

Management of variceal bleeding: PSG guidelines 2006

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Introduction

Gastroesophageal variceal bleeding is a major complication of portal hypertension. It occurs in 25 to 35% patients having cirrhosis causing 80 to 90% bleeding episodes in these cases.¹⁻³ Variceal bleeding is associated with more substantial morbidity and mortality than other causes of gastrointestinal bleeding, as well as higher economical burden.⁴⁻⁶ Up to 30% of initial bleeding episodes are fatal and about 70% survivors will rebleed within one year.^{1,7} One-year survival rate after variceal bleeding ranges from 32 to 80 %.^{7,8}

Over the last decade, there have been numerous advances in the management of variceal bleeding. Many guidelines including UK guidelines⁹, OMGE guidelines¹⁰, Baveno IV workshop¹¹, etc., have been published to suggest the evidence based appropriate management of patients with variceal bleeding. However, all these are based

generally on information obtained from the developed countries and do not take into account the peculiar differences that may exist in the developing countries like Pakistan.

Pakistan has some unique factors like: (1) Prevalence of hepatitis and liver cirrhosis and its associated complications is on a rise, (2) Access to health care is limited, (3) Lack of diagnostic facilities like endoscopic equipment, cost of accessories and maintenance is also high, (3) Training facilities for healthcare workers are deficient, (4) Patient's attitude towards specialized care is equivocal, (5) Issues of affordability (6) Lack of more definitive therapies for cirrhotic patients including Liver Transplant and TIPS. Therefore Pakistan Society of Gastroenterology (PSG) felt the need to develop "National Guidelines for the Management of Variceal Bleeding" taking into consideration all the above issues.

Methodology

These guidelines were formulated in National Consensus Meeting held on January 7 and 8 2006, in Peshawar. During the two day meeting, the invited speakers presented review lectures with an insight of local perspectives. The panelists were asked to critically analyze the scientific data. During the meeting, a series of consensus statements, review articles and available data were discussed and agreed upon.

The available evidence was graded^{12,13} according to the criteria given in Table 1. All recommendations for clinical practice were graded^{9,14-16} according to the criteria given in Table 2. After the meeting, the final draft of Management of Variceal Bleed was sent to all the members for final review and approval. These guidelines are

Table 1. Grading of Evidence.

Grade	Description
Grade Ia	Evidence obtained from meta-analysis of randomized trials
Grade Ib	Evidence obtained from at least one randomized trial
Grade IIa	Evidence obtained from at least one well designed controlled study without randomization
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

Table 2. Grading of Recommendations for Clinical Practice.

Grade	Strength of evidence to guide clinical practice
A.	Supported by two or more level I studies without conflicting evidence from other level I studies AI: The Committee recommends this element of care strongly AII: The Committee considers this element of care as moderately important AIII: Recommendation in this category are unlikely
B.	Supported by two or more level I studies with conflicting evidence from other level I studies or supported by only one level I or two or more level II studies BI: The Committee considers this element of care is very important BII: The Committee considers this element of care as moderately important BIII: The Committee feels this element of care is not practically important, but may be considered in some cases
C.	Supported by level III-IV evidence AI: The Committee feels this element of care is very important AII: The Committee considers this element of care as moderately important AIII: The Committee feels this element of care is relatively unimportant, although may be considered in some cases

Table 3. Child-Pugh classification of the severity of cirrhosis.

Variable	Score		
	1 point	2 points	3 points
Encephalopathy	Absent	Mild to moderate	Severe to coma
Ascites	Absent	Slight to Moderate	Tense
Bilirubin (mg/dl)*	<2	2-3	>3
Albumin (g/L)	>3.2	2.8-3.5	<2.8
Prothrombin Time (sec above normal)	<4	4-6	>6

If the total score is 5 or 6, the cirrhosis is designated as class A; if the score is 7 to 9, the cirrhosis is class B; if the score is 10 or higher, the cirrhosis is class C.

*To convert values for bilirubin to $\mu\text{mol} / \text{L}$, multiply by 17.1

preferred approaches to the diagnostic, therapeutic and preventive aspects of care.

Definitions in the context of variceal bleeding

Variceal Bleeding - Bleeding from an oesophageal or gastric varix at the time of endoscopy or the presence of grade III or IV esophageal or gastric varices with blood in the stomach with no other recognizable cause of bleeding⁹ or evidence of recent bleed in the form of cherry red spots and/or red wale marks on varices.

Clinically Significant Bleeding - when there is a transfusion requirement of 2 units of blood or more within 24 hours of the time zero (time zero is the time of admission to the first hospital)⁹ together with a systolic blood pressure of less than 100 mm of Hg or a postural change of greater than 20 mm Hg and /or pulse rate greater than 100 beats per minute.

Time frame of Acute Bleeding - The acute bleeding is represented by an interval of 120 hours (5 days) from time zero.¹¹ Any bleeding occurring during this time interval is considered as failure to control bleeding. Any evidence of bleeding after 120 hours is the rebleeding.

Failure to Control Bleeding - The definition of failure to control bleeding is divided into two time frames.⁹

Within six hours - any of the following factors:

- * Transfusion requirement of 4 units or more
- * Inability to achieve an increase in systolic blood pressure by 20 mm Hg or to 70 mm Hg or more
- * Inability to achieve a pulse rate reduction to less than 100 beats per minute
- * Reduction of 20 beats /min from baseline pulse rate

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

- * Increase in pulse rate of more than 20 beats per minute 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 or above 27% or haemoglobin to above 9g/dl.

Failure signifies need to change therapy; one criterion defines failure, whichever occurs first¹¹:

- * Fresh haematemesis more than 2 hours after start of specific drug treatment or therapeutic endoscopy. In patients having a nasogastric tube, aspiration of greater than 100 ml of fresh blood represents failure
- * 3 g drop in Hb if no transfusion is administered
- * Death
- * Adjusted Blood Transfusion Requirement Index (ABRI) >0.75 at any time point

$$\text{ABRI} = \frac{\text{Blood units transfused}}{(\text{Final Hct} - \text{initial Hct}) + 0.01}$$
- o Hct (or Hb) is measured at least every 8 h for the first 2 days.
- o The transfusion target should be a haematocrit of 24% or a haemoglobin of 8 g/dL.

Rebleeding - Occurrence of new haematemesis or malena after a period of 120 hours or more from time zero. All bleeding episodes regardless of severity should be counted in evaluating rebleeding.¹¹

Early Mortality - Death within six weeks of the initial episode of bleeding.⁹

Management of variceal bleeding

Variceal haemorrhage is an acute clinical event characterized by severe gastrointestinal bleeding presenting as haematemesis with or without malena or haematochezia. Haemodynamic instability, tachycardia and hypotension are common. A successful outcome, as in all cases of gastrointestinal bleeding, hinges on prompt resuscitation, haemodynamic support, and correction of haemostatic dysfunction, preferably in an ICU. After stabilizing the patient one should focus on the differential diagnosis. Although variceal bleeding is common in patients with cirrhosis who have acute upper GI haemorrhage, other causes of bleeding, such as Peptic ulcer, must also be considered. Empirical pharmacological therapy is indicated in situations where variceal bleeding is likely. Endoscopy should be done subsequently to make final diagnosis and treatment.

Today, endoscopy is the best procedure to detect varices and there are no satisfactory non-endoscopic

indicators for the presence of varices. The hepatic vein pressure gradient (HVPG) is the most reliable predictor of variceal development¹⁰ but it is not used in clinical practice. Therefore, short of endoscopy, detailed history and good physical examination remains the most reliable tool for making the diagnosis of variceal bleeding. Source of upper GI bleed may be considered as variceal if:

- * Patient is a diagnosed case of liver cirrhosis or non-cirrhotic portal hypertension
- * No other cause like NSAIDs, peptic ulcer disease, etc is suggested by the history
- * Presence of signs of liver cirrhosis and/or portal hypertension

"Oesophageal Varices"

Management of patients with oesophageal variceal bleeding includes three scenarios:

1. Treatment of acute variceal bleeding
2. Prevention of the initial bleeding (Primary Prophylaxis)
3. Prevention of re-bleeding after an initial bleeding episode (secondary prophylaxis)

Treatment of acute variceal bleeding:

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. Patients with variceal bleeding should be managed in two phases: early and subsequent management.

Early Management of Variceal Bleeding: The essential components include resuscitation, blood/volume replacement, vasoactive drugs, prevention of associated complications, and referral for specific therapy:

1) Resuscitation of the patient: The essential step in the management of variceal bleeding is to evaluate the patient haemodynamically. If in shock, basic ABC (passing Airway, ensuring good Breathing, and maintaining Circulation - pulse and blood pressure) should be achieved on priority basis. ICU management is recommended (Recommendation grade CII). At least 2 wide bore (16 G preferably) IV cannulae should be passed and ideally 4-6 units of blood should be arranged. Placement of NG tube is optional.

2) Blood volume replacement: Blood volume resuscitation should be done cautiously using plasma expanders to maintain haemodynamic stability and PRBC to maintain the haemoglobin at around 8 g/dl, depending on other factors such as patient's co-morbidities, age, haemodynamic status and presence of ongoing bleeding

clinically (Recommendation grade BI).

3) Vasoactive drugs: Combination of endoscopic and pharmacological therapy should be used in patients with acute variceal bleeding (Recommendation grade AI). In suspected variceal bleeding, vasoactive drugs should be started as soon as possible - even before the diagnostic endoscopy (Recommendation grade BI) and maintained for 2-5 days (Recommendation grade AI). Pharmacological therapy alone may be acceptable in circumstances where endoscopic facilities are not available and patient has stopped bleeding with this therapy. However the patient should be referred for endoscopy and definitive therapy (EVBL) as soon as possible (Recommendation grade CI). At the primary care level, pharmacological therapy should be started at the time of initial contact with the patient (Recommendation grade CI). Recommended dosages for the drugs are: Terlipressin- 2mg stat and then 1mg QID, Octreotide- 100 ug bolus followed by 25-50 ug per hour, Somatostatin- 250 ug bolus followed by 250 ug per hour. The use of intravenous proton pump inhibitors need further study before making a recommendation.

4) Prevention of associated complications:

Antibiotic prophylaxis -Antibiotics should be used from the time of admission for preventing bacterial infections and spontaneous bacterial peritonitis in patients presenting with bleeding (Recommendation grade AI). A parenteral third generation cephalosporin followed by an oral preparation should be given for 3-7 days. Quinolones may be used as an alternative (Recommendation grade CI).

Prevention of hepatic encephalopathy - Lactulose or other drugs should be used in patients who present with or develop encephalopathy (Recommendation grade CI). There are no studies evaluating the usefulness of Lactulose for the prevention of hepatic encephalopathy, but the Committee feels that it may be considered if the treating physician wants it (Recommendation grade CIII)

Management of coagulopathy and thrombocytopenia - Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data but it may be considered on individualized basis. (Recommendation grade CIII)

5) Referral for specific therapy: As soon as the patient is haemodynamically stable, endoscopy should be performed; and if endoscopy is not available in the center then the patient must be referred to a center where endoscopy is available. Vasoactive therapy should be continued until endoscopy is done.

Subsequent Management of Variceal Bleeding:

The subsequent management of patients with variceal bleeding must include measures to control initial bleeding and rebleeding:

Control of initial bleeding: Endoscopic treatment is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause of bleeding (Recommendation grade AI). Variceal Band Ligation is the therapy of choice, but sclerotherapy may be used if ligation is technically difficult or unavailable (Recommendation grade AI). Endoscopic therapy with tissue adhesive (N-butyl Cyanoacrylate) is recommended for acute gastric variceal bleeding (Recommendation grade AI). Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy (Recommendation grade AI). Balloon tamponade should only be used in massive bleeding as a temporary "bridge" until definitive treatment can be instituted (for a maximum of 24 hours preferably in an intensive care facility by personnel familiar with its use) (Recommendation grade BI).

Failure to control active bleeding: Failures of initial therapy with combined pharmacological and endoscopic therapies are best managed by a second or third endoscopic therapy (Recommendation grade BI). Patient may be referred for TIPSS or surgical intervention according to the level of expertise available in the area (Recommendation grade BI). Child A and B patients with failure to control bleeding may be referred for surgical intervention (Recommendation grade BII)

Primary prophylaxis of variceal bleeding

Once oesophageal varices have been identified in a patient with cirrhosis, the risk of variceal bleeding is 25 to 35%.^{1,17-19} Because of the poor outcome of variceal bleeding, the identification of those at high risk of bleeding and prevention of a first bleeding episode are of critical importance. Screening endoscopy is generally recommended for patients with cirrhosis to determine whether large varices are present - although the cost effectiveness of this approach is controversial. The use of clinical features, such as increased INR, low serum albumin, a low platelet count, increased portal vein diameter, may help physicians to predict which patients are likely to have large varices.^{20,21}

All patients with cirrhosis are potential candidates for primary prophylaxis against variceal bleeding. Therefore, all newly diagnosed patients with liver cirrhosis should be endoscoped at the time of diagnosis (Recommendation grade AI) and further decision must be made depending upon the endoscopic findings, as detailed below:

- * If no varices are found, surveillance endoscopies should be performed every three years (Recommendation grade AII) to identify if varices have developed.

- * If grade I varices are found, surveillance endoscopies should be performed every year (Recommendation grade AII). Primary prophylaxis with beta-blockers may be considered in patients in Child class C or showing red wale signs (Recommendation grade AI).
- * If grade II varices are found and patient is in Child class B or C, primary prophylaxis should be given (Recommendation grade BI)
- * If grade III varices are found, then primary prophylaxis should be given irrespective of the severity of cirrhosis (Recommendation grade AI)

Primary prophylaxis may be started before the endoscopic confirmation of esophageal varices in patients with decompensated cirrhosis - i.e. patients with jaundice, ascites, and encephalopathy (Recommendation grade CIII).

In case if endoscopic facilities are not available, primary prophylaxis may be given if the following indirect parameters are present (Recommendation grade CIII)

- * INR > 1.5
- * Bilirubin > 2mg/dl
- * Albumin <28 gm/L
- * Platelet count < 70 x 10⁹/L
- * Portal vein diameter > 13 mm on abdominal ultrasound

Pharmacological therapy (non-selective beta-blockers therapy) is the best available modality of primary prophylaxis at present (Recommendation grade AI). Aim of the therapy is to reduce the HVPG to less than 12 mm Hg (Recommendation grade AI). Propranolol or Nadolol are the drugs of choice (Recommendation grade AI). Propranolol should be started at the dose of 10 mg twice daily (Recommendation grade AI). Dose should be adjusted in an incremental fashion to reduce the heart rate by 25% or to 55 beats per minute (Recommendation grade AI).

Isosorbide mononitrate must not be used alone. There is also not enough data to recommend the combination therapy of nitrates with beta-blockers in primary prophylaxis.

In case of contraindications or intolerance to beta-blockers, variceal band ligation is the treatment of choice for grade 2 and larger varices (Recommendation grade AI). Ligation should be performed every 2 to 6 weeks until the varices have been eradicated (Recommendation grade AI). Variceal band ligation and beta-blocker combination therapy may be used in high risk varices (Recommendation grade CI). Sclerotherapy, TIPSS and surgical therapies are not recommended in primary prophylaxis

Secondary prophylaxis of variceal bleeding:

Variceal bleeding recurs in approximately two-

thirds of patients, most commonly within the first six weeks after the initial episode.²²⁻²⁴ Clinical predictors of early recurrence include: 1) severity of the initial haemorrhage i.e., the development of hypotension or a substantial transfusion requirement, 2) degree of liver decompensation, and 3) the presence of encephalopathy and impaired renal function.²⁴ Endoscopic predictors of early recurrence include: 1) active bleeding at the time of initial endoscopy, 2) stigmata of recent bleeding, and 3) grade III or IV oesophageal varices.²⁴⁻²⁷ In addition, severity of portal hypertension, measured by the HVPG, correlates closely with the risk of rebleeding as well as with the actuarial survival rate after an initial variceal bleeding.²⁷ Because of the risk of rebleeding and its associated morbidity and mortality, secondary prophylaxis must be given after the initial episode of variceal bleeding.

After the control of acute variceal bleeding, secondary prophylaxis must be given to all patients (Recommendation grade AI). It should be started as soon as possible from day 6 of the index variceal bleeding episode. The time of starting the secondary prophylaxis should be documented (Recommendation CIII). Combination of beta-blockers and endoscopic variceal ligation is the treatment of choice, unless beta-blockers are contraindicated (Recommendation grade AII). Ligation should be performed every 4 weeks until the varices have been eradicated (Recommendation grade AI). Following successful eradication of varices, patients should be endoscoped at 3-6 monthly interval thereafter, to look for recurrence of varices. In case of recurrence, band ligation should be repeated (Recommendation grade AII). If band ligation is not available, sclerotherapy should be the alternative treatment (Recommendation grade BI). The interval between treatments should be the same as outlined for band ligation. The sclerosing agents used may vary between institutions (Recommendation grade AII). Non-selective beta-blockers therapy, in combination with endoscopic therapy or alone, should be given as discussed earlier in primary prophylaxis.

In patients who fail endoscopic and beta-blockers therapy, TIPSS and surgical shunts (distal splenorenal shunt or 8 mm H-graft) therapies are the procedures of choice in Child class A/B and Liver transplantation is the procedure of choice in Child class B/C; however, TIPSS may be used as a bridge to liver transplantation. However these options may be used in selected centers with particular expertise (Recommendation grade AI)

Gastric Varices

Gastric variceal bleeding is characterized by massive

bleeding that is more severe than oesophageal variceal bleeding. There is limited data available for the management of bleeding Gastric Varices and no randomized control trials are available in the setting of gastric variceal bleed. Most of the evidence comes from retrospective series and case reports.

The essential components of early management include resuscitation with fluids and blood volume replacement, correction of coagulation with Fresh Frozen Plasma (FFP) or platelets transfusion if indicated, vasoactive drugs like Terlipressin or Octreotide, prevention of associated complications, and referral for specific therapy which really depends upon the type of bleeding gastric varices as classified by Sarin et al.²⁸

GOV1: may be treated with N-butyl-2-cyanoacrylate (Histoacryl) injection sclerotherapy of bleeding varix; otherwise treatment of the esophageal varices by EVL/Sclerotherapy is sufficient.²⁹⁻³¹ (Recommendation grade BII).

GOV2 and IGV: is treated initially with N-butyl-2-cyanoacrylate (Histoacryl) injection sclerotherapy of the bleeding varix. (Recommendation grade AI).

In case of failure to control bleeding, balloon tamponade with Sengstaken-Blakemore tube may be employed as a bridge to buy time while arranging for other definitive modalities of treatment of gastric varices³²⁻³³ (Recommendation grade BII).

Recurrence of gastric variceal bleed or failure to control bleeding may be managed with TIPSS,^{34,35} depending upon availability of expertise, experience of the center and also upon the CTP score because a score of more than 13 is associated with poor outcome.³⁶ In centers where TIPSS is not available, devascularization or shunt surgery may be recommended to Child's class "A" patients only (Recommendation grade BII).

Bleeding from portal hypertensive gastropathy - may be treated with beta-blockers along with proton pump inhibitors and other general measures. Argon plasma coagulation therapy may be of help if available. TIPSS may be needed long-term.¹¹

Areas requiring further studies/facilities

The committee feels that the following areas need further studies:

- * Optimal duration of vasoactive drug therapy
- * Local data on prophylactic antibiotics for patients undergoing EVL with or without ascites.
- * Local data for timing of rebanding of EV as a secondary prophylaxis, 2 weeks Vs 4 weeks Vs 6 weeks.

- * Development of facilities for TIPSS and liver transplant
- * Effectiveness of early TIPSS placement and of covered stents
- * Best treatment of gastric varices; especially glue vs. TIPSS
- * The best treatment of patients with no active bleeding at time of endoscopy on drug therapy
- * Prognostic factors / models for acute bleeding MELD score, variceal size, age, etiology of portal hypertension and other co morbidities
- * Local data on incidence and natural history of varices and variceal bleeding
- * N butyl cyanoacrylate for the primary prophylaxis of gastric varices

References

1. No authors listed. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. *N Engl J Med* 1988; 319: 983-9.
2. Groszmann RJ, Bosch J, Grace ND, Conn HO, Gracia- Tsao G, Navasa M, Alberts J. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990; 99: 1401-7.
3. Gores GJ, Wiesner RH, Dickson ER, Zinsmeister AR, Jorgensen RA, Langworthy A. Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history, and influence on survival. *Gastroenterology* 1989; 96: 1552-9.
4. Gralnek IM, Jensen DM, Kovacs TO, Jutabha R, Machicado GA, Gornbein J, King J. The economic impact of esophageal variceal hemorrhage: cost-effectiveness implications of endoscopic therapy. *Hepatology* 1999; 29: 44-50.
5. Burroughs AK, McCormick PA. Natural history and prognosis of variceal bleeding. *Baillieres Clin Gastroenterol* 1992; 6: 437-50.
6. Cello JP, Grendell JH, Crass RA, Weber TE, Trunkey DD. Endoscopic sclerotherapy versus portacaval shunt in patients with severe cirrhosis and acute variceal hemorrhage. Long-term follow-up. *N Engl J Med* 1987; 316: 11-5.
7. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; 80: 800-9.
8. Koransky JR, Galambos JT, Hersh T, Warren WD. The mortality of bleeding esophageal varices in a private university hospital. *Am J surg* 1978; 136: 339-41.
9. Jalan R, Hayes PC. UK guidelines on the management of variceal hemorrhage in cirrhotic patients. *British Society of Gastroenterology. Gut* 2000; 46 Suppl 3: iii1-iii15 (June)
10. Renner E. OMGE Practice Guideline: Treatment of Esophageal Varices. May 2003. http://www.omge.org/guidelines/guide08/g_data8_en.htm.
11. de Franchis R. Evolving Consensus in Portal Hypertension. Report of the Baveno IV Consensus Workshop on Methodology of Diagnosis and Therapy in Portal Hypertension. *J Hepatology* 2005; 43: 167-76
12. Eccles M, Clapp Z, Grimshaw J, Adams PC, Higgins B, Purves I, Russell I. North of England evidence based guidelines development project: methods of guideline development. *BMJ* 1996; 312: 760-2
13. Eccles M, Rousseau N, Freemantle N. Updating evidence-based clinical guidelines. *J Health Serv Res Policy.* 2002 ;7: 98-103.
14. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. *JAMA* 1995; 274:1800-4
15. Eccles M, Mason J. How to develop cost-conscious guidelines. *Health Technol Assess.* 2001; 5:1-69.

16. Eccles M, Mason J, Freemantle N. Developing valid cost effectiveness guidelines: a methodological report from the north of England evidence based guideline development project. *Qual Health Care.* 2000; 9:127-32.
17. No authors listed. Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease. A randomized, single-blind, multicenter clinical trial. The Veterans affairs Cooperative Variceal Sclerotherapy Group. *N Eng J Med* 1991; 324: 1779-84.
18. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; 19: 475-505.
19. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM et al. Predictors of large esophageal varices in patients with cirrhosis. *Am J Gastroenterol* 1999; 94: 3285-91.
20. Schepis F, Camma C, Niceforo D, Magnano A, Pallio S, Cinquegrani M et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? *Hepatology* 2001; 33:333-8.
21. Albillos A, Lledo JL, Rossi I, Perez-Paramo M, Tabuenca MJ, Banares R et al. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. *Gastroenterology* 1995; 109: 1257-65.
22. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; 80: 800-9.
23. Smith JL, Graham DY. Variceal hemorrhage: a critical evaluation of survival analysis. *Gastroenterology* 1982; 82: 968-73.
24. No authors listed. Sclerotherapy after first variceal hemorrhage in cirrhosis. A randomized multicenter trial. The Copenhagen Esophageal Varices Sclerotherapy Project. *N Engl J Med* 1984; 311: 1594-600.
25. de Franchis R, Primignani M. Why do varices bleed? *Gastroenterol Clin North Am* 1992; 21: 85-101.
26. Lebrech D, De Fleury P, Rueff B, Nahum H, Benhamou JP. Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. *Gastroenterology* 1980; 79: 1139-44.
27. Vinel JP, Cassigneul J, Levade M, Voigt JJ, Pascal JP. Assessment of short-term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of portohepatic gradient. *Hepatology* 1986; 6: 116-7.
28. 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.
29. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2- cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. *Gastrointest Endosc* 2000;52:160-7.
30. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001;33:1060-4.
31. Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002;97:1010-15.
32. Teres J, Cecilia A, Bordas JM, Rimola A, Bru C, Rodes J. Esophageal tamponade for bleeding varices. Controlled trial between the Sengstaken-Blakemore tube and the Linton-Nachlas tube. *Gastroenterology* 1978;75:566-9.
33. 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.
34. Barange K, Peron JM, Imani K, Otal P, Payen JL, Rousseau H, et al. Transjugular intrahepatic portosystemic shunt in the treatment of refractory bleeding from ruptured gastric varices. *Hepatology* 1999;30:1139-43.
35. Azoulay D, Castaing D, Majno P, Saliba F, Ichai P, Smail A, et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. *J Hepatol* 2001;35:590-7.
36. Patch D, Nikolopoulou V, McCormick A, Dick R, Armonis A, Wannamethee G, et al. Factors related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding. *J Hepatol* 1998;28:454-60.