylinder placed in the tip of the endoscope decreases the field of view and blood may fill the cylinder further obscuring the endoscopist's view. In this emergency case it is very difficult for the endoscopist to identify the exact bleeding site and the endoscopist performs the procedure blindly, ligating circular the varices at the distal esophagus. There is evidence (Avgerinos et al, data in publish) that with this technique the lower oesophageal sphincter pressure increases significantly and this, in turn, may reduce intravariceal pressure, further contributing (in association with the mechanical haemostasis) to the immediate control of variceal bleeding

However, in the presence of acute bleeding many experienced endoscopists prefer to perform an emergency sclerotherapy and suggest that ligation should be instituted at subsequent treatment sessions.[66]

ENDOSCOPIC SCLEROTHERAPY PLUS SOMATOSTATIN OR ITS ANALOQUES

The use of somatostatin or its analoques as adjuncts to endoscopic therapy appears to be the most promising approach in the treatment of acute variceal hemorrhage.

In one large randomized placebo-controlled trial,[67] a five-day continuous infusion of octreotide following endoscopic sclerotherapy was found to be more effective than placebo in patients with acute variceal bleeding. However the results of this study were criticized[68] later, mainly because patients randomized to the placebo group had more advanced liver disease than in the octreotide group (child C, 26 vs 47%).

In the first published placebo controlled trial[69] (Figure 3) of 5-day continuous infusion of somatostatin (SMS) as adjuvant to sclerotherapy, failure of therapy was found to be significantly lower in the group that received somatostatin (35%) than in the placebo–treated group (55%). In this study randomization to somatostatin or placebo was done immediately after admission. Somatostatin was administered in continuous infusion in a dose of 6mgr/24h plus up to eight bolus injections of 250mg. Sclerotherapy was performed within 8 hours of randomization. This study also concluded that the emergency endoscopic treatment is much easier in patients receiving somatostatin than placebo. Active bleeding at endoscopy was observed only in the 27% of patients in the somatostatin group compared to 42% in the placebo group.

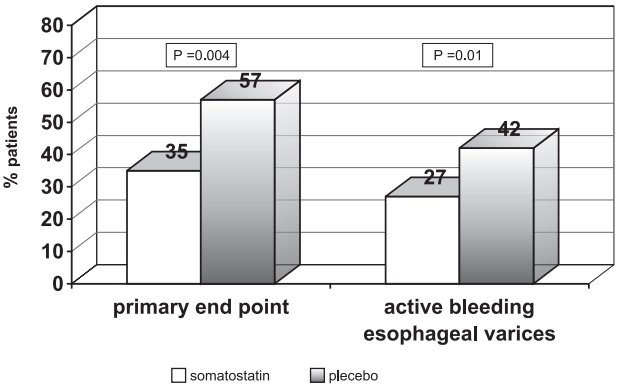

Figure 3. Summary of the results of the study (69) evaluating somatostatin (SMS) in cirrhotic patients with variceal bleeding. Primary end point defined treatment failure during the infusion period indicated by at least one of the following events: hematemesis, hemodynamic instability; transfusion of an excess of blood products; use of rescue therapy; and death.

In another similar (but non–randomized) study[70] (Figure 4), the percentage of active bleeders was further decreased when the dose of somatostatin was increased to a continuous infusion of 12 mgr/24h and boluses of 500 μgr. Furthermore, in patients undergoing sclerotherapy, the infusion of somatostatin for only 48 hours was not found as effective as the 5-day administration. This finding may perhaps explain the negative results obtained in placebo-controlled trials[36,38] where somatostatin was administered for only 24–30 hours and suggests that the drug should be administered for five days.[71] The optimal dose of somatostatin is yet to be defined although there is evidence[72] suggesting that the dose of 500 mgr/h appears much more effective than the lower dose of 250 μgr/h.

More recently, vapreotide was used as adjuvant to emergency sclerotherapy or ligation in the control of acute variceal bleeding[73] (Figure No 5). Vapreotide is a synthetic analogue of somatostatin that has a longer half-

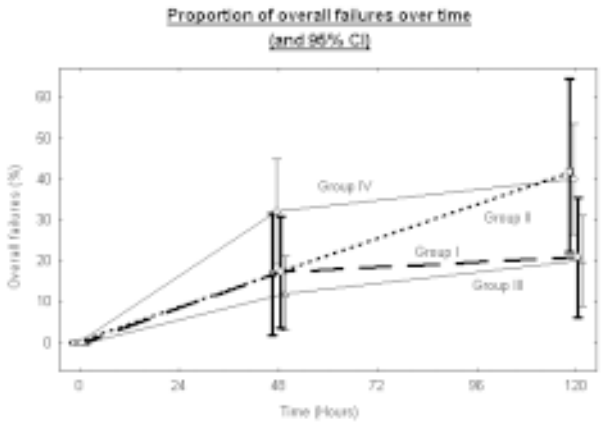

Figure 4. Summary of the results of a study (70) comparing doses and duration of somatostatin. The proportion of overall failures over time in Group I (SST-somatostatin 12mg/24h/120h), Group II (SST 6mg/24h/48h), III (SST 6mg/24h/120h) and IV (placebo). By 48h in Groups I, II and III failure rates were comparable. However, by 120h the overall failure rate n Group II tends to increase towards the corresponding figure in Group IV. At 120h, failure rates observed in Group II and IV are greater than the failure rates in Groups I and III.

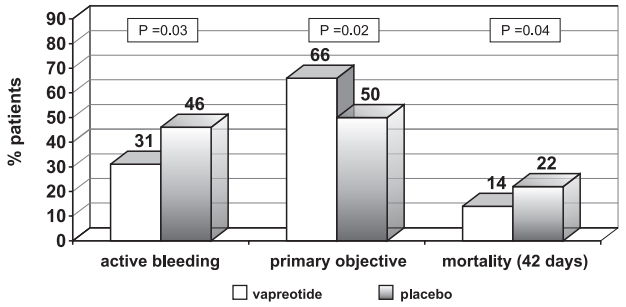

Figure 5. Summary of the results of the study (73) evaluating vapreotide in cirrhotic patients with variceal bleeding. Primary objective was to compare the two groups with respect to the combined end of control of bleeding and survival.

life than the natural hormone (30 min vs. 3 min). The patients were randomized to receive vapreotide (50 μg bolus and infusion of 50 μg/h for five days) or placebo. All patient underwent endoscopic treatment within 12 hours of initiation of drug infusion. The results of this trial confirmed the results of the first published study,[69] which suggested the combined treatment and early drug administration. Active bleeding at endoscopy (46 vs. 31%, p=0.03), primary end points defined as survival and control of bleeding during the first five days (66 vs. 50%, p=0.02) and blood transfusion requirement (p=0.04), were found to be significantly better in the vapreotide group.

TIPS - Emergency Transhepatic Portosysytemic Shunt

The introduction of the TIPS procedure has improved the management of patients who have failed endoscopic therapy. Trained Radiologists and Gastroenterologists in up to 95% of cases can successfully place the TIPS. This shunt effectively lowers portal pressure into the <12 mmHg range and thus greatly reduces the rebleeding rate.[74] The shunts are prone to clotting or stenosis, which needs to be monitored for by ultrasound or, in many cases, by repeat venography.[75] Therefore, TIPS is often an excellent bridge to liver transplantation. Unfortunately, encephalopathy is seen after TIPS, which can limit its utility in patients with poor liver function.

There are no randomised controlled trials of emergency TIPS vs. other forms of treatment. However trials[76-79] including only patients with uncontrolled bleeding (defined as continued bleeding despite two sessions of therapeutic endoscopy within a five-day period from the index bleed) showed an initial haemostasis in 90-100% and early rebleeding in less than 30% of patients.

In conclusion, TIPS seems to be an effective salvage treatment in patients with uncontrolled bleeding from oesophageal and gastric varices. Furthermore, it has been used successfully in the control of bleeding from ectopic varices[80] such as rectal, stomal and intestinal.

CONCLUSIONS AND GENERAL RECOMMENDATIONS

The initial resuscitation of patients with variceal bleeding is as important as the other specific measures. Over-transfusion must be avoided and blood should be replaced to a modest target hematocrit 25-30%. Administration of antibiotics is now recommended, whether sepsis is suspected or not. The antibiotic of choice is currently norfloxacin (400 mgr twice a day for 7 days).

Endoscopic therapy (sclerotherapy or ligation) is the gold standard in the initial management of these patients. The association with pharmacologic therapy, used as soon as diagnosis is suspected (before endoscopy) and continued for five days, currently appears to be the best approach to treatment. Among the vasoactive drugs, SST appears to be the safest. TIPS is indicated in patients in whom bleeding cannot be controlled or recurs after two sessions of endoscopic treatment.

REFERENCES

1. Burroughs AK, Patch DW. Management of variceal haemorrhage in cirrhotic patients. Gut 2001; 48:738-740.
2. Hochain P, Merle V, Tuil S, Michel P, Ducrotte P, Lerebours E, Colin R, Dao T. Transfusion for variceal bleeding in cirrhotic patients. Gut 1996; 38:154.
3. Craxi A, Camma C, Giunta M.Clinical aspects of bleeding complications in cirrhotic patients. Blood Coagul Fibrinolysis. 2000; 11 Suppl 1:S75-79.
4. Gimson AES, Vlavianos T. Resuscitative measures in acute variceal hemorrhage. Gastro End Clin N Amer 1992; 2:31-41.
5. Menon KV, Kamath PS.Managing the complications of cirrhosis. Mayo Clin Proc. 2000; 75:501-509.
6. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. J Hepatol. 2000; 32(1 Suppl):141-156.
7. Goulis J, Patch D, Burroughs AK.Bacterial infection in the pathogenesis of variceal bleeding. Lancet 1999; 353:139-142.
8. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998; 27:1207-1212.
9. Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999; 29:1655-61.
10. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol. 2000; 32:142-153.
11. Moitinho E, Escorsell A, Bandi JC, Salmeron JM, Garcia-Pagan JC, Rodes J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology 1999;117:626-631.
12. Patch D, Armonis A, Sabin C, Christopoulou K, Greenslade L, McCormick A, Dick R, Burroughs AK. Single portal pressure measurement predicts survival in cirrhotic patients with recent bleeding. Gut 1999; 44:264-269.
13. Ready JB, Robertson AD, Goff JS, Rector WG Jr. Assessment of the risk of bleeding from esophageal varices by continuous monitoring of portal pressure. Gastroenterology 1991; 100(5 Pt 1):1403-1410.
14. Imperiale TF, Teran JC, McCullough AJ. A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. Gastroenterology 1995; 109:1289-1294.
15. Soderlund C, Ihre T.Endoscopic sclerotherapy v. conservative management of bleeding oesophageal varices. A 5-year prospective controlled trial of emergency and long-term treatment. Acta Chir Scand 1985; 151:449-456.
16. Larson AW, Cohen H, Zweiban B, Chapman D, Gourdji M, Korula J, Weiner J.Acute esophageal variceal sclerotherapy. Results of a prospective randomized controlled trial. JAMA 1986; 255:497-500.
17. Westaby D, Hayes PC, Gimson AE, Polson RJ, Williams R. Controlled clinical trial of injection sclerotherapy for active variceal bleeding. Hepatology 1989; 9:274-277.
18. 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.
19. Luketic VA, Sanyal AJ. Esophageal varices. I. Clinical presentation, medical therapy and endoscopic therapy. GI Clin North Am 2000; 29:337-385.
20. 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.
21. 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; 25:622-630.
22. 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).
23. Burroughs AK, Patch D. Therapeutic benefit of vasoactive drugs for acute variceal bleeding. A real pharmacological effect, or a side-effect of definitin in trials. Hepatology 1996; 24:737-739.
24. 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. asopressin analogs and portal hypertension. Paris: John Libbey Eurotext, 1987; 155-157.
25. 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; 5:549-553.
26. 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; 5:131-138.
27. 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; 20:206-212.
28. 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; 149-153.
29. Fort E, Sautereau D, Silvaine C, Ingrand P, Pillegand B, Beauchant M. A randomised trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute vasopressin hemorrhage. Hepatology 1990; 11:678-681.
30. Silvain C, Carpentier 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; 18:61-65.
31. Walker S, Kreichgauer HP, Bode JC. Terlipressin vs somatostatin in bleeding esophageal varices: a controlled double blind study. Hepatology 1992; 15:1023-1030.
32. Feu F, Ruiz del Arbol L, Banares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. Variceal Bleeding Study Group. Gastroenterology 1996; 111:1291-1299.
33. Escorsell A, Ruiz del Arbol L, Planas R, Albillos A, Banares R, Cales P, Pateron D, Bernard B, Vinel JP, Bosch J. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. Hepatology 2000; 32:471-476.
34. Cirera I, Few F, Luca A, Garcia-Pagan JC, Fernandez M, Escorsell A, Bosch A, Rodes J: Effects of bolus injections and continuous infusions of somatostatin and placebo in patients with cirrhosis : A double blind hemodynamic investigation. Hepatology 1995; 22:106-111.
35. Avgerinos A, Armonis A, Rekoumis G, Manolakopoulos S, Argirakis G, Raptis S. The effect of somatostatin and octreotide on intravascular oesophageal variceal pressure in patients with cirrhosis. J Hepatol 1995; 22:379-380.
36. 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; 10:958-961.
37. 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; 99:1388-1395.
38. Gotzsche PC, Gjorup I, Bonnen H, Erik N, Brahe B, Becker U, Burcharth F. Somatostatin vs placebo in bleeding esophageal varices:randomized trial and meta analysis. Br Med J 1995; 310:1495-1498.
39. Imperiale TF, Teran JC, McCullough AJ.A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. Gastroenterology 1995; 109:1289-1294.
40. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: A meta-analytic review. Hepatology 1995; 22:332-354.
41. 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; 12:100-105.
42. Avgerinos A, Klonis C, Rekoumis G, Gouma P, Papadimitriou N, Raptis S. A prospective randomized trial comparing somatostatin, balloon tamponade and the combination of both methods in the management of acute variceal haemorrhage. J Hepatol 1991; 13:78-83.
43. Avgerinos A, Armonis A. Balloon tamponade technique and efficacy in variceal haemorrhage. Scand J Gastroenterol Suppl 1994; 207:11-16.
44. Di Febo G, Siringo S, Vacirca M, et al. Somatostatin and urgent sclerotherapy in active esophageal variceal bleeding. Gastroenterology 1990; 98:A583.
45. 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.
46. 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; 16:128-137.
47. 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; 20:370-375.
48. Escorsell A, Bordas JM, del Arbol LR, Jaramillo JL, Planas R, Banares R, Albillos A, Bosch J. Randomized controlled trial of sclerotherapy versus somatostatin infusion in the prevention of early rebleeding following acute variceal hemorrhage in patients with cirrhosis. Variceal Bleeding Study Group.J Hepatol 1998; 29:779-788.
49. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal variceal bleeding: a meta-analysis. Gastroenterology 2001; 120:946-954.
50. Signorelli S, Negrini F, Paris B, Bonelli M, Girola M. Sclerotherapy with or without somatostatin or octreotide in the treatment of acute variceal haemorrhage: our experience. Gastroenterology 1996; 110:A1326 (abstract).
51. Zironi G, Rossi C, Siringo S, Galaveni C, Gaiani S, Piscaglia F, Bolondi L. Short and long term hemodynamic response to octreotide in portal hypertensive patients: a double – blind, controlled study. Liver 1996; 16:225-234.
52. Escorsell A, Bandi JC, Andreu V, Moitinho E, Garcia-Pagan JC, Bosch J, Rodes J. Desensitization to the effects of intravenous Octreotide in cirrhotic patients with portal hypertension. Gastroenterology 2001; 120:161-169.
53. Bhargava DK, Singh B, Dogra R, Dasarathy S, Sharma MP. Prospective randomized comparison of sodium tetradecyl sulfate and polidocanol as variceal sclerosing agents. Am J Gastroenterol 1992; 87:182-186.
54. Jutabha R, Jensen DM, See J, Machicado G, Hirabayashi K. Randomized, controlled study of various agents for endoscopic injection sclerotherapy of bleeding canine gastric varices. Gastrointest Endosc 1995; 41:206-211.
55. Chan AC, Chung SC, Sung JY, Leung JW, Li AK. A double-blind randomized controlled trial comparing sodium tetradecyl sulphate and ethanolamine oleate in the sclerotherapy of bleeding oesophageal varices. Endoscopy 1993; 25:513-517.
56. Meirelles-Santos JO, Carvalho AF Jr, Callejas-Neto F, Magna LA, Yamanaka A, Zeitune JM, Brandalise NA, Ferraz JG. Absolute ethanol and 5% ethanolamine oleate are comparable for sclerotherapy of esophageal varices. Gastrointest Endosc 2000; 51:573-576.
57. Thakeb F, Salama Z, Salama H, Abdel Raouf T, Abdel Kader S, Abdel Hamid H. The value of combined use of

N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. Endoscopy 1995; 27:358-364.
58. Zimmer T, Rucktaschel F, Stolzel U, Liehr RM, Schuppan D, Stallmach A, Zeitz M, Weber E, Riecken EO. Endoscopic sclerotherapy with fibrin glue as compared with polidocanol to prevent early esophageal variceal rebleeding. J Hepatol 1998; 28:292-297.
59. Lux G, Retterspitz M, Stabenow-Lohbauer U, Langer M, Altendorf-Hofmann A, Bozkurt T. Treatment of bleeding esophageal varices with cyanoacrylate and polidocanol, or polidocanol alone: results of a prospective study in an unselected group of patients with cirrhosis of the liver. Endoscopy 1997; 29:241-246.
60. Waring JP, Sanowski RAQ, Pardy K et al. Does the addition of methylene blue to the sclerosant improve the accuracy of endoscopic variceal sclerotherapy? Am J Gastroenterol 1990; 85:1227 (abstract).
61. de Franchis R, Primignani M. Endoscopic treatments for portal hypertension. Baillieres Clin Gastroenterol 1997; 11:289-309.
62. Laine LA. Endoscopic treatment of acute or active variceal bleeding. In Portal Hypertnesion. Blackwell Science 2001; 156-160.
63. Hartigan PM, Gebhard RL, Gregory PB.Sclerotherapy for actively bleeding esophageal varices in male alcoholics with cirrhosis. Veterans Affairs Cooperative Variceal Sclerotherapy Group. Gastrointest Endosc 1997; 46:1-7.
64. de Franchis R, Primignani M. Endoscopic treatments for portal hypertension. Semin Liver Dis. 1999; 19:439-455.
65. Lo GH, Lai KH, Cheng JS, Lin CK, Huang JS, Hsu PI, Chiang HT. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. Hepatology 1997; 25:1101-1104.
66. Avgerinos A, Armonis A, Manolakopoulos S, Poulianos G, Rekoumis G, Sgourou A,Gouma P, Raptis S. Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding. A prospective randomized study. J Hepatol 1997; 26:1034-1041.
67. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, Hochain P, Larricq J, Gourlaouen A, Ribard D, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. N Engl J Med 1995; 333:555-560.
68. Avgerinos A. Approach to the management of bleeding esophageal varices: Role of somatostatin. Digestion 1998; 59(Suppl 1):1-22.
69. Avgerinos A, Nevens F, Raptis S, Fevery J. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. Lancet 1997; 350(9090):1495-1499.
70. Avgerinos A, Viazis N, Vlachogiannakos J, Poulianos G, Armonis A, Manolakopoulos S, Raptis S. Two different doses and duration schedules of somatostatin -14 in the treatment of patients with bleeding oesophageal varices: a non-randomised controlled study. J Hepatol 2000; 32:171-172.
71. Bosch J, Laine A, Burroughs A, Marcon N, Neevens F, Silvain C and Vinel JP. Baveno III consensus Statements: Treatment of the acute bleeding episode. In Portal Hypertension, Blackwell Science 2001; 168-169.
72. Variceal bleeding study group. A multicenter randomized controlled trial comparing different schedules of somatostatin administration in the treatment of acute variceal bleeding. Hepatology 1998; 28:770A (2432).
73. Cales P, Masliah C, Bernard B, et al. Early administration of vapreotide for variceal bleeding in patients with cirrhosis. N Engl J Med 2001; 344:23-28.
74. Rossle M, Siegerstetter V, Huber M, Ochs A. The first decade of the transjugular intrahepatic portosystemic shunt (TIPS): state of the art. Liver 1998; 18:73-89.
75. Patch D, Nikolopoulou V, McCormick A, Dick R, Armonis A, Wannamethee G, Burroughs A.Factors related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding. J Hepatol 1998; 28:454-460.
76. Gerbes AL, Gulberg V, Waggershauser T, Holl J, Reiser M. Transjugular intrahepatic portosystemic shunt (TIPS) for variceal bleeding inportal hypertension: comparison of emergency and elective interventions. Dig Dis Sci 1998; 43:2463-2469.
77. Sanyal AJ, Freedman AM, Luketic VA, Purdum PP 3rd, Shiffman ML, DeMeo J, Cole PE, Tisnado J. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. Gastroenterology 1997; 112:889-898.
78. Chau TN, Patch D, Chan YW, Nagral A, Dick R, Burroughs AK. "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998; 114:981-987.
79. Banares R, Casado M, Rodriguez-Laiz JM, Camunez F, Matilla A, Echenagusia A, Simo G, Piqueras B, Clemente G, Cos E. Urgent transjugular intrahepatic portosystemic shunt for control of acute variceal bleeding. Am J Gastroenterol 1998; 93:75-79.
80. Ryu RK, Nemcek AA Jr, Chrisman HB, Saker MB, Blei A, Omary RA, Vogelzang RL. Treatment of stomal variceal hemorrhage with TIPS: case report and review of the literature. Cardiovasc Intervent Radiol 2000; 23:301-303.