PRACTICE GUIDELINES

Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis

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PREAMBLE

These recommendations provide a data-supported approach to the management of patients with varices and variceal hemorrhage. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic (Medline search); (2) several consensus conferences among experts; (3) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines* (1); (4) guideline policies, including the American Association for the Study of Liver Diseases' Policy Statement on Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use of Medical Practice Guidelines (2); and (5) the authors' years of experience caring for patients with cirrhosis and varices.

Intended for use by healthcare providers, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. As with other practice guidelines, this guideline is not intended to replace clinical judgment but rather to provide general guidelines applicable to the majority of patients. They are intended to be flexible, in contrast to standards of care, which are inflexible policies designed to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a *class* (reflecting benefit versus risk) and *level* (assessing strength or certainty) of evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (3, 4)).

When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Further controlled clinical studies are needed to clarify aspects of this statement, and revision may be necessary as new data appear. Clinical considerations may justify a course of action that differs from these recommendations. These recommendations are fully endorsed by the American Association for the Study of Liver Diseases and the American College of Gastroenterology.

INTRODUCTION

Portal hypertension is a progressive complication of cirrhosis. Therefore, the management of the patient with cirrhosis and portal hypertensive gastrointestinal bleeding depends on the phase of portal hypertension at which the patient is situated, from the patient with cirrhosis and portal hypertension who has not yet developed varices to the patient with acute variceal hemorrhage for whom the objective is to control the active episode and prevent rebleeding.

Practice guidelines for the diagnosis and treatment of gastroesophageal variceal hemorrhage, endorsed by the American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology (ACG), American Gastroenterological Association (AGA), and American Society of Gastrointestinal Endoscopy (ASGE), were published in 1997 (5). Since then, a number of randomized controlled trials have advanced our approach to managing variceal hemorrhage. Three international consensus conferences have been held (Baveno III in 2000, Baveno IV in 2005, and an AASLD/EASL single topic conference in 2007) in which experts in the field have evaluated the changes that have occurred in our understanding of the pathophysiology and management of gastroesophageal hemorrhage (6, 7). In this updated practice guideline we have reviewed the randomized controlled trials and meta-analyses published in the last decade and have incorporated recommendations made by consensus.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION IN CIRRHOSIS

Cirrhosis, the end stage of any chronic liver disease, can lead to portal hypertension. Portal pressure increases initially as

Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

a consequence of an increased resistance to flow mostly due to an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules. In addition to this structural resistance to blood flow, there is an active intrahepatic vaso-constriction that accounts for 20–30% of the increased intra-hepatic resistance (8), and that is mostly due to a decrease in the endogenous production of nitric oxide (9, 10). Portal hypertension leads to the formation of porto-systemic collaterals. However, portal hypertension persists despite the development of these collaterals for 2 reasons: 1) an increase in portal venous inflow that results from splanchnic arterio-lar vasodilatation occurring concomitant with the formation of collaterals (11); and 2) insufficient portal decompression through collaterals as these have a higher resistance than that of the normal liver (12). Therefore, an increased portal pressure gradient results from *both* an increase in resistance to portal flow (intrahepatic and collateral) and an increase in portal blood inflow.

EVALUATION OF PORTAL HYPERTENSION

The preferred, albeit indirect, method for assessing portal pressure is the wedged hepatic venous pressure (WHVP) measurement, which is obtained by placing a catheter in the hepatic vein and wedging it into a small branch or, better still, by inflating a balloon and occluding a larger branch of the hepatic vein. The WHVP has been shown to correlate very closely with portal pressure both in alcoholic and non-alcoholic cirrhosis (13). The WHVP is always corrected for increases in intraabdominal pressure (e.g., ascites) by sub-tracting the free hepatic vein pressure (FHVP) or the intraab-dominal inferior vena cava pressure, which act as internal zeroes. The resultant pressure is the hepatic venous pres-sure gradient (HVPG), which is best accomplished with the use of a balloon catheter, usually taking triplicate readings and, when measured with a proper technique, is very repro-ducible and reliable (14). Since it is a measure of sinusoidal pressure, the HVPG will be elevated in intrahepatic causes of portal hypertension, such as cirrhosis, but will be nor-mal in prehepatic causes of portal hypertension, such as por-

tal vein thrombosis. The normal HVPG is 3–5 mmHg. The HVPG and changes in HVPG that occur over time have pre-dictive value for the development of esophagogastric varices (15, 16), the risk of variceal hemorrhage (17–19), the de-velopment of non-variceal complications of portal hyper-tension (17, 20, 21), and death (19, 21–23). Single mea-surements are useful in the prognosis of both compensated and decompensated cirrhosis, while repeat measurements are useful to monitor response to pharmacological therapy and progression of liver disease. Limitations to the generalized use of HVPG measurement are the lack of local expertise and poor adherence to guidelines that will ensure reliable and reproducible measurements (14), as well as its invasive nature.

NATURAL HISTORY OF VARICES

Gastroesophageal varices are the most relevant porto-systemic collaterals because their rupture results in variceal hemorrhage, the most common lethal complication of cirrho-sis. Varices and variceal hemorrhage are the complications of cirrhosis that result most directly from portal hypertension. Patients with cirrhosis and gastroesophageal varices have an HVPG of at least 10–12 mmHg (15, 24).

Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease (Table 2); while only 40% of Child A patients have varices, they are present in 85% of Child C patients (25). Patients with primary biliary cirrho-sis may develop varices and variceal hemorrhage early in the course of the disease even in the absence of established cirrhosis (26). It has also been shown that 16% of patients with hepatitis C and bridging fibrosis have esophageal varices (27).

Patients without varices develop them at a rate of 8% per year (16, 28), and the strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an HVPG >10 mmHg (16). Patients with small varices develop large varices at a rate of 8% per year. Decompensated cirrhosis (Child B/C),

Table 2. Child-Pugh Classification of the Severity of Cirrhosis

	Points*		
	1	2	3
Encephalopathy	None	Grade 1–2 (or precipitant-induced)	Grade 3–4 (chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Tense (diuretic-refractory)
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.3–3.5	<2.8
PT (sec prolonged) or INR	<4	4–6	>6
	<1.7	1.7–2.3	>2.3

*5–6 points: Child A
7–9 points: Child B
10–15 points: Child C

alcoholic cirrhosis, and presence of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the time of baseline endoscopy are the main factors associated with the progression from small to large varices (28).

Variceal hemorrhage occurs at a yearly rate of 5–15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices (29). Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the endoscopic presence of red wale marks (29). Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients, and despite improvements in therapy over the last decade, it is associated with a mortality of at least 20% at 6 weeks (30–32). Patients with an HVPG >20 mmHg (measured within 24 hours of variceal hemorrhage) have been identified as being at a higher risk for early rebleeding (recurrent bleeding within the first week of admission) or failure to control bleeding (83% vs. 29%) and a higher 1-year mortality (64% vs. 20%) compared to those with lower pressure (33, 34). Late rebleeding occurs in approximately 60% of untreated patients, mostly within 1–2 years of the index hemorrhage (35, 36).

Variceal wall tension is probably the main factor that determines variceal rupture. Vessel diameter is one of the determinants of variceal tension. At an equal pressure, a large diameter vessel will rupture while a small diameter vessel will not rupture (37). Besides vessel diameter, one of the determinants of variceal wall tension is the pressure within the varix, which is directly related to the HVPG. Therefore, a reduction in HVPG should lead to a decrease in variceal wall tension, thereby decreasing the risk of rupture. Indeed, variceal hemorrhage does not occur when the HVPG is reduced to <12 mmHg (17, 20). It has also been shown that the risk of rebleeding decreases significantly with reductions in HVPG greater than 20% from baseline (18). Patients whose HVPG decreases to <12 mmHg or at least 20% from baseline levels ("HVPG responders") not only have a lower probability of developing recurrent variceal hemorrhage (36), but also have a lower risk of developing ascites, spontaneous bacterial peritonitis, and death (21).

GASTRIC VARICES

Gastric varices are less prevalent than esophageal varices and are present in 5–33% of patients with portal hypertension with a reported incidence of bleeding of about 25% in 2 years, with a higher bleeding incidence for fundal varices (38). Risk factors for gastric variceal hemorrhage include the size of fundal varices (large>medium>small, defined as >10 mm, 5–10 mm, and <5 mm, respectively), Child class (C>B>A), and endoscopic presence of variceal red spots (defined as localized reddish mucosal area or spots on the mucosal surface of a varix) (39). Gastric varices are commonly classified based on their relationship with esophageal varices as well as their location in the stomach (38). Gastroesophageal varices (GOV) are an extension of esophageal varices and are categorized into 2 types. The most common are Type 1 (GOV1) varices, which extend along the lesser curvature. They are considered extensions of esophageal varices and should be managed similarly. Type 2 (GOV2) gastric varices extend along the fundus and tend to be longer and more tortuous. Isolated gastric varices (IGV) occur in the absence of esophageal varices and are also classified into 2 types. Type 1 (IGV1) are located in the fundus and tend to be tortuous and complex, and type 2 (IVG2) are located in the body, antrum, or around the pylorus. The presence of IGV1 fundal varices requires excluding the presence of splenic vein thrombosis.

DIAGNOSIS OF VARICES AND VARICEAL HEMORRHAGE

The gold standard in the diagnosis of varices is esophagogastroduodenoscopy (EGD). In a consensus meeting it was recommended that the size classification be as simple as possible, i.e., in 2 grades (small and large) (40), either by semiquantitative morphological assessment or by quantitative size with a suggested cut-off diameter of 5 mm, with large varices being those greater than 5 mm. When varices are classified in 3 sizes—small, medium, or large—as occurs in most centers by a semiquantitative morphological assessment (with small varices generally defined as minimally elevated veins above the esophageal mucosal surface, medium varices

defined as tortuous veins occupying less than one-third of the esophageal lumen, and large varices defined as those occupying more than one-third of the esophageal lumen), recommendations for medium-sized varices are the same as for large varices (29), because this is how they were grouped in prophylactic trials.

As shown below, nonselective β-blockers prevent bleeding in more than half of patients with medium or large varices. Therefore, it is recommended that patients with cirrhosis undergo endoscopic screening for varices at the time of diagnosis (41, 42). Since the point prevalence of medium/large varices is approximately 15–25% (25), the majority of subjects undergoing screening EGD either do not have varices or have varices that do not require prophylactic therapy. There is, therefore, considerable interest in developing models to predict the presence of high-risk varices by non-endoscopic methods. Several studies have evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis, such as the platelet count, Fibrotest, spleen size, portal vein diameter, and transient elastography (43, 44). However, the predictive accuracy of such noninvasive markers is still unsatisfactory, and until large prospective studies of noninvasive markers are performed, endoscopic screening is still the main means of assessing for the presence of esophageal varices (43).

Cost-effective analyses using Markov models have suggested either empiric β-blocker therapy for all patients with cirrhosis (45) or screening endoscopy for patients with compensated cirrhosis, and universal β-blocker therapy without screening EGD for patients with decompensated cirrhosis (46). Neither of these strategies considers a recent trial showing that β-blockers do not prevent the development of varices and are associated with significant side effects (16), nor do they consider endoscopic variceal ligation as an alternative prophylactic therapy. Until prospective studies validate these approaches, screening EGD is still the recommended approach.

The frequency of surveillance endoscopies in patients with no or small varices depends on their natural history. EGD should be performed once the diagnosis of cirrhosis is established (6, 41). In patients with compensated cirrhosis who have no varices on screening endoscopy, the EGD should be repeated in 2–3 years (6). In those who have small varices, the EGD should be repeated in 1–2 years (6). In the presence of decompensated cirrhosis, EGD should be repeated at yearly intervals (41, 42).

EGD is expensive and usually requires sedation. It can be avoided in patients with cirrhosis who are already on nonselective β-blockers for other reasons (e.g., arterial hypertension). In those on a selective β-blocker (metoprolol, atenolol for other reasons), switching to a nonselective β-blocker (propranolol, nadolol) would be necessary. A procedure that may replace EGD is esophageal capsule endoscopy. Two recent pilot studies show that capsule endoscopy is a safe and well-tolerated way to diagnose esophageal varices (47, 48), although its sensitivity remains to be established. Thus, capsule endoscopy may play a future role in screening for esophageal varices if additional larger studies support its use.

EGD also remains the main method for diagnosing variceal hemorrhage (7, 41). The diagnosis of variceal hemorrhage is made when diagnostic endoscopy shows one of the following: active bleeding from a varix, a "white nipple" overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding (40).

Recommendations

1. *Screening esophagogastroduodenoscopy (EGD) for the diagnosis of esophageal and gastric varices is recommended when the diagnosis of cirrhosis is made (Class IIa, Level C).*
2. *On EGD, esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted (Class IIa, Level C).*

MANAGEMENT RECOMMENDATIONS

Rationale for the Management of Varices

Current therapies for the management of varices/variceal hemorrhage and their effect on portal venous inflow, portal resistance, and portal pressure are summarized in Table 3. Pharmacological therapy consists of splanchnic vasoconstrictors (vasopressin and analogues, somatostatin and analogues, nonselective β-blockers) and venodilators (nitrates). Vasoconstrictors act by producing splanchnic vasoconstriction and reducing portal venous inflow. Venodilators theoretically act by decreasing intrahepatic and/or portocollateral resistance. However, all available venodilators (e.g., isosorbide mononitrate) have a systemic hypotensive effect and the decrease in portal pressure appears to be more related to hypotension (i.e., a decrease in flow) rather than a decrease in resistance (49). The combination of a vasoconstrictor and a vasodilator has a synergistic portal pressure-reducing effect (50, 51). Endoscopic therapies, such as sclerotherapy or endoscopic variceal ligation (EVL), are local therapies that have no effect on either portal flow or resistance. Shunting therapy, either radiological (transjugular intrahepatic portosystemic

Table 3. Effect on Portal Flow, Resistance and Pressure with the Different Therapies for Varices/Variceal Hemorrhage

Treatment	Portal Flow	Portal Resistance	Portal Pressure
Vasoconstrictors (e.g. β-blockers)	↓↓	↑	↓
Venodilators (e.g. nitrates)	↓	↓*	↓
Endoscopic therapy	-	-	-
TIPS/Shunt therapy	↑	↓↓↓	↓↓↓

*Although theoretically nitrates act by decreasing resistance, they actually act by decreasing portal flow through a decrease in mean arterial pressure.

shunt) or surgical, by bypassing the site of increased resistance, markedly reduces portal pressure by bypassing the site of increased resistance.

A.   PATIENTS WITH CIRRHOSIS AND NO VARICES

A large multicenter, placebo-controlled, double-blinded trial failed to show a benefit of nonselective β-blockers (timolol) in the prevention of varices in patients with cirrhosis who had portal hypertension at baseline (HVPG >5 mmHg) but had not yet developed varices (16). The study did show, however, that patients who achieved even a mild reduction in HVPG after 1 year of therapy ($\geq$10% from baseline) had a significantly lower development of varices, and that a larger percentage of patients on timolol showed this reduction in HVPG compared to those on placebo. A significantly larger number of patients with moderate or severe adverse events were observed in the timolol group (48%) compared to the placebo group (32%). Serious symptomatic adverse events occurred in 20 patients (18%) in the timolol group and in 6 patients (6%) in the placebo group. These results do not support the suggested universal use of β-blockers in cirrhosis (45). Given the natural history of varices, expert consensus panels have determined that surveillance endoscopies should be performed every 2–3 years in these patients, and annually in the setting of decompensation (6, 42).

Recommendations

3. *In patients with cirrhosis who do not have varices, nonselective β-blockers cannot be recommended to prevent their development (Class III, Level B).*
4. *In patients who have compensated cirrhosis and no varices on the initial EGD, it should be repeated in 3 years (Class I, Level C). If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C).*

B.   PATIENTS WITH CIRRHOSIS AND SMALL VARICES THAT HAVE NOT BLED

A meta-analysis of trials evaluating nonselective β-blockers (i.e., propranolol, nadolol) in the prevention of first variceal hemorrhage (primary prophylaxis) analyzed the results of 3 trials that included patients with small varices (35). In this meta-analysis, the incidence of first variceal hemorrhage was quite low (7% over 2 years), and although it was reduced with β-blockers (2% over 2 years), this reduction was not statistically significant.

Two studies have investigated the efficacy of nonselective β-blockers in preventing the enlargement of small varices, with contradictory results. In the first study (52), the 2-year proportion of patients with large varices was unexpectedly larger in the propranolol group compared to the placebo group (31% vs. 14%). However, the study enrolled patients with no and small varices and over a third of the patients

were lost to follow-up. Another large multicenter, placebo-controlled, but single-blinded trial, showed that patients with small varices treated with nadolol had a significantly slower progression to large varices (11% at 3 years) than patients who were randomized to placebo (37% at 3 years), with no differences in survival (53). The risk of variceal bleeding was lower in patients who started treatment with β-blockers when varices were small (12% at 5 years) compared with patients who started β-blockers once large varices were observed (22% at 5 years). However, this benefit was related to the longer time patients remained in a condition of low-risk (i.e., small) varices, given that once large varices developed and all patients were treated with β-blockers, the risk of bleeding was very similar (53). Similar to other studies, a higher percentage of patients on β-blockers had to be withdrawn from the study because of adverse events (11%) compared to patients on placebo (1%). Prophylaxis with β-blockers should be used in patients with small varices who are at a high risk for bleeding; that is, those with advanced liver disease and the presence of red wale marks on varices (7). Other patients with small varices can receive β-blockers to prevent variceal growth, although their long-term benefit has not been well established. In those who choose not to take β-blockers surveillance endoscopies should be performed every 2 years, and annually in the setting of decompensation (6, 42).

Recommendations

5. *In patients with cirrhosis and small varices that have not bled but have criteria for increased risk of hemorrhage (Child B/C or presence of red wale marks on varices), nonselective β-blockers should be used for the prevention of first variceal hemorrhage (Class IIa, Level C).*
6. *In patients with cirrhosis and small varices that have not bled and have no criteria for increased risk of bleeding, β-blockers can be used, although their long-term benefit has not been established (Class III, Level B).*
7. *In patients with small varices that have not bled and who are not receiving β-blockers, EGD should be repeated in 2 years (Class I, Level C). If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C). In patients with small varices who receive β-blockers, a follow-up EGD is not necessary.*

C.   PATIENTS WITH CIRRHOSIS AND MEDIUM/LARGE VARICES THAT HAVE NOT BLED

A meta-analysis of 11 trials that included 1,189 patients evaluating *nonselective β-blockers* (i.e., propranolol, nadolol) versus non-active treatment or placebo in the prevention of first variceal hemorrhage shows that the risk of first variceal bleeding in patients with large- or medium-sized varices is significantly reduced by β-blockers (30% in controls vs. 14% in β-blocker-treated patients) (35), and indicates that

1 bleeding episode is avoided for every 10 patients treated with β-blockers. Mortality is also lower in the β-blocker group compared with the control group and this difference has recently been shown to be statistically significant (54). Additionally, a cost-effectiveness study comparing nonselective β-blockers, sclerotherapy, and shunt surgery shows that β-blockers were the only cost-effective form of prophylactic therapy (55).

Nonselective β-blockers (propranolol, nadolol) reduce portal pressure by decreasing cardiac output (β-1 effect) and, more importantly, by producing splanchnic vasoconstriction (β-2 effect), thereby reducing portal blood flow. Selective β-blockers (atenolol, metoprolol) are less effective and are suboptimal for primary prophylaxis of variceal hemorrhage. A decrease in HVPG <12 mmHg essentially eliminates the risk of hemorrhage and improves survival (17), while reductions >20% from baseline (56) or even >10% from baseline (57) significantly decrease the risk of first variceal hemorrhage.

In the majority of the published studies, the dose of β-blockers was titrated to decrease the heart rate 25% from baseline. However, since HVPG measurement is not widely available and a reduction in heart rate does not correlate with reduction in HVPG (58), the dose of nonselective β-blockers (propranolol, nadolol) is adjusted to maximal tolerated doses. Propranolol is usually started at a dose of 20 milligrams (mg) twice a day (BID). Nadolol is is usually started at a dose of 40 mg once a day (QD). Because a randomized trial showed that the risk of bleeding recurs when treatment with β-blockers is stopped (59), prophylactic therapy should be continued indefinitely.

Approximately 15% of patients from trials have relative contraindications to the use of β-blockers, such as asthma, insulin-dependent diabetes (with episodes of hypoglycemia), and peripheral vascular disease (60). The most common side effects related to β-blockers in cirrhosis are lightheadedness, fatigue, and shortness of breath. Although some of these side effects disappear with time or after dose reduction, treatment withdrawal occurs in 15% of patients. Trials in which nadolol was used have reported lower rates of side effects (∼10 %) than those involving propranolol (∼17 %) (60); however, direct comparisons have not been performed.

Endoscopic Variceal Ligation (EVL) has been compared to β-blockers in several randomized trials in patients with high-risk varices (large varices with or without red wale markings). Two recent meta-analyses of these trials have been performed: the first included 8 trials and comprised 596 subjects (285 with EVL, 311 with β-blockers) (61); and the second included 12 studies comprising 839 subjects (410 with EVL, 429 with β-blockers) (62). Both showed that EVL is associated with a small but significant lower incidence of first variceal hemorrhage without differences in mortality. The results are the same when only fully published trials or high-quality trials are analyzed. Although the EVL group has a significantly lower rate of adverse events (4% vs. 13%),

the EVL events are more severe and include bleeding from ligation-induced esophageal ulcers in 10 patients (with 2 fatal outcomes) and overtube-induced esophageal perforation in 1 patient. This last complication is currently less likely to occur given the use of multi-band ligation devices that minimize the use of overtubes for band placement. In the β-blocker group, severe adverse events necessitating withdrawal (hypotension, fatigue, shortness of breath) resolved after discontinuation of the medication, although 10 patients bled on withdrawal of β-blockers (with 2 fatal outcomes). One of the more recent studies included in these meta-analyses had to be stopped before the planned number of patients was enrolled and after a mean follow-up of only 18 months, because interim analysis showed a significantly higher number of treatment "failures" (bleeding or a severe side effect) in the propranolol group compared to the EVL group (6 vs. 0) (63). The unfortunate premature discontinuation of this trial is discussed in recent editorials that argue that bleeding rates were not significantly different between groups, and that only one "failure" in the EVL group would have rendered the differences non-significant (64, 65). In contrast, the 2 largest randomized trials (66, 67) and a more recent trial (68), not included in the above cited meta-analyses, have shown that EVL is equivalent to nadolol (66) or to propranolol (67, 68) in preventing the first variceal hemorrhage. After careful review of the available data, a recent consensus panel of experts concluded that both nonselective β-blockers and EVL are effective in preventing first variceal hemorrhage and therefore the decision should be based on patient characteristics and preferences, local resources, and expertise (7).

Therapies Not Recommended for Primary Prophylaxis
The *combination of a nonselective β-blocker and isosorbide mononitrate (ISMN)* has a synergistic portal pressure-reducing effect and could theoretically be more effective than β-blockers alone in preventing first variceal hemorrhage (51). In fact, a non-blinded trial comparing nadolol alone with nadolol plus ISMN demonstrated a significantly lower rate of first hemorrhage in the group treated with combination therapy (69). These results were maintained after 55 months of follow-up, without differences in survival (70). However, 2 more recent larger double-blinded, placebo-controlled trials were unable to confirm these favorable results (71, 72), and a greater number of side effects were noted in the combination therapy group (71). Therefore, the use of a combination of a β-blocker and ISMN cannot be recommended currently for primary prophylaxis until there is further proof of efficacy.

The *combination of a nonselective β-blocker and spironolactone* (which has been shown to lower portal pressure by reducing plasma volume and splanchnic blood flow) has been recently examined in a preliminary double-blind, placebo-controlled trial (73). The results suggest that the addition of spironolactone does not increase the efficacy of nadolol in the prophylaxis of first variceal hemorrhage.

The role of combination of a nonselective *β-blocker and EVL* in the prevention of first variceal hemorrhage was recently evaluated in a randomized but not placebo-controlled trial performed in patients with and without cirrhosis who had high-risk varices (74). There were no differences in the incidence of bleeding or death between groups, and even though varices recurred more frequently in the EVL alone group, side effects were more common in the EVL + propranolol group. Given the lack of differences in the primary outcomes, combination therapy cannot be currently recommended.

ISMN alone was shown in one study to be as effective as propranolol in preventing first variceal hemorrhage (75). However, long-term follow-up of patients enrolled in this study showed higher mortality in patients older than 50 years (76). ISMN, a potent venodilator, may lead to a higher mortality in these patients by aggravating the vasodilatory state of the cirrhotic patient (77), as shown in shorter-term hemodynamic trials using other vasodilators such as losartan (78) and irbesartan (79). In fact, in a recent multicenter trial, 133 cirrhotic patients with varices and contraindications or intolerance to *β*-blockers were randomized to ISMN (n = 67) or to placebo (n = 66) (80). Surprisingly, there was a greater 1- and 2-year probability of first variceal hemorrhage in the ISMN group (p = 0.056), with no differences in survival. Side effects were more frequent in patients receiving ISMN. These results were further supported in another randomized trial of cirrhotic patients with ascites (81). Therefore, nitrates alone should not be used in patients with cirrhosis.

Shunt surgery trials have shown conclusively that, although very effective in preventing first variceal hemorrhage, shunting blood away from the liver is accompanied by more frequent encephalopathy and higher mortality (82). These results can be extrapolated to the *transjugular intrahepatic portosystemic shunt (TIPS)* because its physiology is the same as that of surgical shunts (i.e., diversion of blood away from the liver) (83). Therefore, shunt therapy (surgery or TIPS) should not be used in the primary prevention of variceal hemorrhage.

Endoscopic sclerotherapy trials have yielded controversial results. While early studies showed promising results, later studies showed no benefit (82, 84). A VA prospective, randomized, cooperative trial comparing prophylactic sclerotherapy and sham therapy had to be terminated 22.5 months after it began because the mortality rate was significantly higher in the sclerotherapy group than in the sham-therapy group (85). Sclerotherapy should therefore not be used for the primary prevention of variceal hemorrhage.

Recommendations

8. ***In patients with medium/large varices that have not bled but have a high risk of hemorrhage (Child B/C or variceal red wale markings on endoscopy), nonselective β-blockers (propranolol or nadolol) or EVL may be recommended for the prevention of first variceal hemorrhage (Class I, Level A).***

9. ***In patients with medium/large varices that have not bled and are not at the highest risk of hemorrhage (Child A patients and no red signs), nonselective β-blockers (propranolol, nadolol) are preferred and EVL should be considered in patients with contraindications or intolerance or non-compliance to β-blockers (Class I, Level A).***

10. ***If a patient is placed on a nonselective β-blocker, it should be adjusted to the maximal tolerated dose; follow-up surveillance EGD is unnecessary. If a patient is treated with EVL, it should be repeated every 1–2 weeks until obliteration with the first surveillance EGD performed 1–3 months after obliteration and then every 6–12 months to check for variceal recurrence (Class I, Level C).***

11. ***Nitrates (either alone or in combination with β-blockers), shunt therapy, or sclerotherapy should not be used in the primary prophylaxis of variceal hemorrhage (Class III, Level A).***

D.   PATIENTS WITH CIRRHOSIS AND AN ACUTE EPISODE OF VARICEAL HEMORRHAGE

There is evidence that current treatment strategies for acute variceal hemorrhage, including general and specific measures, have resulted in an improved survival both in the U.S. (86) and elsewhere (31, 32).

D.1. General Measures
Patients with suspected acute variceal hemorrhage should be admitted to an intensive care unit setting for resuscitation and management. Initial resuscitation involves basic measures including assessing the patient's airway and obtaining peripheral venous access.

Blood volume resuscitation should be undertaken promptly but with caution, with the goals of maintaining hemodynamic stability and a hemoglobin of approximately 8 g/dL (7). This recommendation is based on experimental studies that show that restitution of all lost blood leads to increases in portal pressure to levels higher than baseline (87), and to more rebleeding and mortality (88). Similarly, vigorous resuscitation with saline solution should generally be avoided because, in addition to possibly precipitating recurrent variceal hemorrhage, this can worsen or precipitate the accumulation of ascites or fluid at other extravascular sites. Given that aspiration of blood can occur, elective or more emergent tracheal intubation may be required for airway protection prior to endoscopy, particularly in patients with concomitant hepatic encephalopathy.

The transfusion of fresh frozen plasma and platelets can be considered in patients with significant coagulopathy and/or thrombocytopenia. A multicenter placebo-controlled trial of recombinant factor VIIa (rFVIIa) in cirrhotic patients with gastrointestinal hemorrhage failed to show a beneficial effect of rFVIIa over standard therapy (89). Although *post hoc*

analysis of a subpopulation of Child-Pugh B and C cirrhotic patients indicated that administration of rFVIIa significantly decreased the proportion of patients with failure to control variceal bleeding, confirmatory studies are needed before this expensive therapy can be recommended in patients with coagulopathy and variceal bleeding.

Cirrhotic patients with upper GI bleeding have a high risk of developing severe bacterial infections (spontaneous bacterial peritonitis and other infections) that are associated with early recurrence of variceal hemorrhage and a greater mortality (90, 91). Although patients with less-severe liver disease (i.e., Child A) are at an increased risk of developing bacterial infections, this risk is highest in those with more severe liver disease (i.e., Child B and C) (92, 93). The use of *short-term prophylactic antibiotics* in patients with cirrhosis and GI hemorrhage with or without ascites has been shown not only to decrease the rate of bacterial infections but also to increase survival (94, 95). This improved survival is partly related to a decrease in the incidence of early rebleeding in patients with variceal hemorrhage who receive prophylactic antibiotics (96). Therefore, short-term antibiotic prophylaxis should be considered standard practice in all patients with cirrhosis and acute variceal hemorrhage (97). The recommended antibiotic schedule is norfloxacin administered orally at a dose of 400 mg BID for 7 days (97). The rationale behind the oral administration of norfloxacin, a poorly absorbed quinolone, is the selective eradication (or at least reduction) of gram-negative bacteria in the gut, the source of bacteria. However, quinolone antibiotics with similar spectrum of activity, such as ciprofloxacin, could also be recommended. When oral administration is not possible, quinolones can be administered intravenously (IV). In a recent study performed in patients with advanced cirrhosis (Child B/C) and GI hemorrhage, IV ceftriaxone (1 g/day) was more effective than oral norfloxacin in preventing bacterial infections (98), mostly those due to gram-negative organisms. The prevalence of quinolone-resistant organisms in the study centers was not specified and this could have contributed importantly to the results.

D.2. Specific Measures to Control Acute Hemorrhage and Prevent Early Recurrence

Pharmacological therapy has the advantages of being generally applicable and capable of being initiated as soon as a diagnosis of variceal hemorrhage is suspected, even prior to diagnostic EGD. A recent meta-analysis of 15 trials comparing emergency sclerotherapy and pharmacological treatment (vasopressin $\pm$ nitroglycerin, terlipressin, somatostatin, or octreotide) shows a similar efficacy with fewer side effects with pharmacological therapy, thereby suggesting that pharmacological therapy should be considered first-line treatment of variceal bleeding (99). Beta-blockers should not be used in the acute setting as they will decrease blood pressure and will blunt a physiologic increase in heart rate associated with bleeding.

Vasopressin is the most potent splanchnic vasoconstrictor. It reduces blood flow to all splanchnic organs, thereby leading to a decrease in portal venous inflow and to a decrease in portal pressure. The clinical usefulness of vasopressin is limited by its multiple side effects, which are related to its potent vasoconstrictive properties, including cardiac and peripheral ischemia, arrhythmias, hypertension, and bowel ischemia (60). Although its efficacy and safety are significantly improved by the addition of nitrates (50), side effects of combination therapy are still higher than those associated with terlipressin, somatostatin, or somatostatin analogues (35) and, therefore, it can only be used continuously at the highest effective dose for a maximum of 24 hours to minimize the development of side effects. Vasopressin is administered at a continuous IV infusion of 0.2–0.4 units/minute that can be increased to a maximal dose of 0.8 units/minute. It should always be accompanied by IV nitroglycerin at a starting dose of 40 μg/minute, which can be increased to a maximum of 400 μg/minute, adjusted to maintain a systolic blood pressure >90 mmHg.

Terlipressin, a synthetic analogue of vasopressin that has a longer biological activity and significantly fewer side effects, is effective in controlling acute variceal hemorrhage and has been associated with a decreased mortality (35), but is not yet available in the United States. Terlipressin is administered at an initial dose of 2 mg IV every 4 hours and can be titrated down to 1 mg IV every 4 hours once hemorrhage is controlled (99).

Somatostatin and analogues such as octreotide and vapreotide also cause splanchnic vasoconstriction at pharmacological doses. Although it has been considered that this effect is due to an inhibition of the release of vasodilatory peptides (mainly glucagon), recent studies suggest that octreotide has a local vasoconstrictive effect. The advantage of somatostatin and analogues such as octreotide and vapreotide is that they are safe and can be used continuously for 5 days or even longer. Of these, only octreotide is available in the United States and it has been mostly used as an initial IV bolus of 50 μg followed by a continuous infusion of 50 μg/hour. Use of somatostatin consists of a 250 μg IV bolus followed by infusion of 250 μg/hour. Vapreotide is given as a 50 μg IV bolus followed by infusion of 50 μg per hour. However, results of meta-analyses of trials of octreotide are controversial (35, 100) and a more recent meta-analysis of trials of somatostatin analogues in general showed a negligible beneficial effect (101). The reason octreotide alone may not be useful is because its administration has been associated with tachyphylaxis (102) and a more transient effect when compared to terlipressin (103). However, as shown below, octreotide appears to be useful as an adjunct to endoscopic therapy.

Even though pharmacological therapy, particularly *safe* pharmacological therapy, should be initiated once the diagnosis of variceal hemorrhage is suspected, EGD should be performed as soon as possible after admission (e.g., within 12 h) and endoscopic therapy should be performed if the suspected variceal source of hemorrhage is confirmed (7).

Regarding the best endoscopic therapy, a meta-analysis of 10 randomized controlled trials including 404 patients shows an almost significant benefit of *EVL* in the initial control of bleeding compared to sclerotherapy (pooled relative risk of 0.53 with a confidence interval of 0.28–1.01) (62). In addition, one of the studies included in the meta-analysis showed that although HVPG increased significantly immediately after both EVL and sclerotherapy, it remained elevated for the duration of the study (5 days) in the sclerotherapy group while HVPG had decreased to baseline levels by 48 hours after EVL (104). Therefore, by consensus, EVL is the preferred form of endoscopic therapy for acute esophageal variceal bleeding, although sclerotherapy is recommended in patients in whom EVL is not technically feasible (7).

Combination of pharmacological therapy and endoscopic therapy is the most rational approach in the treatment of acute variceal hemorrhage. The use of pharmacological agents with few side effects allows prolonging therapy to 5 days, the period during which the risk of rebleeding is the highest. A meta-analysis of 8 trials showed that, compared to endoscopic therapy alone (sclerotherapy or EVL), endoscopic plus pharmacological (octreotide, somatostatin, vapreotide) therapy improved the initial control of bleeding and 5-day hemostasis without differences in mortality or severe adverse events (105).

Rescue Therapies

Despite urgent endoscopic and/or pharmacological therapy, variceal bleeding cannot be controlled or recurs early in about 10–20% of patients. An elevated HVPG >20 mmHg (measured within 24 hours of presentation) has been shown to be predictive of treatment failure (33). Shunt therapy, either *shunt surgery* (in Child A patients) or *TIPS*, has proven clinical efficacy as salvage therapy for patients who fail to respond to endoscopic or pharmacological therapy (106, 107). A surgical group has reported almost universal control of bleeding and a low mortality with the performance of portocaval shunt within 8 hours of onset of bleeding in unselected cirrhotic patients collected over a 30-year period (108). This approach has not been validated by other groups and is not widely practiced. More recently, a small study has suggested that early TIPS placement (within 24 hours of hemorrhage) is associated with a significant improvement in survival in "high-risk" patients (defined as those with an HVPG >20 mmHg) with acute variceal hemorrhage (34). These results will require confirmation in a larger number of patients followed for a longer period before early TIPS can be recommended. The performance of both shunt surgery and TIPS are dependent on local expertise.

Balloon tamponade is very effective in controlling bleeding temporarily with immediate control of hemorrhage in over 80% of patients (109). However, its use is associated with potentially lethal complications such as aspiration, migration, and necrosis/perforation of the esophagus with mortality rates as high as 20%. Therefore, it should be restricted to patients with uncontrollable bleeding for whom a more

definitive therapy (e.g., TIPS) is planned within 24 hours of placement. Airway protection is strongly recommended when balloon tamponade is used.

Recommendations

12. *Acute GI hemorrhage in a patient with cirrhosis is an emergency that requires prompt attention with intravascular volume support and blood transfusions, being careful to maintain a hemoglobin of ∼8 g/dL (Class I, Level B).*

13. *Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage (Class I, Level A). Oral norfloxacin (400 mg BID) or intravenous ciprofloxacin (in patients in whom oral administration is not possible) is the recommended antibiotic (Class I, Level A). In patients with advanced cirrhosis intravenous ceftriaxone (1 g/day) may be preferable particularly in centers with a high prevalence of quinolone-resistant organisms (Class I, Level B).*

14. *Pharmacological therapy (somatostatin or its analogues octreotide and vapreotide; terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 3–5 days after diagnosis is confirmed (Class I, Level A).*

15. *EGD, performed within 12 hours, should be used to make the diagnosis and to treat variceal hemorrhage, either with EVL or sclerotherapy (Class I, Level A).*

16. *TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level C).*

17. *Balloon tamponade should be used as a temporizing measure (maximum 24 hours) in patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS or endoscopic therapy) is planned (Class I, Level B).*

GASTRIC VARICES

The literature on the management of gastric variceal hemorrhage is not nearly as robust as that for esophageal variceal hemorrhage. Because there are so few controlled clinical trials, much less confidence can be placed on guidelines for the management of gastric varices. Type 1 gastric varices (GOV1) constitute an extension of esophageal varices along the lesser curvature of the stomach. Therefore, the approach to their management should be the same as for esophageal varices (see above). On the other hand, there are very limited data regarding the management of bleeding from fundal varices, except when IGV1 are secondary to isolated splenic vein thrombosis, in which case therapy consists of splenectomy.

Compared to endoscopic sclerotherapy or EVL, endoscopic variceal obturation with tissue adhesive such as

N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin is more effective for acute fundal gastric variceal bleeding, with better control of initial hemorrhage as well as lower rates of rebleeding (110, 111). A relatively large prospective, randomized trial compared gastric variceal obturation (GVO) with N-butyl-cyanoacrylate versus EVL in patients with acute gastric variceal hemorrhage demonstrating that control of active bleeding was similar in both groups but that rebleeding over a follow-up period of 1.6–1.8 years occurred significantly less frequently in the GVO group (23% vs. 47%), with an average of only 1.5 sessions (range 1–3) (112). In an uncontrolled pilot study, 2-octyl cyanoacrylate, an agent approved for skin closure in the United States, has been described as effective for achieving initial hemostasis and preventing rebleeding from fundal varices (113). Therefore, the use of these agents is preferred in the endoscopic therapy of fundal varices. However, in the absence of these agents or if the operator is unfamiliar with this type of therapy, TIPS should be considered first line therapy. Several studies demonstrate the value of TIPS for uncontrolled bleeding from gastric varices with bleeding control rates of over 90%. Although it had been suggested that bleeding from gastric varices was more difficult to control with TIPS than bleeding from esophageal varices, a prospective study compared salvage TIPS in patients with uncontrolled gastric fundal (n = 28) versus uncontrolled esophageal (n = 84) variceal bleeding and showed equal efficacy with control of hemorrhage in all but one patient in each group (114).

The threshold to place TIPS for gastric variceal hemorrhage is lower than for esophageal variceal hemorrhage and TIPS can be recommended if endoscopic therapy is not possible or after a single failure of endoscopic treatment.

Recommendations
18. *In patients who bleed from gastric fundal varices, endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available. Otherwise, EVL is an option (Class I, Level B).*
19. *A TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level B).*

E. PATIENTS WITH CIRRHOSIS WHO HAVE RECOVERED FROM ACUTE VARICEAL HEMORRHAGE

Patients who survive an episode of acute variceal hemorrhage have a very high risk of rebleeding and death. The median rebleeding rate in untreated individuals is around 60% within 1–2 years of the index hemorrhage, with a mortality of 33% (35, 36). It is therefore essential that patients who have recovered from an episode of variceal hemorrhage and have had no evidence of hemorrhage for at least 24 hours be started on therapy to prevent recurrence prior to discharge from the hospital. Patients who required shunt surgery/TIPS to control

the acute episode do not require further preventive measures. All these patients should be referred to a transplant center if they are otherwise a candidate (i.e., Child-Pugh score $\geq$7 or a MELD score $\geq$15).

Nonselective β-blockers or sclerotherapy reduce rates of variceal rebleeding to around 42–43% (35, 36, 82, 115), although patients treated with sclerotherapy have a higher rate of side effects. However, there are better pharmacological and endoscopic therapeutic options.

Regarding pharmacological therapy, the *combination of a nonselective β-blocker and ISMN* has a synergistic portal pressure-reducing effect and could theoretically be more effective than β-blockers alone. Only one study has performed a direct comparison between the combination of propranolol plus ISMN and propranolol alone in patients with prior variceal hemorrhage (116). This study showed a benefit of combination therapy (33% vs. 41% rebleeding rate), but it was not statistically significant. Data collected from different randomized clinical trials show that the median rebleeding rate in patients treated with combined pharmacological therapy is around 33–35% (35, 36), lower than that obtained with β-blockers alone. Therefore, the pharmacological therapy of choice in the prevention of variceal rebleeding is probably the combination of a nonselective β-blocker and a nitrate. However, this combination has significantly greater side effects compared to β-blockers alone (35, 116) and is poorly tolerated in clinical practice so that most patients end up taking β-blockers alone.

Regarding endoscopic therapy, EVL is the endoscopic method of choice for preventing variceal rebleeding since it has been shown to be superior to sclerotherapy (115, 117). Data collected from different randomized clinical trials show a median rebleeding rate in patients treated with EVL of around 32% (36). EVL sessions are repeated at 7- to 14-day intervals until variceal obliteration, which usually requires 2 to 4 sessions (118). Once eradicated, EGD is usually repeated every 3 to 6 months to evaluate for variceal recurrence and need for repeat EVL. Complications of EVL occur in about 14% of cases but are usually minor. The most common complication is transient dysphagia and chest discomfort. Shallow ulcers at the site of each ligation are the rule, and they may bleed. In a small (n = 43) randomized placebo-controlled trial of pantoprazole (40 mg IV after EVL followed by 40 mg oral every day for 9 days), the number of post-EVL ulcers at day 10 after EVL was the same in both groups; however, ulcers were significantly smaller in the pantoprazole group and, although not statistically significant, all 3 post-EVL bleeding episodes occurred in the placebo group (119). These results would favor the use of proton pump inhibitors in patients treated with EVL.

Optimal pharmacological therapy (β-blockers plus nitrates) versus optimal endoscopic therapy (EVL) has been compared in 3 randomized studies showing different results. One study showed a benefit of combination pharmacological therapy (23), another showed a benefit of EVL (120), and a third showed no difference between treatment groups,

despite a clear tendency in favor of pharmacological therapy (121). These differences probably reflect the dosage of medications used, patient population and, ultimately, center expertise (122). Both therapies would appear to be at least equivalent in the prevention of variceal rebleeding with rebleeding rates of 32–35%.

Combination endoscopic plus pharmacological therapy is the most rational approach because nonselective β-blockers theoretically will protect against rebleeding prior to variceal obliteration and would prevent variceal recurrence. Two randomized trials demonstrate the superiority of combined therapy versus EVL alone (123, 124). Rebleeding rates in these 2 trials were 23% and 14%, respectively, for EVL plus nadolol compared to 47% and 38% for EVL alone. These results support the use of combination therapy to prevent rebleeding, even though a recent consensus conference recommended EVL *or* β-blocker + nitrates as first-line therapy in treatment naïve patients (7). The combination EVL plus a nonselective β-blocker is clearly recommended in patients who develop variceal hemorrhage (first or recurrent) while on EVL or a β-blocker alone.

The lowest rate of variceal rebleeding (∼10%) is obtained in patients who are HVPG responders; that is, patients in whom pharmacological therapy (either β-blockers alone or β-blockers + nitrates) leads to a reduction in HVPG to <12 mmHg or a reduction >20% from baseline (19, 36). In patients who are HVPG responders, it would not be rational to use endoscopic therapy. As suggested recently, perhaps the most rational therapy would be to adapt the different therapies to prevent variceal rebleeding in the context of HVPG response (125, 126); however, this would require standardization of the HVPG technique, including the best timing to perform the repeat HVPG measurement. Existing studies have performed the second HVPG measurement a median of 90 days after the first measurement (range 19–159 days), and there is evidence suggesting that the predictive value of the change in HVPG is reduced with increasing time between measurements (19).

Shunt surgery is very effective in preventing rebleeding. However, it markedly increases the risk of hepatic encephalopathy and has no effect on survival (82, 127, 128). Not surprisingly, recent meta-analyses of 11 trials that compared *TIPS* to endoscopic therapy as first-line therapy show similar results (129, 130). That is, even though rebleeding is significantly less frequent with TIPS, post-treatment encephalopathy occurs significantly more often after TIPS, and there is no difference in mortality between groups. Furthermore, a recent trial showed that, even though pharmacological (propranolol plus nitrates) therapy was less effective than TIPS in preventing rebleeding, it was associated with less encephalopathy, identical survival, and more frequent improvement in Child-Pugh class with lower costs than TIPS (131). Therefore, TIPS should not be used as a first-line treatment, but as a rescue therapy for patients who have failed pharmacological plus endoscopic treatment (83).

A large multicenter trial of TIPS versus distal splenorenal shunts (DSRS) showed similar rates of rebleeding, encephalopathy, and mortality in patients with Child A or B cirrhosis who had failed pharmacological/endoscopic therapy, with a higher rate of shunt dysfunction in the TIPS group (132). Because both procedures have equivalent outcomes, the choice is dependent on available expertise and ability to monitor the shunt and reintervene when needed.

Notably, the above-mentioned trials have all been performed using uncovered TIPS stents. The advent of covered stents that have been shown to have a lower occlusion rate and lower rates of encephalopathy (133) may increase the enthusiasm for TIPS. However, given past results with surgical shunts (83), it is likely that TIPS will remain a second-line therapy after endoscopic/pharmacological therapy.

Therapies Not Recommended for Secondary Prophylaxis
Sclerotherapy should no longer be used in the secondary prophylaxis of variceal hemorrhage. A meta-analysis of 13 trials which included 1,091 patients comparing EVL versus sclerotherapy in the prevention of variceal rebleeding showed that the risk of variceal rebleeding is significantly reduced by EVL (pooled odds ratio 0.46, 95% CI 0.35–0.60). Furthermore, while there were no differences in mortality, complications are significantly less frequent and less severe with EVL, and the number of endoscopic sessions needed to achieve eradication is significantly lower than with sclerotherapy (115).

Trials suggest that EVL is followed by a higher rate of variceal recurrence in comparison with sclerotherapy. Even though the above-mentioned meta-analysis found no significant difference in variceal recurrence between treatments (115), the efficacy of combination *EVL plus sclerotherapy* compared with EVL alone in reducing variceal recurrence has been explored. Two meta-analyses, one comprising 7 trials (134) and a more recent one comprising 8 trials (135), show no differences in rebleeding, death, or number of sessions to variceal obliteration between groups and a higher incidence of esophageal strictures in the combination therapy group. Therefore, EVL should not be combined with sclerotherapy.

Recommendations
20. *Patients with cirrhosis who survive an episode of active variceal hemorrhage should receive therapy to prevent recurrence of variceal hemorrhage (secondary prophylaxis) (Class I, Level A).*
21. *Combination of nonselective β-blockers plus EVL is the best option for secondary prophylaxis of variceal hemorrhage (Class I, Level A).*
22. *The nonselective β-blocker should be adjusted to the maximal tolerated dose. EVL should be repeated every 1–2 weeks until obliteration with the first surveillance EGD performed 1–3 months after obliteration and then*

every 6–12 months to check for variceal recurrence (Class I, Level C).

23. *TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy. In centers where the expertise is available, surgical shunt can be considered in Child A patients (Class I, Level A).*

24. *Patients who are otherwise transplant candidates should be referred to a transplant center for evaluation (Class I, Level C).*

SUGGESTIONS FOR FUTURE RESEARCH

The following are important areas in the diagnosis and treatment of varices and variceal hemorrhage where additional research/data are needed:

1. Non-invasive markers that predict presence of high risk varices
2. Role of capsule endoscopy in the diagnosis of varices and variceal hemorrhage
3. Role of HVPG in directing therapy
4. Alternatives to HVPG measurements
5. New pharmacological therapies with a greater effect on HVPG
6. Best therapy for fundal varices and fundal variceal hemorrhage

CONCLUSIONS

In the decade since the initial practice guidelines were published, a number of advances have changed our management of variceal hemorrhage. HVPG measurements have clearly been established as a clinically important diagnostic and prognostic tool. Nonselective β-blockers have no role in the prevention of the development of esophagogastric varices but are the gold standard in the prevention of first variceal hemorrhage in patients with medium/large varices. Endoscopic variceal ligation has been established as an alternative to nonselective β-blockers for the prevention of initial variceal hemorrhage. The combination of vasoconstrictive pharmacological therapy and variceal ligation is the preferred approach to the management of acute variceal hemorrhage. Prophylactic antibiotic therapy is considered standard of care as adjunctive treatment of the acute bleeding episode. Both combination pharmacological therapy and EVL plus pharmacological therapy have been proven effective for the prevention of recurrent variceal hemorrhage. For failures of medical therapy, TIPS or surgically created shunts are excellent salvage procedures. Over the next decade, the management of patients with varices may improve with the availability of additional pharmacological agents that specifically target the intrahepatic circulation, improved endoscopic techniques, more efficacious coated stents for TIPS, and greater availability of liver transplantation.

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