ARQGA/1490

VARICEAL BLEEDING: consensus meeting report from the Brazilian Society of Hepatology

Paulo Lisboa **BITTENCOURT**[1], Alberto Queiroz **FARIAS**[2], Edna **STRAUSS**[3], Angelo Alves de **MATTOS**[4] and Members of the Pannel of the 1st Brazilian Consensus of Variceal Bleeding, Brazilian Society of Hepatology*

ABSTRACT - In the last decades, several improvements in the management of variceal bleeding have resulted in a significant decrease in morbidity and mortality of patients with cirrhosis and bleeding varices. Progress in the multidisciplinary approach to these patients has led to a better management of this disease by critical care physicians, hepatologists, gastroenterologists, endoscopists, radiologists and surgeons. In this respect, the Brazilian Society of Hepatology has, recently, sponsored a consensus meeting in order to draw evidence-based recommendations on the management of these difficult-to-treat subjects. An organizing committee comprised of four people was elected by the Governing Board and was responsible to invite 27 researchers from distinct regions of the country to make a systematic review of the subject and to present topics related to variceal bleeding, including prevention, diagnosis, management and treatment, according to evidence-based medicine. After the meeting, all participants met together for discussion of the topics and the elaboration of the aforementioned recommendations. The organizing committee was responsible for writing the final document. The meeting was held at Salvador, May 6th, 2009 and the present manuscript is the summary of the systematic review that was presented during the meeting, organized in topics, followed by the recommendations of the Brazilian Society of Hepatology.

HEADINGS – Gastrointestinal hemorrhage. Liver cirrhosis. Esophageal and gastric varices. Consensus.

INTRODUCTION

Due to the frequency and bad prognosis associated with gastrointestinal bleeding in patients with portal hypertension (PH), the Governing Board of the Brazilian Society of Hepatology organized on May 6th 2009 at Salvador, Bahia, Brazil, a consensus meeting to establish national guidelines on prevention, management and treatment of portal hypertensive bleeding. A consensus committee made of four delegates was chosen, who elected a panel of 27 Brazilian researchers from different regions of the country to act as moderators or speakers of previously selected topics focused on: 1) screening of varices and prevention of the first bleeding episode; 2) treatment of acute variceal bleeding; 3) management of treatment failure, recurrence of bleeding and secondary prophylaxis, and 4) management of special situations. All moderators were asked to provide key questions concerning fundamental or controversial issues on the aforementioned topics to be answered by the presenters according to level of scientific available data ranked by the Oxford System, as suggested by the Brazilian Medical Association. Each presentation was opened for discussion with the panel and the audience and after the meeting, the entire panel gathered together to draw recommendations that were summarized in the present manuscript after a brief description of each presentation.

PART I. SCREENING OF VARICES AND PREVENTION OF THE FIRST BLEEDING EPISODE

1) Screening of varices in patients with portal hypertension due to cirrhosis

Approximately 30% of the patients with compensated cirrhosis and 60% of those with decompensated cirrhosis

*Adriana Vaz Safatle Ribeiro[2], Ajácio Bandeira de Mello Brandão[4], André Lyra[5], Andréa Ribeiro Cavalcanti[1], Arnaldo Dominici[6], Carlos Terra[7], Cláudio Augusto Marroni[4], Cristiane Valle Tovo[4], Débora Crespo[8], Edison Roberto Parise[9], Fábio Marinho[10], Flair José Carrilho[2], Francisco José Dutra Souto[11], Helma Cotrim[5], Henrique Sérgio Coelho[12], Igelmar Paes[5], João Galizzi[13], Jorge Segadas Soares[14], Luciana Silva[5], Luiz Guilherme Lyra[5], Marcelo Abrahão Costa[15], Paulo Herman[2], Ramiro Mascarenhas[5], Raymundo Paraná[5]

[1] Hospital Português, Salvador, BA; [2] Departamento de Gastroenterologia da Faculdade de Medicina da Universidade de São Paulo; [3] Faculdade de Medicina da Universidade de São Paulo; [4] Universidade Federal de Ciências da Saúde de Porto Alegre e Irmandade da Santa Casa de Misericórdia de Porto Alegre , RS; [5] Faculdade de Medicina da Universidade Federal da Bahia, BA; [6] Universidade Federal do Maranhão, MA; [7] Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro, RJ; [8] Universidade Federal do Pará, PA; [9] Universidade Federal de São Paulo, SP; [10] Real Hospital Português de Beneficência de Pernambuco e Hospital das Clínicas da Universidade Federal de Pernambuco, PE; [11] Universidade Federal de Mato Grosso, MT; [12] Departamento de Gastroenterologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, RJ; [13] Faculdade de Medicina da Universidade Federal da Minas Gerais, MG; [14] Serviço de Hepatologia, Universidade Federal do Rio de Janeiro, RJ; [15] Hospital de Base do Distrito Federal, DF

Correspondence: Dr. Paulo Lisboa Bittencourt - Rua Prof. Clementino Fraga, 220/1901 - 40170-050 - Salvador, BA, Brazil. Email: plbbr@uol.com.br

have varices at endoscopy[42, 43, 117]. One study from Italy involving 111 subjects with cirrhosis revealed a cumulative incidence of varices of 5% and 20% in 2 and 5 years, respectively[117]. Merli et al.[100] evaluated 206 cirrhotics with annual endoscopy and disclosed the appearance of varices in 5% and 28% of the subjects at 1 and 3 years of follow-up, respectively. Of note, no baseline clinical parameter was predictive of the development of esophageal varices[100]. On the other hand, Groszmann et al.[75] followed 213 patients with cirrhosis and PH, identified by a hepatic vein pressure gradient (HVPG) ≥6 mm Hg, without varices at baseline endoscopy and observed the appearance of varices in 40% of them after a median follow-up of 54 months. In this study, the most important predictor for the development of varices was the presence of baseline HVPG. In this regard, the incidence of varices at 5 years increased from 25% to 50% in those subjects with HVPG >10 mm Hg[75].

Progression of small varices to large varices is reported to occur in 5%-30% of the cases per year[48]. A longitudinal study revealed progression of varices from small to medium or large caliber in 12% and 31% of the cases at 1 and 3 years of follow-up, respectively[100]. These data altogether suggested that the rate of progression of varices from small to large caliber is higher than the rate of their development in cirrhotics[48]. Based on these data, screening of varices should be performed in all patients with cirrhosis. Subjects without varices at baseline and classified as Child-Pugh A should be submitted to screening each 2 to 3 years. However, this interval should be shortened to 1 year in patients classified as Child-Pugh B or C or with recent disease decompensation. On the other hand, subjects with compensated disease and small varices at baseline, not submitted to any prophylactic treatment, should undergo screening every 1 to 2 years[68].

Several methods including clinical, laboratory and echographic parameters, the fibroscan®, the HVPG, and more recently, the capsule endoscopy have been proposed as methods for screening of varices in cirrhotics. However, up to now upper digestive endoscopy remains the gold-standard method for the screening of varices[22, 49, 68]. The most reliable predictors of variceal bleeding are variceal size, presence of red signs on varices, severity of liver disease and HVPG ≥12 mm Hg[43, 67, 74, 92, 100, 107]. Two of them are assessed by endoscopy and have been measured according to different classifications[68]. The Brazilian Society of Hepatology endorsed the classification of varices in small, medium and large size adopted by the majority of Brazilian endoscopists. In this regard, small, medium and large varices were considered as those with a caliber less than 3 mm, between 3 and 5 mm and more than 5 mm, respectively[112]. Red signs on varices were recognized as cherry-red spots, red wale marks, hematocystic spots and diffuse redness.

Recommendations:

1) *Screening for esophageal varices should be performed in all patients with cirrhosis at diagnosis independently of the grade of liver dysfunction*
2) *Upper digestive endoscopy is the most reliable method for screening*
3) *Variceal size should be classified at endoscopy in small, medium and large according to the findings of variceal caliber of less than 3 mm, between 3 and 5 mm and more than 5 mm, respectively. The presence of red signs on varices should be reckoned.*
4) *Patients with Child-Pugh A cirrhosis without varices at baseline should be submitted to endoscopy every 2 years.*
5) *Patients with Child-Pugh B cirrhosis without varices at baseline should be submitted to endoscopy every year.*
6) *Patients with small varices not undergoing any prophylactic treatment should be submitted to endoscopy every year, independently of severity of chronic liver disease.*

2) Pre-primary prophylaxis: what is the evidence?

The concept of pre-primary prophylaxis is under debate. Some authors employ it to define any measure aimed to prevent the appearance or progression of esophageal varices in subjects with PH either without or with small size varices[24, 50, 71, 108, 141], while others use it only to characterize interventions employed solely to avoid the development of varices[1, 62, 66, 139]. Depending on its appropriate definition, the objectives of this prophylaxis may vary, but its basic proposal is to prevent the development of varices or their progression in order to avoid variceal bleeding in cirrhotic patients.

Even though four randomized controlled trials (RCT) concerning the efficacy of pre-primary prophylaxis have been published in the literature[27, 75, 99, 102], only one included solely patients which had no varices at baseline endoscopy[75]. In this study, no differences were observed in treatment outcomes. The authors do not recommend pre-primary prophylaxis in cirrhotic patients with PH and no varices.

Recommendations:

1) *Pre-primary prophylaxis should be defined as any measure aimed to prevent the development of varices in patients with PH*
2) *Pre-primary prophylaxis as previously defined can not be recommended due to the lack of current evidence of clinical benefit*

3) Indication of prophylaxis of the first episode of variceal bleeding: what is the evidence?

Knowledge about the natural history of portal hypertensive bleeding in cirrhotics is crucial to determine the timing for institution of prophylactic measures. In this respect, D'Amico et al.[47], have recently evaluated the clinical course according to the probability of death of cirrhotic patients. The authors have classified patients in stage 1 (no varices, no ascitis), stage 2 (varices, no ascitis), stage 3 (ascitis with or without varices) and stage 4 (variceal bleeding with or without ascitis). One-year mortality was 1%, 3%, 20% and 57% in stages 1, 2, 3 and 4, respectively, demonstrating the adverse impact of variceal bleeding on survival of patients with cirrhosis.

The most important parameters associated with progression from small to medium and medium to large varices are severity of liver disease, expressed by scores B or C of Child-Pugh classification, the presence of red signs on varices and alcohol as etiology for cirrhosis[22, 100]. On the other hand, as previously

mentioned, recognized predictors of variceal bleeding are variceal size, red signs on varices, severity of liver disease and the presence of HVPG ≥12 mm Hg.

Primary prophylaxis is defined as any intervention focused on prevention of the first episode of variceal bleeding. Several studies and meta-analysis have been published concerning primary prophylaxis in cirrhotic patients with medium to large varices, but few reports have included subjects with small varices. Studies to evaluate primary prophylaxis in patients with small varices are difficult to perform, mainly because they may require a large number of patients[69]. Merkel et al.[99] evaluated the role of non-selective beta blockers (NSBB) in the progression from small to large varices and on the prevention of the first bleeding episode in 166 patients with cirrhosis and small varices. The authors have demonstrated progression of varices to medium or large size in 11% of the subjects in the nadolol group vs 37% of the patients in the control group after a mean follow-up period of 36 months. On the other hand, variceal bleeding was observed in 12% of the patients in the nadolol group vs 22% of the subjects in the control group at 5 years of follow-up. Of note, mortality was similar in both groups, but adverse events were higher in the treatment-arm (11% vs 1%)[99].

Based on current data, it can be suggested that patients with small varices without contraindications to NSBB may be submitted to primary prophylaxis at least to prevent progression to medium or large varices. Likewise, patients with small varices and Child-Pugh B or C cirrhosis or with red signs on varices can also be considered as candidates for primary prophylaxis because they have a similar risk of bleeding, when compared to patients with medium or large varices[95, 99, 100, 107].

In regard to patients with varices from all sizes, one meta-analysis, that evaluated 11 RCT (9 with propranolol and 2 with nadolol), including 1,189 patients revealed a significant reduction in the frequency of the first bleeding episode in subjects treated with NSBB with a non-significant decrease in mortality[44]. Another meta-analysis from the Cochrane group evaluating primary prophylaxis from 11 RCT including 1,344 patients demonstrated that therapy with NSBB had a significant impact in mortality from the first episode of variceal bleeding in cirrhotics, irrespective of variceal size[35]. Therefore, there is no doubt that primary prophylaxis is required in cirrhotic patients with medium or large varices with or without risk factors for variceal bleeding[49, 68]. Although unavailable for routine assessment, measurement of HVPG is a valuable tool for guiding prophylactic therapy with NSBB. Efficacy of such strategy can be predicted whenever a reduction of HVPG below 12 mm Hg or to a level lower than 20% of the baseline value is achieved[46, 57, 74].

Recommendations:

1) *Patients with small varices and advanced cirrhosis (Child-Pugh B or C) have high risk of bleeding and should be submitted to primary prophylaxis*
2) *Patients with small varices and Child-Pugh A cirrhosis without red signs on varices may benefit from primary prophylaxis, but there is no evidence to support any recommendation*
3) *Patients with medium or large varices should be submitted to prophylaxis independently of the presence of advanced liver disease or red signs on varices.*
4) *Determination of HVPG is valuable in the selection of higher-risk patients for variceal bleeding either before or after the institution of primary prophylaxis, but its routine use in the management of patients with PH can not be recommended outside specialized centers.*

4) What is the best treatment strategy for primary prophylaxis?

There are two main treatment modalities to be employed in primary prophylaxis of patients with PH: NSBB or endoscopic band ligation (EBL) of varices. Sclerotherapy is no longer recommended due to its adverse impact on patient survival[42, 151]. As previously shown, use of NSBB was associated with reduction of the frequency of the first bleeding episode in cirrhotics with esophageal varices, when compared to placebo[44]. Recently, two meta-analyses compared the effect of NSBB and EBL in reducing the frequency of the first bleeding episode and mortality in cirrhotics with PH[65, 83]. Lower frequency of bleeding was demonstrated with EBL with no effect in mortality, when compared to NSBB. Adverse events were more often in subjects treated with NSBB, but were more severe in those submitted to EBL. It is worth to mention that NSBB, but not EBL, are also able to prevent bleeding from gastric and ectopic varices[69]. Based on these data, it is possible to employ either NSBB or EBL as agents for primary prophylaxis in subjects with medium or large varices. In addition, EBL can also be offered to those subjects with serious side effects, non-adherence or contraindications to NSBB[49, 68, 69]. As outlined elsewhere[69], the dosage of NSBB should be adjusted to the maximal dose tolerated by the patient, considered as the dose immediately below the one capable of inducing side-effects[69]. The sessions of EBL should be performed every 2 weeks until variceal eradication, with the first endoscopic control performed 3 months thereafter and then every 6-12 months[68, 69].

In subjects with small varices, the use of NSBB can be considered, particularly in patients with a higher risk of bleeding such as those with advanced Child-Pugh B or C cirrhosis and with red signs on varices, in whom primary prophylaxis is highly recommended[68, 69].

It is important to stress that there is no evidence concerning the role of nitrates and endoscopic sclerotherapy as treatment modalities for primary prophylaxis[63, 64, 68, 69].

Even though proton pump inhibitors are currently used to favor ulcer healing, there is no evidence for its use to prevent post-banding ulcer bleeding. Likewise, there is no rationale for the use of platelets or fresh frozen plasma before EBL in subjects with PH with low platelets count or prolonged INR submitted to primary prophylaxis[152].

Recommendations:

1) *Either NSBB or EBL can be employed as strategies for primary prophylaxis in patients with cirrhosis and medium or large varices with high risk of bleeding (Child B or C cirrhosis or red signs on varices)*

2) *NSBB should be preferred in primary prophylaxis of patients with cirrhosis and medium or large varices without high risk of bleeding (Child A cirrhosis or absence of red signs on varices). EBL should be offered to those subjects with non-adherence, intolerance, serious side effects or contraindications to NSBB*
3) *NSBB should be employed for primary prophylaxis in patients with cirrhosis and small varices with high risk of bleeding (Child B or C cirrhosis or red signs on varices)*
4) *NSBB can be considered for primary prophylaxis in patients with cirrhosis and small varices without high risk of bleeding (Child A cirrhosis or absence of red signs on varices), but their use must be individualized due to the lack of evidence of benefit.*

PART II: TREATMENT OF THE ACUTE VARICEAL BLEEDING EPISODE

1) Initial management of patients with variceal bleeding

In the last two decades, major achievements in the care of the cirrhotic patient with variceal bleeding led to a reduction in mortality from the first bleeding episode from 43% to 14%. This improvement was due to a significant change in the multidisciplinary approach of those patients from the pre-hospital setting to the intensive care unit (ICU) by emergency medical staff, paramedics, hepatologists, gastroenterologists, endoscopists, intensive care physicians, interventional radiologists and surgeons[31, 41, 45].

Variceal bleeding usually manifests as a clinically relevant bleeding, characterized by hemorrhage associated with hemodynamic instability or with transfusion requirements of more than two packed red blood cell units or with a reduction of hemoglobin levels of more than 2,0 g/dL. It is a medical emergency that need immediate volemic restoration in order to provide homodynamic support to improve prognosis and reduce mortality[69]. Variceal bleeding should be ideally managed in the ICU setting.

The first approach to the patient with variceal bleeding should be done according to basic life support measures including basic maneuvers of A (airway), B (breathing) and C (circulation) aimed at airway opening, breathing and heart rate (HR) evaluation as well as blood pressure (BP) measurement. Laboratory measurement of complete blood count with platelets, prothrombin time with INR, serum electrolytes such as sodium and potassium, urea and creatinine should be initially performed. Volemic restoration should be attempted to shock reversal and correction of hypovolemia based on blood loss estimates according to hemodynamic parameters[25]. However, it should be kept in mind that those parameters are usually employed for volemic restoration of patients without cirrhosis, and that subjects with chronic liver disease even at basal conditions can have BP lower than 90 mm Hg and tachycardia due to circulatory dysfunction and hyperdynamic circulation.

Peripheral venous access is advisable, whenever possible, with a large-bore catheter. Central venous lines should be reserved for those patients who fail to respond to intravenous fluids or whenever measurement of central venous pressure (CVP) is required. Experimental studies[33, 87, 88] have suggested that vigorous fluid infusion may enhance bleeding or induce rebleeding from esophageal varices. Thus, it is wise to recommend caution with volemic resuscitation, using preferentially crystalloids (isotonic saline or lactated Ringer's solution), to achieve hemodynamic compensation with the goal of systolic blood pressure of 90-100 mm Hg. There is no evidence in favor of the use colloids, including albumin in the management of patients with variceal bleeding[49, 69].

Endotracheal intubation should not be postponed in comatose patients with shock, hepatic encephalopathy or in at-risk patients for gastric aspiration during upper digestive endoscopy.

Sengstaken-Blakemore tubes should be placed only in those cases of massive bleeding and ongoing shock despite the use of intravenous fluids. Their use is associated with several complications, including aspiration of gastric contents, respiratory tract infection, tube displacement, esophageal wall laceration or perforation and pressure necrosis of the nose. Therefore, they should be left in place for no longer than 24 hours as a bridge for a definite treatment such as endoscopic hemostasis or transjugular intrahepatic portosystemic shunt (TIPS)[49]. Airway protection is highly recommended in this setting.

There are some pitfalls in monitoring systemic perfusion in subjects with advanced chronic liver disease. Arterial lactate measurement is usually employed as a parameter of systemic perfusion, but abnormal levels could be found in cirrhotics even without tissue hypoxia due to its delayed hepatic clearance. Likewise, measurement of central venous oxygen saturation (ScVO2) has been employed in the ICU setting as a tool for evaluation of hemodynamic status as well as to guide fluid resuscitation. At least in septic patients, levels of ScVO2 higher than 70% are indicative of adequate fluid replacement. However, it is important to stress that in cirrhotics, levels of ScVO2 higher than 70% may not reflect volemic restoration due to the presence of hyperdynamic circulation. Thus, arterial lactate and ScVO2 should be employed with some caution in cirrhotics with variceal bleeding [29].

Recommendations:

1) *Cirrhotics with acute variceal bleeding should be ideally managed in the ICU*
2) *Fluid resuscitation should be employed with caution in order to maintain levels of systolic blood pressure of 90-100 mm Hg and heart rate of 100 beats per minute*
3) *Airway protection is advisable for those patients with depression of the level of consciousness and massive hematemesis as well as for those subjects who require Sengstaken-Blakemore tubes*
4) *Use of Sengstaken-Blakemore tubes at admission should be reserved for those cases of massive hemorrhage with hemodynamic compromise not responsive to intravenous fluids, as a bridge for a definite treatment and for no longer than 24 hours.*

2) Indications and contraindications for the use of blood and blood products

Fluid overload may aggravate PH and induce recurrence of variceal bleeding[17, 87, 88]. Thus, it is advisable to adopt conservative measures concerning blood replacement and use of blood products in cirrhotics with variceal bleeding. Goals for hematocrit and hemoglobin are, respectively, 21%-27% and 7 g/dL-9 g/dL. Use of blood and blood products may also vary according to patients age, comorbidity and ongoing bleeding[8, 22, 30], particularly in subjects with coronary heart disease, for whom hematocrit levels higher than 30% are advisable[49, 85].

Use of fresh frozen plasma or platelets can be considered in patients with severe coagulopathy and plaquetopenia, however, there are no data to support benefit of these strategies in subjects with variceal bleeding[69]. It is generally recommended to administer one unit of fresh frozen plasma after requirement of more than 4-6 units of packed red blood cells, but its efficacy in reversing coagulopathy induced by massive transfusions remains to be proven.

It is important to note that abnormalities of prothrombin time, INR and partial thromboplastin time do not show correlation with a higher risk for bleeding in cirrhosis[4, 144, 145]. In subjects with chronic liver disease, the INR usually reflects reduction in the synthesis of pro-coagulant factors, but do not estimate the deficit of anticoagulant proteins (protein C, S and anti-thrombin III) also produced by the liver[144, 145]. Thus, it is not hard to understand why commonly used blood products such as cryoprecipitate and fresh frozen plasma rarely reverse coagulopathy of severe liver disease. On the other hand, prothrombin complex conjugate and recombinant activated factor VII (rFVIIa) are more effective in correcting the prothrombin time in cirrhotics. However, they have not been associated with more effective control of variceal bleeding or with a reduced frequency of recurrence of variceal hemorrhage in cirrhotics. On the contrary, thromboembolic events have been reported with the use of these agents[23]. Current data do not support the use of these agents as first line treatment for patients with cirrhosis and variceal bleeding, but they could still be considered as rescue therapy in very well selected patients with intractable bleeding.

There is also no evidence favoring prophylactic use of platelets or fresh frozen plasma to reverse coagulopathy of chronic liver disease. Their use should be individualized according to the clinical setting.

Occurrence of transfusion related acute lung injury (TRALI) depends on variables from blood donors and not from blood recipients and there is no data showing higher predisposition of cirrhotics to develop this severe event[129, 151].

Recommendations:

1) *Transfusion therapy should be aimed to achieve goals for hematocrit and hemoglobin of 21%-27% e 7 g/dL-9 g/dL, but higher levels may be required depending on patient's age, comorbidity and presence of ongoing bleeding*
2) *The are no data to support recommendations for management of coagulopathy and thrombocytopenia in patients with cirrhosis*

3) Pharmacological treatment of acute variceal bleeding. What is the evidence?

Portal hypertension is the result of increased intrahepatic resistance to portal flow and increased portal flow due to splancnic vasodilatation. Esophageal varices usually develop in the presence of PH with HVPG greater than 10 mm Hg, whereas variceal bleeding and bleeding refractory to endoscopic and/or pharmacologic treatment tend to occur with HVPG greater than 12 mm Hg and 20 mm Hg, respectively[66, 103]. In the acute episode of variceal bleeding, vasoactive drugs that reduce portal pressure either directly or indirectly are able to control bleeding besides lowering rebleeding rates from esophageal varices[106]. Four vasoactive drugs are available for treatment of variceal hemorrhage in Brazil, including octreotide (Sandostatin®), somatostatin (Stilamin®), vasopressin (Encrise®) and terlipressin (Glypressin®).

Terlipressin is a long-acting analogue of vasopressin which is related to fewer cardiovascular side-effects, when compared to vasopressin due to its preferential binding to V1 receptors. Its use is associated with a significant reduction in portal pressure, intravariceal pressure and azigos vein flow, lasting for approximately 4 hours[106]. It is recommended to use terlipressin as an intravenous bolus of 2 mg followed by intermittent boluses of 1-2 mg according to body weight for 2-5 days[58, 68, 106]. Side effects include angina pectoris, acute myocardial infarction, bradiarrhimias, peripheral vascular ischemia, mesenteric ischemia and systemic arterial hypertension. This drug should be avoided or used with caution in patients with coronary heart disease or severe peripheral vascular disease. It should not be used during pregnancy due to an increased risk of spontaneous abortion.

Somatostatin also induces a significant decrease in portal and intravariceal pressure as well as in azigos vein flow, but its effect tends to be transient in dosages of 250 mcg/kg/hour and more prolonged in higher dosages of 500 mcg/kg/hour[104, 106]. It is recommended to administer somatostatin intravenously as a bolus of 250 mcg, followed by continuous infusion of 250 mcg/kg/hour for 2-5 days[58, 68, 106].

Octreotide is a somatostatin analogue. Its use has been associated acutely either with a transient or no reduction in portal pressure, however continous infusion of the drug was shown to block the postprandial rebound increase in portal pressure. It is commonly used as an intravenous bolus of 50-100 mg, followed by a continuous infusion of 25-50 mcg/hour for 2-5 days. The most common side effects of somatostatin and its analogues are abdominal pain, diarrhea, hyperglycemia and headache[106]. With the advent of newer vasoactive drugs, the use of vasopressin even with nitrates has been abandoned in favor of drugs with better safety profiles, such as octreotide, somatostatin and terlipressin.

The efficacy of vasoactive drugs in the treatment of acute variceal bleeding has been analyzed in two recent meta-analyses. The Cochrane group evaluated 12 RCT, involving 1,452 patients, which evaluated the role of somatostatin and its analogues in variceal bleeding. They have demonstrated a benefit on the initial control of bleeding (RR = 0,68) and use

of blood products, but no impact in mortality was disclosed[73]. The same group also performed another meta-analysis, including 22 RCT, comparing the efficacy of terlipressin vs placebo and terlipressin vs either somatostatin or endoscopic treatment, or Sengstaken-Blakemore tube placement or vasopressin or octreotide. The authors have demonstrated a significant impact on mortality with the use of terlipressin, when compared to placebo[79].

Even though the use of vasoactive drugs has been shown to be comparable to endoscopic treatment in the control of bleeding[45], there are data showing that combined treatment with vasoactive drugs and endoscopic hemostasis is superior to each treatment modality in the control of bleeding and prevention of bleeding recurrence[7, 9, 72, 94, 155]. Of note, impact in reduction of mortality was observed in only one RCT that evaluated combination treatment of variceal bleeding with terlipressin and endoscopic therapy[94]. It is important to point out that secondary prophylaxis with NSBB should be instituted early in the 6th day after variceal bleeding, whenever possible[49].

Recommendations:

1) *Vasoactive drugs should be employed as early as possible in patients with or with suspicion of variceal bleeding even before endoscopy*
2) *Terlipressin, somatostatin or octreotide could be used according to their profile of efficacy, tolerability, cost and safety. Due to its impact on survival, terlipressin can be considered the agent of choice, but its use should not be advisable in subjects with coronary heart disease, severe peripheral vascular disease and non-controlled arterial hypertension. The use of vasopressin with or without nitrates should be abandoned in the management of variceal bleeding*
3) *Employment of those drugs should be extended for 2 to 5 days. Their use for 5 days may reduce variceal rebleeding*

4) Endoscopic treatment of acute variceal bleeding

Upper digestive endoscopy should be performed in the first 12 hours of admission of patients with suspected variceal bleeding for diagnosis, as well as for evaluation of endoscopic hemostasis[49]. Airway protection is strongly recommended before endoscopy in patients with massive bleeding, grades III and IV hepatic encephalopathy and whenever oxygen saturation fall below 90% despite adequate oxygen delivery. Most of the agents employed for sedation of patients undergoing endoscopy, including 10% xylocain, midazolan, flumazenil and propofol have longer half-lives in subjects with advanced cirrhosis and may need adjustment of dosage. Midazolan may also induce hepatic encephalopathy in those patients[5], but its efficacy and safety has been shown to be similar to propofol in subjects with Child-Pugh A and B cirrhosis[159]. Propofol has the advantage of a titulated rapid onset of action (40 seconds) followed by a quick awakening. It can be used in lower doses in association with low doses of midazolan or narcotics, enhancing its safety profile[98]. However, it has the propensity to induce bradyarrhythmias, particularly when used in subjects under therapy with terlipressin. Even in the absence of active bleeding, endoscopic treatment of esophageal varices is recommended after exclusion of other possible bleeding lesions, since a third of these patients with variceal hemorrhage have no signs of active bleeding at the moment of endoscopy[91].

Combined endoscopic and pharmacologic treatment is superior to each treatment modality[7, 9, 72, 94, 156], but the use of vasoactive drugs should precede endoscopic hemostasis. Esophageal band ligation is the endoscopic treatment of choice[132]. When compared to sclerotherapy, EBL is associated with a minor risk of rebleeding, adverse events and mortality, as well as less requirement for endoscopic procedures for variceal obliteration[90]. Use of cyanoacrylate glue injection has been evaluated for treatment of esophageal varices[96], but there are no RCT comparing its use to EBL in subjects with cirrhosis.

Proton pump inhibitors (PPI) have been employed for prevention of bleeding from esophageal ulcers induced by sclerotherapy or EBL, however major benefit with the use of these agents have not been observed in prevention of ulcers after esclerotheraphy[70] and in the healing of postbanding ulcers[19]. Treatment of bleeding from postbanding ulcers or ulcers after sclerotherapy should be individualized.

Recommendations:

1) *Upper gastrointestinal endoscopy should be ideally performed in the first 12 hours of bleeding from esophageal varices*
2) *Airway protection is recommended in patients with massive bleeding, grades III and IV hepatic encephalopathy or respiratory failure*
3) *Esophageal band ligation is the endoscopic procedure of choice, but sclerotherapy remains an option in the unavailability of EBL or when EBL is technically not feasible*
4) *Combined endoscopic and pharmacologic treatment with vasoactive drugs is superior to each treatment modality and should be recommended for patients with variceal hemorrhage*

5) Prevention and management of complications: infections, hepatic encephalopathy and renal failure

Infections are observed in approximately 20% of the patients with variceal bleeding at admission and in 50% of them during hospitalization[18, 52]. In addition, worsening of PH and higher variceal bleeding recurrence have been observed in subjects with variceal hemorrhage and bacterial infections. The occurrence of these infections is associated with a five-fold increase in bleeding recurrence with an adverse impact on survival[12, 76, 133, 134].

The most frequent infections seen in cirrhosis are urinary tract infection, spontaneous bacterial peritonitis (SBP), lower respiratory tract infection and spontaneous bacteremia with or without sepsis. These infections should be systematically sought in every subject with variceal bleeding by means of blood cultures, abdominal tap for ascitic fluid analysis and culture, in blood culture bottles, as well as urine sediment analysis and chest X-rays[28].

Antibiotic prophylaxis has been associated with reduction of 58% in the risk of infections in cirrhosis with variceal bleeding and with a decrease of 29% in the relative risk for

mortality[14, 130]. Several antibiotics have been evaluated, but oral norfloxacin 400 mg 2 times per day for 7 days is the most commonly prescribed regimen due to its safety profile and cost[69]. Recently, Fernandez et al.[56] compared in a RCT intravenous ceftriaxone 1 g/day to the standard oral norfloxacin regimen of 400 mg 2 times per day for 7 days in subjects with cirrhosis and variceal bleeding with at least two of the following criteria: ascitis and/or malnutrition and/or encephalopathy and/or bilirubin greater than 3 mg/dL. The authors have described a significant reduction in the frequency of infections (11% vs 26%) and SBP (2% vs 12%) in the group treated with ceftriaxone.

Gastrointestinal bleeding is a recognized risk factor for hepatic encephalopathy. However, there is no evidence to support the use of non-absorbable disaccharides, benzodiazepine antagonists, antibiotics or L-Ornitine L-Aspartate in the prevention of hepatic encephalopathy in subjects with variceal bleeding.

Hypovolemia with or without acute tubular necrosis and renal injury induced by infections are the most common types to renal failure (RF) seen in cirrhotics. Hepatorenal syndrome (HRS) can however occur in the course of both of aforementioned conditions. Cárdenas et al.[32] described the occurrence of RF in 11% of the subjects with variceal bleeding. In those patients, RF was associated with the magnitude of the bleeding episode, shock, the need for transfusions and with severity of liver disease according to the Child-Pugh classification. Evolution to HRS was shown in 35% of the cases. Even though high-dose albumin infusion has been recommended for patients with HRS by the International Ascitis Club[121], it should be used with caution in order to avoid volume overload with worsening of PH and variceal rebleeding. Patients with variceal bleeding which develop HRS are amenable to treatment with high-dose albumin and terlipressin.

Recommendations:

1) *Infections, particularly urinary tract infection, SBP and lower respiratory tract infection should be sought in all patients with variceal bleeding*
2) *Screening for infections should include at least blood cultures, ascitic fluid analysis and culture, urine sediment analysis and chest X rays*
3) *Antibiotic prophylaxis is mandatory to reduce the incidence of infections, variceal rebleeding and mortality*
4) *Oral quinolones, particularly norfloxacin 400 mg twice a day, or third generation cephalosporin, particularly intravenous ceftriaxone 1 g a day, could be recommended for prophylaxis during 7 days. Patients with advanced cirrhosis and/or hemodynamic instability should receive preferentially intravenous ceftriaxone*
5) *Based on current data, there is no evidence to recommend any prophylaxis for hepatic encephalopathy in patients with variceal bleeding*
6) *Even though hypovolemia is the most common cause of renal failure in subjects with variceal bleeding, the occurrence of HRS should be evaluated and whenever indicated treated with high-dose albumin and terlipressin.*

PART III: TREATMENT FAILURE, VARICEAL BLEEDING RECURRENCE AND SECONDARY PROPHYLAXIS

1) Treatment failure

There are some controversies on the appropriate definition of treatment failure for acute variceal bleeding. The Baveno II and III consensus have considered 2 time periods for evaluation of treatment failure, either before or after 6 hours of admission[49]. The Baveno IV consensus extended this period for 5 days and adopted the following criteria to characterize treatment failure to initial treatment: a) onset of hematemesis 2 or more hours after pharmacologic or endoscopic therapy; b) fall in hemoglobin levels in 3 g/dL in non-transfused cases; c) need for transfusions according to the ABRI index (adjusted blood requirement index) ≥0,75. This index takes into consideration the number of units of packed blood cells transfused (UT), the initial and final hematocrit (Ht) and a constant value of 0,01, according to the equation: ABRI = UT/(final Ht – initial Ht) + 0,01[49].

Other criteria have also been employed at the bedside to define treatment failure to control bleeding, including tachycardia >120 beats per minute; fall of arterial pressure of more than ≥20 mm Hg despite blood transfusions and fluids; hematemesis, hematochezia or fresh blood aspirates from nasogastric suction of more than 100 mL/hour after 6 hours of treatment.

The management of treatment failure should be individualized. Placement of Sengstaken-Blakemore tubes should be considered in patients with massive bleeding as a bridge for definite therapy with TIPS or surgery[6]. In patients with failure of pharmacologic treatment, vasoactive drugs could be adjusted, increasing terlipressin dosage to 2 mg every 4 hours, in the absence of contraindications or somatostatin up to 500 mcg/hour. However, there is no data to support the efficacy of such approach. In cases where endoscopic treatment has not yet been performed, it should be prioritized[9, 49].

In cases of failure of endoscopic treatment, one more attempt of endoscopic hemostasis, preferably with EBL should be performed. In cases where no vasoactive drugs have been used, pharmacologic therapy should be promptly introduced.

Failure of combined endoscopic and pharmacologic treatment could be managed with one more endoscopic attempt of hemostasis and with an increase in dosage of vasoactive drugs. As treatment failure is often associated with severity of PH that is frequently refractory to endoscopic and/or pharmacologic therapies, eligibility for TIPS should be evaluated as early as possible[22, 105].

Recommendations:

1) *In cases of treatment failure, initial treatment options should be reassessed. Endoscopic or pharmacologic treatments should be instituted in subjects that have not received initially combined therapy*
2) *After the first endoscopic treatment, one more attempt of endoscopic hemostasis is indicated in the presence of treatment failure*

3) *Use of escalating doses of vasoactive drugs, up to 2 mg every 4 hours of terlipressin and 500 mcg/hour of somatostatin could be tried in cases of treatment failure to pharmacologic treatment, but there is no evidence to support this approach*
4) *Sengstaken-Blakemore tubes remain an option for patients with massive bleeding as a bridge for more definitive treatment modalitie.*
5) *Shunt surgery and preferably TIPS, should be employed in patients with variceal bleeding refractory to standard combined pharmacologic and endoscopic therapy*

2) What is the best strategy for secondary prophylaxis?

Variceal rebleeding after treatment of the acute bleeding episode occurs in 63% of the subjects that are not submitted to secondary prophylaxis with an associated cumulative mortality of 33%[13].

Non-selective betablockers decrease the cardiac load and induce splancnic arterial vasoconstriction, thereby reducing portal flow and pressure. Several RCT have shown benefits with the use of NSBB in secondary prophylaxis of variceal bleeding. Two meta-analyses[13, 42] confirmed a significant reduction of rebleeding from 68% to 48% at 2 years of follow-up with a reduction in mortality of 5%[42]. In addition, three other RCT with prolonged follow-up periods have demonstrated that patients with a satisfactory response to NSBB, determined by a fall of HVPG <12 mm Hg, have lower risk of bleeding recurrence and mortality as well as other complications of cirrhosis such as ascitis, SBP, hepatic encephalopathy and renal failure[2, 148, 154].

Therefore, NSBB remains the first-line drug for secondary prophylaxis of variceal bleeding[13, 42]. They should be instituted early after hemodynamic compensation, usually in the 6th day after variceal bleeding. Contraindications for their use include chronic obstructive pulmonary disease, heart failure, severe bradyarrhythmias, cardiac conduction disturbances and arterial hypotension. Drug adjustments should be made to attain the maximal dose tolerated by the patient, usually starting with propranolol 20 mg 2 times a day. Adherence to treatment is crucial, since drug interruption may lead to a rebound increase in portal pressure and variceal bleeding.

Only 40% of treated patients achieve the desired response to NSBB characterized by a reduction of portal pressure below 12 mm Hg or to levels 20% lower than baseline values. In non-responders, association of NSBB with isosorbide mononitrate can increase in 10%-20% the response rate. However, as measurement of HVPG is unavailable outside reference centers, selection of candidates for combination therapy with NSBB and isosorbide mononitrate is not feasible in clinical practice and the usefulness of such approach is still under debate[49, 68].

Sclerotherapy was the first endoscopic treatment employed for secondary prophylaxis approximately 30 years ago. With the advent of EBL[150], several RCT have demonstrated better outcomes with the use of EBL when compared to sclerotherapy[90]. In fact, prevention of bleeding recurrence was shown to be similar with both treatment modalities, but adverse events were significantly increased with sclerotherapy when compared to EBL[82]. Up to now, EBL is considered the endoscopic method of choice for secondary prophylaxis.

Studies comparing combination treatment with sclerotherapy and NSBB vs treatment with either sclerotherapy or NSBB have yielded similar results. Several other RCT have been performed comparing NSBB vs EBL for secondary prophylaxis with conflicting results. On the other hand, combination of NSBB and EBL was shown to be superior to either EBL or NSBB and is currently considered as the best therapeutical choice for secondary prophylaxis[51, 126].

In patients with intolerance or contraindications to NSBB, EBL is recommended. In subjects without an hemodynamic response to NSBB, there is no consensus on the efficacy of EBL[26, 157].

Recommendations:

1) *Combination of NSBB and EBL is recommended for secondary prophylaxis of variceal bleeding in subjects with cirrhosis*
2) *NSBB should be adjusted to the maximal tolerated dosage and must not be abruptly discontinued since treatment interruption may lead to variceal bleeding*
3) *EBL is the best endoscopic treatment modality for secondary prophylaxis*

3) Management of patients with recurrent bleeding

Failure of secondary prophylaxis is defined as the occurrence of any significant bleeding episode related to PH in patients on therapy aimed at prevention of variceal rebleeding[49].

According to Baveno IV criteria, early rebleeding is considered when variceal hemorrhage recurs within 6 weeks after the first bleeding episode. It is observed in 30% to 40% of the cases and is significantly associated with an increased risk of mortality. It differs from treatment failure, which is defined by the occurrence of any bleeding in the first 5 days after variceal hemorrhage[21, 49].

Risk factors for recurrent bleeding include Child-Pugh C advanced liver disease, presence of hepatocellular carcinoma, failure of variceal obliteration with endoscopic treatment and HVPG levels higher than 20 mm Hg[20, 22].

Measurement of HVPG within 2 to 3 months after any pharmacological intervention is valuable for assessing prognosis due to its ability to predict rebleeding, particularly in patients on NSBB, but this approach can not yet be routinely recommended for a la carte management of patients with PH[153].

It should be also stressed that recurrent bleeding can occur in 25% of the patients before variceal obliteration while on endoscopic treatment for secondary prophylaxis. After endoscopic eradication of varices, the frequency of rebleeding falls significantly[132].

Current evidence have disclosed better results for combined endoscopic and pharmacologic treatment for management of recurrent bleeding in patients under either treatment modalities[72]. In the occurrence of failure of combined treatment, TIPS or shunt surgery are treatment options, but TIPS is a more reasonable alternative because it is less

aggressive when compared to surgery and has the same efficacy to control bleeding. It is currently indicated as rescue therapy, but no impact in mortality has been associated with this approach[37, 77, 113]. Sengstaken-Blakemore tube placement can be life-saving and may act as a bridge for TIPS in patients with massive bleeding

Recommendations:

1) *Patients under secondary prophylaxis should be closely followed particularly those at risk for recurrent bleeding*
2) *In the presence of failure of secondary prophylaxis, treatment should be reassessed and combined therapy with EBL and NSBB should be started on patients who were either on EBL or NSBB*
3) *When combined treatment with NSBB and EBL fails, rescue therapy with TIPS or shunt surgery, when TIPS is unavailable, are reasonable options*

4) Role of TIPS and surgery on variceal bleeding

Transjugular intrahepatic portosystemic shunt is performed by placement of an intrahepatic stent between the portal vein and the hepatic vein branches, directing the portal blood flow to the systemic circulation and thereby reducing portal pressure. Several meta-analysis and systematic reviews have demonstrated efficacy for TIPS in the control of bleeding from esophageal varices. However, there is no evidence to support its impact on survival when used as rescue therapy[37, 77, 113]. Small-caliber and/or covered stents are more expensive when compared to standard stents, but are associated with better outcomes due to a decrease in the frequency of complications such as encephalopathy and of TIPS dysfunction due to thrombosis or occlusion[37].

Absolute contraindications for TIPS are present or past history of persistent or recurrent hepatic encephalopathy, heart failure, severe portopulmonary hypertension, severe end-stage liver disease, polycystic liver disease, liver abscess and ongoing sepsis, while the presence of liver tumors, hepatic or portal vein thrombosis and biliary obstruction are considered as relative contraindications for TIPS placement. Bad outcomes were reported in patients with MELD scores higher than 18, bilirubin levels higher than 3 mg/dL and multiple organ dysfunction[37].

Subjects with variceal bleeding with HVPG higher than 20 mm Hg at admission are frequently refractory to standard therapy and may have benefit from early TIPS placement[105], however more data is needed to confirm the role of such strategy.

Emergency shunt surgery may be needed when TIPS is unavailable in order to rescue patients from treatment failure, but it is important to acknowledge that nowadays not so many surgeons have expertise in less morbid surgical options such as selective splenorenal, mesocaval or 8 mm H-graft portacaval shunts, which are more suitable in the setting of cirrhosis[77, 120]. Azigos-portal vein disconnection with splenectomy has a role in the management of schistosomal PH, but not in PH due to cirrhosis. Recurrence of variceal bleeding is an issue after azygous portal disconnection, whereas distal splenorenal shunt can be associated with difficult-to-treat hepatic encephalopathy. Shunt surgery should not be performed in patients with portopulmonary hypertension.

Recommendations:

1) *TIPS is effective as a rescue therapy for variceal hemorrhage after failure of treatment with EBL and NSBB, but current evidence do not support better survival rates*
2) *Use of calibrated and/or covered stents are associated with better outcomes, but cost remains an important issue*
3) *When surgery is needed as rescue therapy, selective splenorenal, mesocaval or 8 mm H-graft portacaval shunts are preferable in cirrhotics, while azygos-portal vein disconnection with splenectomy remains the most appropriate surgical choice in patients with schistosomal PH. Surgical expertise is required to achieve better outcomes*

PART IV: SPECIAL SITUATIONS

1) Management of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE)

Portal hypertensive gastropathy and GAVE are distinct entities capable of inducing either acute upper gastrointestinal bleeding or occult blood losses and chronic anemia. Portal hypertensive gastropathy is secondary to gastric mucosa and submucosa abnormalities due to PH related or not to cirrhosis. The natural history of PHG have been evaluated in 315 cirrhotic patients. Gastric lesions have been demonstrated at endoscopy to remain stable, to aggravate or to partially regress in 29%, 23% and 23% of the patients, respectively. In the other 25% of the cases, the severity of the lesions was shown to fluctuate in follow-up endoscopies. Acute upper gastrointestinal bleeding and occult blood losses occurred in 2.5% and 11% of those subjects, respectively[118]. The most frequent endoscopic lesions seen in patients with PHG are the mosaic pattern with or without mucosal bleeding that is more commonly found in the body and the fundus of the stomach, but also occur in the gastric antrum as well as in the small bowel and colon. Severe PHG is associated with the presence of red signs such as cherry-red spots, red wale signs or an scarlatin-like appearence[138]. It should be remembered that these findings are fairly unespecific and that data concerning the accuracy of endoscopy for the diagnosis of PHG are scarce. In this regard, Papazian et al[114] reported sensitivity and specificity of 93% and 99% of endoscopy with biopsies for the detection of the mosaic pattern.

Gastric antral vascular ectasia can occur in patients with PH, but approximately 70% of the cases of GAVE have been reported in subjects without liver diseases. Three patterns of GAVE have been recognized at endoscopy including: 1) watermelon stomach, defined by the presence of red stripes consisting of columns of dilated cappilaries that converges toward the pylorus; 2) diffuse type, characterized by the coalescence in the antrum of red honeycomb-lyke lesions, and 3) nodular or mushroom pattern, characterized by elevated red lesions formed by ectatic blood vessels[138].

In respect to the management of PHG, the use of NSBB was associated with reduction in portal pressure and gastric mucosal blood flow[78, 93], as well as with lower rates of bleeding

recurrence in one RCT[115]. Despite these findings, there is insufficient data to support straightforward recommendations. Iron supplementation may be required in subjects with iron-deficiency anemia due to chronic gastrointestinal losses. In patients with active bleeding, vasoactive drugs such as somatostatin, octreotide and terlipressin have been shown to reduce portal blood flow and to control bleeding in uncontrolled studies[54, 86], but endoscopic hemostasis is usually not feasible due to the presence of diffuse oozing lesions. However, when dominant bleeding lesions are encountered, endoscopic injection or thermal therapy can be empirically performed. Few studies have investigated the role of TIPS or shunt surgery for treatment of PHG[81, 110]. Kamath et al.[81] have reported the results of TIPS placement in 40 patients with PHG and 14 subjects with GAVE. Partial regression of endoscopic lesions and reduction in the requirement for blood transfusions were seen in 75% of the cases of PHG, but no benefit was observed in subjects with GAVE.

Other treatment modalities were described anedoctally for patients with GAVE. Antrectomy remains a choice for patients without liver disease, but carry a high mortality rate in subjects with cirrhosis[131]. Gastric acid suppression is ineffective[88]. Laser or argon beam coagulation as well as hormones, tranexamic acid and octreotide have been tried with varying results[11, 36, 89, 97, 140, 147]. Despite the lack of RCT, argon beam coagulation is considered to be good option for treatment of patients with GAVE due to its cost and safety profile[60].

Recommendations:

1) *PHG and GAVE are causes of upper gastrointestinal bleeding in patients with PH with or without cirrhosis but are recognized as two separate entities with distinct management and therapeutical options*
2) *Due to the lack of data, no recommendations can be drawn for primary prophylaxis of bleeding in PHG*
3) *First-line therapy for occult blood losses from PHG is NSBB and iron supplementation*
4) *Endoscopic therapy with injection or thermal methods, particularly argon beam coagulation, may be attempted in those subjects with PHG and GAVE with amenable bleeding lesions identified at endoscopy*
5) *In respect to patients with acute bleeding from PHG, vasoactive drugs (terlipressin, somatostatin or octreotide) should be employed despite lack of good data. NSBB should as well be introduced after control of the acute bleeding episode. There is no role for vasoactive drugs or NSBB for treatment of GAVE*
6) *TIPS or shunt surgery can be tried as a last resource for patients with PHG refractory to standard treatment, particularly for patients with severe or recurrent bleeding or subjects with anemia requiring multiple red blood cells transfusions to maintain adequate hematocrit levels. There is no role for TIPS or shunt surgery in GAVE*

2) Management of gastric and ectopic varices

Gastric varices occur in less than one fifth of the patients with PH, often in association with esophageal varices. When compared to esophageal varices, they tend to bleed less often, but hemorrhage is frequently more severe and is associated with higher risks for rebleeding and mortality[125, 137, 146]. Due to its lower prevalence, there is less data corcerning the management of gastric varices in comparison with esophageal varices.

Gastric varices are classified in different types according to Sarin et al.[124], who recognized two groups of varices: gastro-oesophageal varices (GOV) and isolated gastric varices (IGV). The GOV are further classified in: a) GOV type 1, defined as varices that occur as extension of esophageal varices through the lesser curvature of the stomach and b) GOV type 2, referred as those varices that extends from the esophagus toward the gastric fundus. The IGV are subclassified as: a) IGV type 1, when localized in the gastric fundus and b) IGV type 2, when they occur elsewhere in the stomach. Other varices anywhere in the gastrointestinal tract are named ectopic varices.

Seventy per cent of the cases of gastric varices are classified as GOV type 1, whereas GOV type 2 and IGV type 1 are identified in 21% and 7% of the cases, respectively. Findings of IGV type 2 are exceptional. Bleeding can occur in 70% of the patients with GOV type 1 and in 10% of the cases of GOV type 2 and IGV-1[124, 143]. Subjects with varices larger than 5 mm, red signs on varices, advanced cirrhosis have higher risk for bleeding[84]. There are no data on primary phophylaxis for patients with gastric varices, but NSBB could be beneficial due to its lowering effect on portal pressure. There is insufficient data on cyanoacrylate endoscopic injection, but the use of this agent in primary prophylaxis is hampered by its safety profile. Balloon-occluded retrograde transvenous obliteration (BRTO) have been reported in Asia as a relatively safe method for obliteration of fundal varices in subjects with gastrorenal shunts. Obliteration was achieved in 90% of the cases with a recurrence rate of only 7%[84, 109]. Thus, in those subjects with gastric varices and gastrorenal shunts under a high risk for bleeding, BRTO could be a reliable option for primary prophylaxis, but consistent data is still lacking.

Therapeutic measures employed for the management of acute bleeding from esophageal varices can also be applied to hemorrhage due to gastric varices. Hovewer, endoscopic therapy with band ligation or sclerotherapy remains options only for selected cases of GOV type 1. In other gastric varices, cyanoacrylate endoscopic injection is more effective for the control of bleeding, when compared to other endoscopic therapies (23% vs 47%)[136]. However, there are no data favoring the use of cyanoacrylate endoscopic injection when it is compared to TIPS as the first-line treatment of acute or recurrent bleeding due to gastric varices. Due to the safety profile and cost of TIPS, cyanoacrylate endoscopic injection is preferred for treatment of the acute bleeding episode. TIPS has been shown to control bleeding in 90% of the cases with recurrence rates of 10%-30% at 1 year[10, 34]. However, some studies[122, 142] failed to demonstrate efficacy of TIPS in patients with gastric varices.

Acute hemorrhage from gastric varices has also been successfully treated with BRTO in the aforementioned selected cases, with no bleeding recurrence on up to 2 years after treatment and no bleeding recurrence[109]. However,

experience with this technique is limited outside Asia. It has the propensity to worsen esophageal varices and as previously mentioned can be applied only to those subjects with concurrent gastrorenal shunts[61, 109].

Recommendations:

1) *There is no data regarding primary prophylaxis of bleeding from gastric varices. As NSBB can reduce portal pressure, they are an acceptable treatment option. In patients with a high risk for bleeding, BRTO may be employed in those subjects with gastrorenal shunts, depending on local expertise*
2) *Cyanoacrylate endoscopic injection is preferred for treatment of hemorrhage from GOV type 2 and IGV. NSBB should be introduced after the control of bleeding. However, as cyanoacrylate endoscopic injection can induce fatal thromboembolic events, it should be avoided in patients with hepatopulmonary syndrome and intracardiac shunts*
3) *The management of GOV type 1 should be the same as esophageal varices*
4) *There are paucity of data to rely on to draw any recommendation concerning ectopic varices. Depending on variceal size, cyanoacrylate endoscopic injection and band ligation are acceptable choices*
5) *TIPS should be considered as a rescue therapy after failure to control active or recurrent bleeding*
6) *BRTO may be employed in selected patients with gastric varices and gastrorenal shunts with active or recurrent bleeding, but experience with this method is limited*

3) Management of PH in patients with extrahepatic portal vein obstruction (EHPVO) and non-cirrhotic portal hypertension

Most of the cases of non-malignant EHPVO in adults are associated with acquired and/or inherited thrombophilia (60%-70%) or with the presence of end-stage chronic liver disease[15]. It is estimated that 8%-15% of the patients with cirrhosis can develop EHPVO even in the absence of hepatocellular carcinoma[3, 59].

Up to now, there are no RCT comparing treatment options for adult patients with EHPVO. Most of the guidelines regarding its management are based on uncontrolled data or experts opinions[16, 40, 49, 149].

Uncontrolled studies have demonstrated obliteration of varices and reduction of bleeding episodes from esophageal varices in patients with EHPVO submitted to sclerotherapy, but there are no data concerning EBL, which is superior to sclerotherapy in subjects with cirrhosis[80, 158]. Two studies have shown benefit with the use of NSBB or endoscopic therapy in the prevention of bleeding and recurrent bleeding[39, 111], but data are not so strong to support any recommendation.

TIPS has been employed, particularly in subjects with associated hepatic vein thrombosis. However, it is difficult to ascertain its efficacy in the management of patients with associated EHPVO[128]. Data concerning splenectomy or disconnection procedures are also limited.

There are no RCT regarding the management of acute variceal bleeding in patients with EHPVO. The theoretical concern that vasoactive drugs could lead to thrombus extension has never been proved[127].

Mesentericoportal shunt, also named Rex shunt procedure, could be indicated particularly in children and young adults with variceal bleeding refractory to standard therapy or with severe hypersplenism or growth retardation[135].

The influence of the subjacent thromboembolic disorder associated with EHPVO on its natural history should be carefully evaluated. Anticoagulation of patients with recent portal vein thrombosis leads to either complete or partial portal vein recanalization in 37% and 56% of the patients, respectively[38]. Two previous consensus conferences have recommended anticoagulation for at least 3 months in subjects with recent portal vein thrombosis. Life-long anticoagulation may be needed for those patients with documented acquired and/or inherited thrombophilia. In patients with chronic EHPVO (cavernoma), prolonged anticoagulation has not been related either to an increased risk or to severity of bleeding from esophageal varices[39]. In those subjects, anticoagulation should be considered, particularly in the presence of prothrombotic risk factors due to the risk of recurrent thrombosis in the splancnic or in the systemic circulation[39, 40, 116].

Recommendations:

1) *For EHPVO, there is no evidence to support recommendations regarding the use of NSBB or endoscopic treatment for primary prophylaxis of hemorrhage due to esophageal varices, but both treatment options are acceptable for patients at risk for bleeding*
2) *In the absence of data, management of acute variceal bleeding should include the same measures currently employed in cirrhosis, including vasoactive drugs and EBL*
3) *EBL can be used for secondary prophylaxis due to its safety and efficacy. There are no data to suggest a role for NSBB or for the association of EBL and NSBB to prevent recurrent bleeding in EHPVO*
4) *Anticoagulation should be instituted for patients with recent portal vein thrombosis no more than 30 days after its diagnosis and should be continued for 3-6 months, In subjects with chronic EHPVO and inherited or acquired thrombofilia anticoagulation should be life-long.*

4) Management of portal hypertension due to schistosomiasis

Data concerning the management of PH due to schistosomiasis are either scarce or uncontrolled and mainly based on experts opinion[15, 123]. As a matter of fact, for primary prophylaxis and control of the acute bleeding episode, treatment options do not differ from those employed in cirrhosis[15]. For secondary prophylaxis, there are controlled data indicating that azigos portal disconnection is the best surgical treatment[119], but there are no RCT comparing surgery to EBL or NSBB[15].

Short-term hemodynamic studies have suggested that high doses of NSBB are required to lower portal pressure in patients with PH due to schistosomiasis[101], but these findings were not reproduced in another study that measured variceal pressure in subjects with PH due to schistosomiasis[55].

Furthermore, one study has shown benefit on rebleeding rates and mortality with the use of propranolol[53].

Recommendations

1) *In PH due to schistosomiasis, there are no data to suggest efficacy for NSBB or EBL on primary prophylaxis of variceal bleeding, but both strategies are acceptable for patients at risk for bleeding. Sclerotherapy should be avoided*
2) *Despite lack of data, the same treatment options employed for the control of acute variceal hemorrhage in cirrhosis may be applied in subjects with PH due to schistosomiasis*
3) *For secondary prophylaxis of variceal bleeding, either EBL or the association of EBL and NSBB are acceptable, but evidence is not strong*
4) *There are no data favoring surgery over EBL or NSBB for secondary prophylaxis in PH due to schistosomiasis. Due to its efficacy and safety, EBL with or without NSBB should be recommended. Surgery, on the other hand, is recommended as rescue therapy in cases of failure of endoscopic or combined treatment*
5) *Surgical treatment options do influence clinical outcomes and azygos portal disconnection is the surgical procedure of choice in subjects with PH due to schistosomiasis*

Bittencourt PL, Farias AQ, Strauss E, Mattos AA; Membros do Painel do 1º Consenso Brasileiro de Hemorragia Varicosa da Sociedade Brasileira de Hepatologia. Hemorragia digestiva alta varicosa: relatório do 1º Consenso da Sociedade Brasileira de Hepatologia. Arq Gastroenterol. 2010;47(2):202-16.

RESUMO - Vários avanços científicos obtidos nas últimas duas décadas foram incorporados no manejo da hemorragia digestiva alta varicosa, levando a uma redução significante da sua morbimortalidade, atribuída à abordagem multidisciplinar do sangramento varicoso por paramédicos, emergencistas, intensivistas, gastroenterologistas, hepatologistas, endoscopistas, radiologistas intervencionistas e cirurgiões. Recentemente, a Sociedade Brasileira de Hepatologia patrocinou uma reunião de consenso, visando o estabelecimento de recomendações nacionais, sobre o manejo da hemorragia digestiva alta varicosa, incluindo sua prevenção, diagnóstico e tratamento, de acordo com a melhor evidência científica disponível. A diretoria da Sociedade Brasileira de Hepatologia elegeu quatro membros para a comissão organizadora que, por sua vez, convidou 27 pesquisadores de diferentes regiões do país, para realizar uma revisão sistemática sobre tópicos relacionados ao manejo hemorragia digestiva alta varicosa. A reunião de consenso ocorreu em Salvador, BA, em 6 de março de 2009. Após o encontro, todos os participantes se reuniram para elaboração das recomendações, cuja redação ficou sob a responsabilidade da comissão organizadora. O presente artigo descreve as recomendações da Sociedade Brasileira de Hepatologia sobre o manejo do sangramento associado à hipertensão portal, divididas em módulos e precedidas por resumo das apresentações realizadas na reunião de consenso.

DESCRITORES – Hemorragia gastrointestinal. Cirrose hepática. Varizes esofágicas e gástricas. Consenso.

REFERENCES

1. Abraldes JG, Bosch J. Novel approaches to treat portal hypertension. J Gastroenterol Hepatol. 2002;17:s232-s41.
2. Abras JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology. 2003;37:902-8.
3. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736-41.
4. Argo CK, Balogun RA. Blood products, volume control, and renal support in the coagulopathy of liver disease. Clin Liver Dis. 2009;13:73-85.
5. Assy N, Paizi M, Gaitini D, Baruch Y, Spira G. Clinical implication of VEGF serum levels in cirrhotic patients with or without portal hypertension. World J Gastroenterol. 1999;5:296-300.
6. Avgerinos A, Armonis A. Balloon tamponade technique and efficacy in variceal haemorrhage. Scand J Gastroenterol Suppl. 1994;207:11-6.
7. Avgerinos A, Nevens F, Raptis S, Fevery J; The ABOVE Study Group. Early administration of somatostatine and efficacy of sclerotherapy in acute esophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. Lancet. 1997;350:1495-9.
8. Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut. 2008;57:814-20.
9. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, Salcedo M, Molinero LM. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology. 2002;35:609-15.
10. Barange K, Péron JM, Imani K, Otal P, Payen JL, Rousseau H, Pascal JP, Joffre F, Vinel JP. Transjugular intrahepatic portosystemic shunt in the treatment of refractory bleeding from ruptured gastric varices. Hepatology. 1999;30:1139-43.
11. Barbara G, De Giorgio R, Salvioli B, Stanghellini V, Corinaldesi R. Unsuccessful octreotide treatment of the watermelon stomach. J Clin Gastroenterol. 1998;26: 345-6.
12. Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology. 1995;108:1828-34.
13. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. Hepatology. 1997;25:63-70.
14. Bernard B, Grangé 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.
15. Bittencourt PL. Portal fibrosis and schistosomal portal hypertension: what is the best strategy for primary and secondary prevention of hemorrhage from esophageal varices. Arq Gastroenterol. 2003;40:1-3.
16. Bittencourt PL, Couto CA, Ribeiro DD. Portal vein thrombosis and Budd-Chiari syndrome. Clin Liver Dis. 2009;13:127-44.
17. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal hemorrhage. Br J Surg. 1986;73:783-5.
18. Bleichner G, Boulanger R, Squara P, Sollet JP, Parent A. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. Br J Surg. 1986;73:724-6.
19. Boo GB, Oh JC, Lee BJ, Lee DM, Kim YD, Park CG, Kim MW. The effect of proton pump inhibitor on healing of post-esophageal variceal ligation ulcers. Korean J Gastroenterol. 2008;51:232-40.
20. Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology. 1999;117:626-31.
21. Bosch J, Abraldes JG, Groszmann R. Current management of portal hypertension. J Hepatol. 2003;38(suppl 1):s54-s68.
22. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. J Hepatol. 2008;48:s68-s92.
23. Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, D'Amico G, Lebrec D, de Franchis R, Fabricius S, Cai Y, Bendtsen F; International Study Group on rFVIIa in UGI Hemorrhage. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. Hepatology. 2008;47:1604-14.

24. Boyer T. Portal hypertension and bleeding esophageal varices. In: Boyer TD, Wright TL, Manns MP, editors. Zakim & Boyer's hepatology: a textbook of liver disease. 5th ed. Philadelphia: Saunders Elsevier; 2006. p.372
25. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut. 2002;51(suppl 4):iv1-6.
26. Bureau C, Péron JM, Alric L, Morales J, Sanchez J, Barange K, Payen JL, Vinel JP. "A La Carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology. 2002;36: 1361-6.
27. Calés P, Oberti F, Payen JL, Naveau S, Guyader D, Blanc P, Abergel A, Bichard P, Raymond JM, Canva-Delcambre V, Vetter D, Valla D, Beauchant M, Hadengue A, Champigneulle B, Pascal JP, Poynard T, Lebrec D. Lack of effect of propranolol in the prevention of large esophageal varices in patients with cirrhosis: a randomized trial. French-Speaking Club for the Study of Portal Hypertension. Eur J Gastroenterol Hepatol. 1999;11:741-5.
28. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. J Hepatol. 1993;18:353-8.
29. Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. Curr Opin Crit Care. 2008;14:189-97.
30. Cappell MS, Friedel D. Initial management of acute upper gastrointestinal bleeding: from initial evaluation up to gastrointestinal endoscopy. Med Clin North Am. 2008;92:491-509.
31. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology. 2004;40:652-9.
32. Cárdenas A, Ginès P, Uriz J, Bessa X, Salmerón JM, Mas A, Ortega R, Calahorra B, De Las Heras D, Bosch J, Arroyo V, Rodés J. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology. 2001;34:671-6.
33. Castañeda B, Morales J, Lionetti R, Moitinho E, Andreu V, Pérez-Del-Pulgar S, Pizcueta P, Rodés J, Bosch J. Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats. Hepatology. 2001;33:821-5.
34. 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;114:981-7.
35. Chen W, Nikolova D, Frederiksen SL, Gluud C. Beta-blockers reduce mortality in cirrhotic patients with oesophageal varices who have never bled (Cochrane review) [abstract]. J Hepatol. 2004;40(suppl 1):67.
36. Cho S, Zanati S, Yong E, Cirocco M, Kandel G, Kortan P, May G, Marcon N. Endoscopic cryotherapy for the management of gastric antral vascular ectasia. Gastrointest Endosc. 2008;68:895-902.
37. Colombato L. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. J Clin Gastroenterol. 2007;41(suppl 3):s344-s51.
38. Condat B, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. Hepatology. 2000;32:466-70.
39. Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, Hadengue A, Erlinger S, Valla D. Current outcome of portal vein in adults: risk and benefit of anticoagulant therapy. Gastroenterology. 2001;120:490-7.
40. Condat B, Valla D. Nonmalignant portal vein thrombosis in adults. Nat Clin Pract Gastroenterol Hepatol. 2006;3:505-15.
41. Conn HO, Lebrec D, Terblanche J. The treatment of oesophageal varices: a debate and a discussion. J Intern Med. 1997;241:103-8.
42. D'Amico G, Bosch J. The treatment of portal hypertension: a metanalityc review. Hepatology. 1995;22:332-54.
43. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. Bailliere's Clin Gastroenterol. 1997;11:243-56.
44. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis. 1999;19:475-505.
45. D'Amico G, de Franchis R. Upper digestive bleeding in cirrhosis. Posttherapeutic outcome and prognostic indicators. Hepatology. 2003;38:599-612.
46. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein presure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology. 2006;131:1611-24.
47. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44: 217-31.
48. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. Clin Liver Dis. 2001;5:645-63.
49. 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 Hepatol. 2005;43:167-76.
50. de Franchis R, Dell'Era A. Novel developments in esophageal vascular disorders. Curr Opin Gastroenterol. 2008;24:490-5.
51. de la Peña J, Brullet E, Sanchez-Hernández E, Rivero M, Vergara M, Martin-Lorente JL, Garcia Suárez C. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology. 2005;41:572-8.
52. Deschênes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. Am J Gastroenterol. 1999;94:2193-7.
53. El-Tourabi H, el Amin AA, Shaheen M, Woda SA, Homeida M, Harron DW. Propranolol reduces mortality in patients with portal hypertension secondary to schistosomiasis. Ann Trop Med Parasitol. 1994;88:493-500.
54. Escorsell A, Bandi JC, Andreu V, Moitinho E, García-Pagán JC, Bosch J, Rodés J. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. Gastroenterology. 2001;120:161-9.
55. Farias AQ, Kassab F, da Rocha EC, dos Santos Bomfim V, Vezozzo DP, Bittencourt PL, Carrilho FJ. Propranolol reduces variceal pressure and wall tension in schistosomiasis presinusoidal portal hypertension. J Gastroenterol Hepatol. 2009;24:1852-6.
56. Fernández J, Ruiz del Arbol L, Gómez C, Durandez R, Serradilla R, Guarner C, Planas R, Arroyo V, Navasa M. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology. 2006;131:1049-56.
57. Feu F, García-Pagán JC, Bosch J, Luca A, Terés J, Escorsell A, Rodés J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet. 1995;346:1056-9.
58. Feu F, Ruiz del Arbol L, Bañares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. Variceal Bleeding Study Group. Gastroenterology. 1996;111:1291-9.
59. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, Denninger MH, Sauvanet A, Valla D, Durand F. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54:691-7.
60. Fuccio L, Zagari Rm, Serrani M, Eusebi LH. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia-related bleeding in patients with liver cirrhosis. Digestion. 2009;79:143-50.
61. Fukuda T, Hirota S, Sugimura K. Long-term results of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices ad hepatic encephalopathy. J Vasc Interv Radiol. 2001;12:327-36.
62. Garcia N Jr, Sanyal AJ. Portal hypertension. Clin Liver Dis. 2001;5:509-40.
63. García-Pagán JC, Villanueva C, Vila MC, Albillos A, Genescà J, Ruiz-Del-Arbol L, Planas R, Rodriguez M, Calleja JL, González A, Solà R, Balanzó J, Bosch J; MOVE Group. Mononitrato Varices Esofágicas. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. Gastroenterology. 2001;121:908-14.
64. García-Pagán JC, Morillas R, Bañares R, Albillos A, Villanueva C, Vila C, Genescà J, Jimenez M, Rodriguez M, Calleja JL, Balanzó J, García-Durán F, Planas R, Bosch J; Spanish Variceal Bleeding Study Group. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. Hepatology. 2003;37:1260-6.
65. Garcia-Pagan JC, Bosch J. Endoscopic band ligation in the treatment of portal hypertension. Nat Clin Pract Gastroenterol Hepatol. 2005;2:526-35.
66. Garcia-Pagan JC, De Gottardi A, Bosch J. The modern management of portal hypertension - primary and secondary prophylaxis of variceal bleeding in cirrhotic patients [review article]. Aliment Pharmacol Ther. 2008;28:178-86.
67. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;5:419-24.
68. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W; Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922-38.
69. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. Hepatology. 2008;47:1764-72.
70. Garg PK, Sidhu SS, Bhargava DK. Role of omeprazole in prevention and treatment of postendoscopic variceal sclerotherapy esophageal complications. Double-blind randomized study. Dig Dis Sci. 1995;40:1569-74.
71. Gonzalez-Alonso R, Gomez EG, Martinez AA. Pre-primary prophylaxis of variceal bleeding. Rev Esp Enferm Dig. 2007;99:714-21.
72. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Ann Intern Med. 2008;149:109-22.

73. Gøtzsche PC. Somatostatin analogues for acute bleeding oesophageal varices. Cochrane Database Syst Rev. 2002;(1):CD000193.
74. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, Alberts J, Rodes J, Fischer R, Bermann M. Hemodynamic events in a prospective randomized trial of propranolol vs placebo in the prevention of the first variceal hemorrhage. Gastroenterology. 1990;99:1401-7.
75. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Gao H, Makuch R; Portal Hypertension Collaborative Group. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353:2254-61.
76. Guarner C, Soriano G. Spontaneous bacterial peritonitis. Semin Liver Dis. 1997;17:203-17.
77. Henderson JM, Boyer TD, Kutner MH, Galloway JR, Rikkers LF, Jeffers LJ, Abu-Elmagd K, Connor J; DIVERT Study Group. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. Gastroenterology. 2006;130:1643-51.
78. Hosking SW, Kenedy HJ, Seddon I, Triger DR. The role of propranolol in congestive gastropathy of portal hypertension. Hepatology. 1987;7:437-41.
79. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev. 2003;(1):CD002147.
80. Kahn D, Krige JE, Terblanche J, Bornman PC, Robson SC. A 15-year experience of injection sclerotherapy in adult patients with extrahepatic portal venous obstruction. Ann Surg. 1994;219:34-9.
81. Kamath PS, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology. 2000;118:905-11.
82. Karsan HA, Morton SC, Shekelle PG, Spiegel BM, Suttorp MJ, Edelstein MA, Gralnek IM. Combination endoscopic band ligation and sclerotherapy compared with endoscopic band ligation alone for the secondary prophylaxis of esophageal variceal hemorrhage: a meta-analysis. Dig Dis Sci. 2005;50:399-406.
83. Khuroo MS, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. Aliment Pharmacol Ther. 2005;21:347-61.
84. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, Akiyoshi N, Iida T, Yokoyama M, Okumura M. Risk factors for hemorrhage from gastric fundal varices. Hepatology. 1997;25:307-12.
85. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. Lancet. 2007;370:415-26.
86. Kouroumalis EA, Koutroubakis IE, Manousos ON. Somatostatin for acute severe bleeding from portal hypertensive gastropathy. Eur J Gastroenterol Hepatol. 1998;10:502-12.
87. Kravetz D, Sikuler E, Groszmann RJ. Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution. Gastroenterology. 1986;90:1232-40.
88. Kravetz D, Bosch J, Arderiu M, Pilar Pizcueta M, Rodés J. Hemodynamic effects of blood volume restitution following a hemorrhage in rats with portal hypertension due to cirrhosis of the liver: influence of the extent of portal-systemic shunts Hepatology. 1989;9:808-14.
89. Kuroiwa Y, Suzuki N, Mizue N, Hori T, Endo T, Yoshida Y, Tsutsumi H. Gastric antral vascular ectasia in 2-yr-old girl undergoing unrelated cord blood stem cell transplantation. Pediatr Transplant. 2005;9:788-91.
90. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med. 1995;123: 280-7.
91. Laine L. Management of actively bleeding esophageal varices. Gastrointest Endosc. 1997;46:83-4.
92. Lebrec 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.
93. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. N Engl J Med. 1981;305:1371-4.
94. Levacher S, Letoumelin P, Pateron D, Blaise M, Lapandry C, Pourriat JL. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet. 1995;346:865-8.
95. Longacre AV, Garcia-Tsao G. A commonsense approach to esophageal varices. Clin Liver Dis. 2006;10:613-25.
96. Maluf-Filho F, Sakai P, Ishioka S, Matuguma SE. Endoscopic sclerosis versus cyanoacrylate endoscopic injection for the first episode of variceal bleeding: a prospective, controlled, and randomized study in Child-Pugh class C patients. Endoscopy. 2001;33:421-7.
97. McCormick PA, Ooi H, Crosbie O. Tranexamic acid for severe bleeding gastric antral vascular ectasia in cirrhosis. Gut. 1998;42:750-2.
98. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc. 2008;67:910-23.
99. Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, Cavallarin G, Bolognesi M, Donada C, Bellini B, Torboli P, Gatta A; Gruppo Triveneto per l'Ipertensione Portale. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology. 2004;127:476-84.
100. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, Attili AF, Riggio O. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38:266-72.
101. Mies S, Neto OB, Beer A Jr, Baía CE, Alfieri F Jr, Pereira LM, Sette MJ, Raia S. Systemic and hepatic hemodynamics in hepatosplenic Manson's schistosomiasis with and without propranolol. Dig Dis Sci. 1997;42:751-61.
102. Mishra SR, Kumar A, Sharma P. Early primary prophylaxis with beta-blockers and role of measuring hepatic venous pressure gradient in prevention of growth of small esophageal varices in cirrhosis [abstract]. J Gastroenterol Hepatol. 2008;23:a71.
103. 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;117:626-31.
104. Moitinho E, Planas R, Banares R, Albillos A, Ruiz-del-Arbol L, Galvez C, Bosch J; Variceal Bleeding Study Group. Multicenter randomized controlled trial comparing different schedules of somatostatin in the treatment of acute variceal bleeding. J Hepatol. 2001;35:712-8.
105. Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, Marrero JM, Buceta E, Sánchez J, Castellot A, Peñate M, Cruz A, Peña E. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology. 2004;40:793-801.
106. Nevens F. A critical comparison of drug therapies in currently used therapeutic strategies for variceal haemorrhage [review article]. Aliment Pharmacol Ther. 2004;20:18-22.
107. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (NIEC). Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319:983-9.
108. Oberti F. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterol Clin Biol. 2005;29:622-5.
109. Oho K,Iwao T, Sakai T, Tayama C. Randomized prospective trial for bleeding fundal varices: endoscopic sclerotherapy versus transvenous obliteration. Gastroenterology. 1997;112:a1351.
110. Orloff MJ, Orloff MS, Orlof SL, Haynes KS. Treatment of bleeding from portal hypertensive gastropathy by portacaval shunt. Hepatology. 1995;21:1011-7.
111. Orr DW, Harrison PM, Karani J, Rela M. Chronic portomesenteric and portosplenomesenteric venous thrombosis: evaluation of long term follow-up and determinants of survival. Hepatology. 2005;42:212a.
112. Palmer ED, Brick IB. Correlation between the severity of esophageal varices in cirrhosis and their propensity toward hemorrhage. Gastroenterology. 1956;30: 85-90.
113. Papatheodoridis GV, Goulis J, Leandro G, Patch D, Burroughs AK. Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: a meta-analysis. Hepatology. 1999;30:612-22.
114. Papazian A, Braillon A, Dupas JL, Sevenet F, Capron JP. Portal hypertensive gastric mucosa: an endoscopic study. Gut. 1986;27:1199-203.
115. Pérez-Ayuso RM, Piqué JM, Bosch J, Panés J, González A, Pérez R, Rigau J, Quintero E, Valderrama R, Viver J. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. Lancet. 1991;337:1431-4.
116. Plessier A, Murad SD, Hernandez Guerra M. A prospective multicentric follow-up study on 105 patients with acute portal vein thrombosis (PVT): results from the European Network for Vascular Disorders of the Liver (EM-VIE). Hepatology. 2007:46:309a.
117. Primignani M, Albè R, Preatoni P, Carnevale P, Bianchi MB, Parravicini ML, Del Ninno E, de Franchis R. De novo development of esophageal varices in patients with a recent histologic diagnosis of liver cirrhosis. Gastroenterology. 1998;114:a1324.
118. Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, Cestari R, Angeli P, Gatta A, Rossi A, Spinzi G, De Franchis R. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). Gastroenterology. 2000;119:181-7.
119. Raia S, da Silva LC, Gayotto LC, Forster SC, Fukushima J, Strauss E. Portal hypertension in schistosomiasis: a long-term follow-up of a randomized trial comparing three types of surgery. Hepatology. 1994;20:398-403.

120. Rosemurgy AS, Bloomston M, Clark WC, Thometz DP, Zervos EE. H-graft portacaval shunts versus TIPS: ten-year follow-up of a randomized trial with comparison to predicted survivals. Ann Surg. 2005;241:238-46.
121. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310-8.
122. Sanyal AJ, Freedman AM, Luketic VA, Purdum PP 3rd. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. Gastroenterology. 1997;112:889-98.
123. Sarin SK, Groszmann RJ, Mosca PG, Rojkind M, Stadecker MJ, Bhatnagar R, Reuben A, Dayal Y. Propranolol ameliorates the development of portal-systemic shunting in a chronic murine schistosomiasis model of portal hypertension. J Clin Invest. 1991;87:1032-6.
124. 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;16:1342-9.
125. Sarin SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. Gastrointest Endosc. 1997;46:8-14.
126. Sarin SK, Wadhawan M, Gupta R, Shahi H. Evaluation of endoscopic variceal ligation (EVL) versus propanolol plus isosorbide mononitrate/nadolol (ISMN) in the prevention of variceal rebleeding: comparison of cirrhotic and noncirrhotic patients. Dig Dis Sci. 2005;50:1538-47.
127. Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, Jafri W, Kumar A, Kudo M, Lesmana LA, Sharma BC, Shiha G, Janaka de Silva H; Members of the APASL Working Party on Portal Hypertension. Consensus on extra-hepatic portal vein obstruction. Liver Int. 2006;26:512-9.
128. Senzolo M, Tibbals J, Cholongitas E, Triantos CK, Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with and without cavernous transformation. Aliment Pharmacol Ther. 2006;23:767-75.
129. Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. Blood. 2005;105:2266
130. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. Cochrane Database Syst Rev. 2002;(2):CD002907.
131. Spahr L, Villeneuve JP, Dufresne MP, Tassé D, Bui B, Willems B, Fenyves D, Pomier-Layrargues G. Gastric antral vascular ectasia in cirrhotic patients: absence of relation with portal hypertension. Gut. 1999;44:739-42.
132. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, Reveille RM, Sun JH, Lowenstein SR. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992;326:1527-32.
133. Strauss E, Ribeiro MF, Albano A, Honain NZ, Maffei RA Jr, Caly WR. Long-term follow up of a randomized, controlled trial on prophylactic sclerotherapy of small esophageal varices in liver cirrhosis. J Gastroenterol Hepatol. 1999;14:225-30.
134. Strauss E, Gomes de Sá Ribeiro M de F. Bacterial infections associated with hepatic encephalopathy: prevalence and outcome. Ann Hepatol. 2003;2:41-5.
135. Superina R, Shneider B, Emre S, Sarin S, de Ville de Goyet J. Surgical guidelines for the management of extra-hepatic portal vein obstruction. Pediatr Transplant. 2006;10:908-13.
136. Tan PC, Hou MC, Lin HC, Liu TT, Lee FY, Chang FY, Lee SD. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. Hepatology. 2006;43:690-7.
137. Thakeb F, Salem SA, Abdallah M el Batanoyny M. Endoscopic diagnosis of gastric varices. Endoscopy. 1994;26:287-91.
138. Thuluvath PH, Yoo HY. Portal hypertensive gastropathy. Am J Gastroenterol. 2002;97:2973-8.
139. Tiani C, Abraldes JG, Bosch J. Portal hypertension: pre-primary and primary prophylaxis of variceal bleeding. Dig Liver Dis. 2008;40:318-27.
140. Tran A, Villeneuve JP, Bilodeau M, Willems B, Marleau D, Fenyves D, Parent R, Pomier-Layrargues G. Treatment of chronic bleeding from gastric antral vascular ectasia (GAVE) with estrogen-progresterone in cirrhotic patients: an open pilot study. Am J Gastroenterol. 1999;94:2909-11.
141. Triantos CK, Burroughs AK. Prevention of the development of varices and first portal hypertensive bleeding episode. Best Pract Res Clin Gastroenterol. 2007;21:31-42.
142. Tripathi D, Therapondos G, Jackson E, Redhead DN, Hayes PC. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. Gut. 2002;51:270-4.
143. Tripathi DJ, Ferguson JW, Therapondos G, Plevris JN, Hayes PC.: Recent advances in the management of bleeding gastric varices [review article]. Aliment Pharmacol Ther. 2006;24:1-17.
144. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology. 2005;41:553-8.
145. Tripodi A. Tests of coagulation in liver disease. Clin Liver Dis. 2009;13:55-61.
146. Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. Gastrointest Endosc. 1986;32:264-8.
147. Tsai HH, Smith J, Danesh BJ. Successful control of bleeding from gastric antral vascular ectasia (watermelon stomach) by laser photocoagulaton. Gut. 1991;32: 93-4.
148. Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol. 2006;101:506-12.
149. Valla DC. The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. Hepatology. 2003;38:793-803.
150. Van Stiegmann G, Cambre T, Sun JH. A new endoscopic elastic band ligating device. Gastrointest Endosc. 1986;32:230-3.
151. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease. A randomized, single-blind, multicenter clinical trial. N Engl J Med. 1991;324:1779-84.
152. Vieira da Rocha EC, D'Amico EA, Caldwell SH, Flores da Rocha TR, Soares E Silva CS, Dos Santos Bomfim V, Felga G, Barbosa WF, Kassab F, Polli DA, Carrilho FJ, Farias AQ. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol. 2009;7:988-93.
153. Villanueva C, Aracil C, Colomo A, Lopez-Balaguer JM, Piqueras M, Gonzalez B, Bureau C, Péron JM, Alric L, Morales J, Sanchez J, Barange K, Payen JL, Vinel JP. "A la carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology. 2002;36:1361-6.
154. Villanueva C, López-Balaguer JM, Aracil C, Kolle L, González B, Miñana J, Soriano G, Guarner C, Balanzó J. Maintenance of hemodynamic response to treatment for portal hypertension and influence on complications of cirrhosis. J Hepatol. 2004;40:757-65.
155. Villanueva C, Piqueras M, Aracil C, Gómez C, López-Balaguer JM, Gonzalez B, Gallego A, Torras X, Soriano G, Sáinz S, Benito S, Balanzó J. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. J Hepatol. 2006;45:560-7.
156. Villanueva C, Colomo A, Aracil C, Guarner C. Current endoscopic therapy of variceal bleeding. Best Pract Res Clin Gastroenterol. 2008;22:261-78.
157. Villanueva C, Aracil C, Colomo A, Lopez-Balaguer JM, Piqueras M, Gonzalez B, Torras X, Guarner C, Balanzo J. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. Aliment Pharmacol Ther. 2009;29:397-408.
158. Vleggaar FP, van Buure HR, Schalm SW. Endoscopic sclerotherapy for bleeding oesophagogastric varices secondary to extrahepatic portal vein obstruction in na adult Caucasian population. Eur J Gastroenterol Hepatol. 1998;10:81-5.
159. Weston BR, Chadalawada V, Chalasani N, Kwo P, Overley CA, Symms M, Strahl E, Rex DK. Nurse-administered propofol versus midazolam and meperidine for upper endoscopy in cirrhotic patients. Am J Gastroenterol. 2003;98:2440-7.

Received 1/7/2009.
Accepted 17/8/2009.