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TOPIC HIGHLIGHT

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Treatment of portal hypertension

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Abstract

Portal hypertension is the main complication of cirrhosis and is defined as an hepatic venous pressure gradient (HVPG) of more than 5 mmHg. Clinically significant portal hypertension is defined as HVPG of 10 mmHg or more. Development of gastroesophageal varices and variceal hemorrhage are the most direct consequence of portal hypertension. Over the last decades significant advancements in the field have led to standard treatment options. These clinical recommendations have evolved mostly as a result of randomized controlled trials and consensus conferences among experts where existing evidence has been reviewed and future goals for research and practice guidelines have been proposed. Management of varices/variceal hemorrhage is based on the clinical stage of portal hypertension. No specific treatment has shown to prevent the formation of varices. Prevention of first variceal hemorrhage depends on the size/characteristics of varices. In patients with small varices and high risk of bleeding, non-selective β-blockers are recommended, while patients with medium/large varices can be treated with either β-blockers or esophageal band ligation. Standard of care for acute variceal hemorrhage consists of vasoactive drugs, endoscopic band ligation and antibiotics prophylaxis. Transjugular intrahepatic portosystemic shunt (TIPS) is reserved for those who fail standard of care or for patients who are likely to fail ("early TIPS"). Prevention of recurrent variceal hemorrhage consists of the combination of β-blockers and endoscopic band ligation.

Key words: Cirrhosis; Portal hypertension; Varices; Variceal hemorrhage; Primary prophylaxis; Secondary prophylaxis

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INTRODUCTION

Portal hypertension is the increase in porto-systemic pressure gradient in any portion of the portal venous system. Although portal hypertension could result from pre-hepatic abnormalities (e.g., portal or splenic vein thrombosis), post-hepatic abnormalities (e.g., Budd-Chiari syndrome) or intrahepatic non-cirrhotic causes (e.g., schistosomiasis, sinusoidal obstruction syndrome), cirrhosis is by far the most common cause of portal hypertension and, as such, has been the most widely investigated. In cirrhosis, the portosystemic gradient is assessed by measuring the wedged hepatic venous pressure (a measure of sinusoidal hepatic pressure) and subtracting the free hepatic venous pressure (systemic pressure) thus obtaining the hepatic

venous pressure gradient (HVPG). A normal HVPG is 3-5 mmHg. An HVPG above 5 mmHg defines portal hypertension, however an HVPG of 10 mmHg or greater defines clinically significant portal hypertension as this pressure gradient predicts clinical course in patients with cirrhosis including development of varices[1], clinical decompensation (i.e., development of ascites, variceal hemorrhage and encephalopathy)[2], decompensation or death after liver resection[3], and hepatocellular carcinoma[4].

The complications that most directly result from portal hypertension are the development of varices and variceal hemorrhage. This review summarizes the current standard management for varices and variceal hemorrhage in the context of cirrhotic portal hypertension.

Over the last decades, research on animal models and clinical trials have evolved and have led to our current management recommendations. The field has moved forward in large part through consensus conference among experts where events and endpoints have been defined and the existing evidence has been carefully reviewed leading to practice recommendations. The first such conference took place in 1986 in Groningen, the Netherlands and since then consensus conferences have been alternating between Europe (Baveno conference) and the United States [American association for the study of liver diseases (AASLD) or AASLD single topic conference (STC)], and are briefly summarized below (Table 1).

HISTORY OF CONSENSUS CONFERENCES ON PORTAL HYPERTENSION

Baveno is a small town in Northern Italy located on the west shore of Lake Maggiore. It has become the epicenter of the portal hypertension consensus workshops aimed to reach a consensus on the definitions of key events related to portal hypertension and variceal bleeding and to provide guidelines for future research as well as reviewing the evidence, eventually leading to clinical practice guidelines. The first Baveno consensus workshop was held in April 1990[5] in which significant advances in diagnosis and management of varices and variceal bleeding including vasoactive drugs and endoscopic sclerotherapy were reviewed. In addition to defining certain terms including size of varices, clinically significant bleeding and rebleeding; this workshop also provided recommendations on diagnostic modalities, imaging and directions for future clinical trials. The therapeutic recommendations included β-blockers for primary prophylaxis of large varices, sclerotherapy and vasoactive drugs for acute hemorrhage and endoscopic sclerotherapy, β-blockers or surgical shunt to prevent recurrent hemorrhage.

The Baveno Ⅱ workshop was held in April 1995[6]. Definitions of key clinical events were revised and new definitions were proposed. Based on multiple randomized controlled trials, non-selective β-blockers (NSBB) were recommended to be the treatment of choice for primary prophylaxis of variceal hemorrhage, while isosorbide-5 mononitrate (ISMN) was recommended in patients who did not tolerate β-blockers. Endoscopic sclerotherapy was not recommended in the prevention of first hemorrhage. Treatment of acute hemorrhage was mainly based on endoscopic therapy, terlipressin was deemed the most effective of the vasoactive agents, with somatostatin showing some efficacy. The transjugular intrahepatic portosystemic shunt (TIPS) was recommended in case of treatment failure of endoscopic and pharmacologic therapy. The recommendations to prevent recurrent hemorrhage included β-blockers or endoscopic variceal ligation (EVL) that had been shown to be better than sclerotherapy[7]. TIPS and surgical shunts were to be used only for patients with frequent repeated episodes of variceal hemorrhage.

In June 1996, the AASLD STC took place in Reston, Virginia, United States, with the objective of identifying important areas in the treatment of variceal hemorrhage and future research[8]. Guidelines for initial variceal screening and follow-up endoscopy were described in detail depending on severity of liver disease and the size of varices on first endoscopy. Areas of further research were identified as the role of sequential portal pressure measurements and their timing, and defining new predictors of first hemorrhage. Primary prophylaxis recommendations were the same as in the Baveno Ⅱ conference, with β-blockers as the mainstay of treatment and EVL requiring further studies. Vasoactive drugs in combination with endoscopic treatment (sclerotherapy or EVL) became the established treatment for acute hemorrhage, recognizing the advantage of initiating vasoactive therapy prior to diagnostic endoscopy[9]. For secondary prophylaxis EVL or β-blockers were recommended. TIPS or surgical shunts were considered acceptable therapies for failure to control acute hemorrhage or recurrent hemorrhage despite standard treatments.

The Baveno Ⅲ conference was held in April 2000[10], and introduced the concept of clinically significant portal hypertension (CSPH) which was defined as HVPG of 10 mmHg or more. The presence of varices, variceal hemorrhage or ascites is indicative of the presence of CSPH. Non-selective β-blockers remained the treatment of choice to prevent first hemorrhage from large/medium varices, while EVL required further assessment. The goals of therapy with β-blockers were defined (25% reduction in baseline heart rate or a heart rate of 55 beats/min). ISMN, previously recommended as an alternative to β-blockers, was no longer recommended[11]. For treatment of acute hemorrhage, the early administration of vasoactive drugs and continued use for up to 5 d along with endoscopic therapy (EVL or sclerotherapy) were considered standard. Additional measures included use of antibiotics to prevent bacterial infection[12], and lactulose to treat hepatic encephalopathy. With regard to prevention of rebleeding, β-blockers were considered first-line therapy[13] as was EVL, with TIPS reserved for treatment failures. The complications of treatment of portal hypertension were also defined for use in clinical settings and in research trials.

The Baveno Ⅳ conference was held in April 2005[14], and some of the key criteria (failure to control bleeding,

Table 1 Portal hypertension consensus conferences in the last two decades

Title	Year	Venue
21st meeting of the European association for the study of liver	1986	Groningen, The Netherlands
Definitions, methodology and therapeutic strategies in portal hypertension. A consensus development workshop	1990	Baveno, Italy
Developing consensus in portal hypertension	1995	Baveno, Italy
Portal hypertension and variceal bleeding. AASLD single topic symposium	1996	Virginia, United States
Updating consensus in portal hypertension. Reports of the Baveno Ⅲ consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension	2000	Baveno, Italy
Evolving consensus in portal hypertension. Report of the Baveno Ⅳ consensus workshop on methodology of diagnosis and therapy in portal hypertension	2005	Baveno, Italy
Portal hypertension and variceal bleeding-unresolved issues. Summary of an AASLD and European association for the study of the liver single-topic conference	2007	Atlanta, United States
Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension	2010	Baveno, Italy

AASLD: American association for the study of liver diseases.

failure of secondary prophylaxis) were revised. For primary prophylaxis, β-blockers remained the treatment of choice but endoscopic band ligation emerged as an excellent alternative for patients with medium or large varices, and contraindications or intolerance to β-blockers[15,16]. Isosorbide mononitrate as a single agent therapy was not recommended even in a combination of pharmacological therapies[17]. Primary prophylaxis of small varices could only be considered if they were high risk (red wale sign or Child C)[18]. There was no significant change in the recommendations of acute variceal hemorrhage from Baveno Ⅲ. Small changes included the use of vasoactive drugs for at least 5 d, and the use of balloon tamponade only in massive bleeding as a temporary bridge until definitive treatment could be instituted. EVL was declared superior to sclerotherapy and as the endoscopic procedure of choice in the control of acute hemorrhage[16,19]. Secondary prophylaxis should be initiated 6 d after the index variceal bleed, and included the combination of EVL and β-blockers[20,21]. TIPS or surgical shunts were reserved for patients with failure of secondary prophylaxis.

The second AASLD STC was held in 2007 in Atlanta, Georgia[22]. The objective of this conference was to make clinical recommendations in areas that did not require further investigation and to identify research directions for the remaining areas. Compensated and decompensated cirrhosis were identified as separate entities to be studied separately both in clinical practice and in research[23]. The main differences compared with Baveno Ⅳ included the emergence of capsule endoscopy as a non-invasive alternative to esophagogastroduodenoscopy (EGD) for assessment of varices, a firm recommendation regarding use of β-blockers for primary prophylaxis of small varices with high-risk features, and consideration of β-blockers for small varices and no high-risk features[24]. EVL was considered as effective and safe as β-blockers for primary prophylaxis of medium to large sized varices. Early TIPS emerged as an option in patients at high risk of rebleeding[25], but required further investigation.

The Baveno V conference in May 2010 revised the definitions of failure to control variceal bleeding, and failure of secondary prophylaxis[26]. Primary prophylaxis for small varices was the same as recommended in the 2007 AASLD STC. There was no significant change in the recommendations for primary prophylaxis of medium to large varices (β-blockers or EVL) with the choice of therapy dictated by local resources, expertise and patient preference[27]. The recommendations on the treatment of acute variceal bleeding were unchanged except that a stronger recommendation was made to consider early TIPS (within 72 h) in patients with high risk of treatment failure[28]. Recommendations for the prevention of recurrent hemorrhage, as in the AASLD STC, consisted of the combination of β-blockers and EVL.

Evidence-based guidelines endorsed by the AASLD[29] and the American College of Gastroenterology[30] as well as a recent comprehensive review[31] on the treatment of portal hypertension have been heavily based on these consensus conferences. These guidelines and review form the bases of the current recommendations that are described in the following section in which the advantages (pros) and disadvantages (cons) of these therapies are also discussed.

CURRENT STANDARD TREATMENT OF PORTAL HYPERTENSION IN ADULTS

Therapy of varices and variceal hemorrhage in the adult patient with cirrhosis needs to be stratified depending on the different clinical stages in the natural history of portal hypertension: (1) the patient with cirrhosis and portal hypertension who has not yet developed varices and in whom the goal is to prevent the formation of varices (pre-primary prophylaxis); (2) the patient with gastroesophageal varices who has never had bleeding from them, and in whom the goal is to prevent their rupture (primary prophylaxis); (3) the patient with acute variceal hemorrhage in whom the goal is to stop the hemorrhage and prevent its early recurrence; and (4) the patient who has survived an episode of acute variceal hemorrhage, in whom the goal of therapy is to prevent late recurrence of hemorrhage (secondary prophylaxis).

Prevention of formation of varices (pre-primary prophylaxis)

Every patient with a new diagnosis of cirrhosis should have an EGD to look for the presence and size of varices. In patients who do not have gastroesophageal varices, a large multicenter, randomized, controlled trial showed no differences between placebo and β-blockers in the prevention of varices[1]. Therefore, no specific treatment for portal hypertension is recommended in this setting. The main focus at this stage is to treat the underlying cause of cirrhosis which will reduce portal hypertension and may therefore prevent the development of clinical complications.

Prevention of first variceal hemorrhage (primary prophylaxis)

First variceal hemorrhage occurs at an annual rate of about 15% and although current mortality from an episode of variceal hemorrhage is lower than in the past two decades, it still carries a significant mortality of 7%-15%[32-34], and is still associated with significant morbidity and healthcare costs. Prevention of first hemorrhage, therefore, is an important part of treatment of portal hypertension. The size of varices, red wale signs on varices (visualized on EGD), and severity of liver disease (Child class C) identify the patients with highest risk of variceal hemorrhage[18]. Therefore, within this stage, patients need to be stratified by the risk of hemorrhage into (1) high-risk patients, i.e. ,those with medium/large varices or those with small varices that have red wale signs, or a Child C patient; and (2) low risk patients, i.e., those with small varices without red wale signs or occurring in a Child A or B patient.

In patients with medium/large varices, quality trials have shown that non-selective β-blockers (propranolol, nadolol) are as effective as EVL in preventing first variceal hemorrhage[35,36], and the recommendation is to use therapy based on local resources, expertise and patient preference.

In patients with high-risk small varices the mainstay of treatment is NSBB because technically performing EVL in these varices may be challenging (although there is no clear evidence for this).

In patients with low-risk small varices, there is limited evidence that shows that their growth may be slowed by the use of NSBB[24]. Therefore, the use of NSBB in this setting is considered optional and should be discussed with the patient.

The doses are shown in Table 2, with therapeutic goals and follow-up procedures for each of the recommended therapies.

Pros

NSBB decrease portal pressure through a reduction in portal blood flow. Their mechanism of action involves decreasing cardiac output *via* β-1 receptors and causing splanchnic vasoconstriction by blocking β-2 receptors, resulting in unopposed α-1 activity. The latter is the most important effect and therefore it is essential that NSBB (as opposed to selective β-blockers) be used. Advantages of NSBB include low cost, ease of administration and no requirement for specific expertise. As they act by decreasing portal pressure, NSBB may also reduce other complications of cirrhosis such as bleeding from portal gastropathy, ascites and spontaneous bacterial peritonitis[37,38]. In fact, a significant reduction in portal pressure has been related to an improvement in survival[38,39]. Additionally, once the patient is on NSBB there is no need for repeat EGD.

EVL has the advantage that the procedure can be done at the same time as screening endoscopy, although in some centers a screening EGD time slot will not allow for the performance of EVL, and a separate therapeutic EGD time slot is required. Also, there are relatively few contraindications to EVL and it has been associated with a lower incidence of side-effects compared with NSBB[15].

Cons

The main inconvenience of NSBB is that approximately 15% of patients may have absolute or relative contraindications to therapy, and that another 15% require dose-reduction or discontinuation due to its common side-effects (e.g., fatigue, weakness, shortness of breath) that resolve upon discontinuation but discourage patients from using these drugs[27].

EVL requires specific expertise. The risks include that of the endoscopic procedure and conscious sedation (bleeding, aspiration, perforation and reaction to medications), plus the risk of bleeding from ligation-induced ulcers. In fact, although the quantity of side-effects is greater with NSBB than with EVL[15], the severity of side-effects is greater with EVL. While no lethal side-effects have been reported with the use of NSBB[16], three deaths resulting from EVL-induced bleeding ulcers have been reported[15,16].

Recommendation

The issue of which is the best treatment for primary prophylaxis (NSBB or EVL) has not yet been settled, and there are centers that perform predominantly EVL while others prefer the more rational approach of starting with NSBB and switching to EVL if there is intolerance to NSBB. Carvedilol is a NSBB with an added vasodilatory effect through anti-α-1 adrenergic activity that has recently been shown to be more effective than EVL in preventing first variceal hemorrhage[40]. Although considered a promising alternative, further research is necessary before it can be widely recommended.

MANAGEMENT OF ACUTE VARICEAL HEMORRHAGE

Acute variceal hemorrhage is a medical emergency requiring intensive care. The basic medical principles of airway, breathing and circulation are followed to achieve hemodynamic stability. Blood transfusion is done conservative-

Table 2 Primary prophylaxis and secondary prophylaxis of variceal hemorrhage

Therapy	Starting dose	Therapy goals	Maintenance/follow-up
Propranolol	(1) 20 mg orally twice a day; (2) Adjust every 2-3 d until treatment goal is achieved; (3) Maximal daily dose should not exceed 320 mg	(1) Maximum tolerated dose; (2) Aim for resting heart rate of 50-55 beats per minute	(1) At every outpatient visit make sure that patientis appropriately β-blocked; (2) Continue indefinitely; (3) No need for follow-up EGD
Nadolol	(1) 40 mg orally once a day; (2) Adjust every 2-3 d until treatment goal is achieved; (3) Maximal daily dose should not exceed 160 mg	As for propranolol	As for propranolol
EVL	Every 2-4 wk until the obliteration of varices	Obliteration of varices; Eradication of new varices following initial obliteration	First EGD performed 1-3 mo after obliteration and every 6-12 mo thereafter
Propranolol	(1) 20 mg orally twice a day; (2) Adjust every 2-3 d until treatment goal is achieved; (3) Maximal daily dose should not exceed 320 mg	(1) Maximum tolerated dose; (2) Aim for resting heart rate of 50-55 beats per minute	(1) At every outpatient visit make sure that patient is appropriately β-blocked; (2) Continue indefinitely
Nadolol	(1) 40 mg orally once a day; (2) Adjust every 2-3 d until treatment goal is achieved; (3) Maximal daily dose should not exceed 160 mg	As for propranolol	As for propranolol
ISMN	(1) Only to be used in conjunction with propranolol or nadolol; (2) 10 mg orally at night every day; (3) Adjust every 2-3 d by adding 10 mg in am and then pm; (4) Maximal dose is 20 mg twice a day	(1) Maximal tolerated dose; (2) Systolic blood pressure remains over 95 mmHg	Continue indefinitely
EVL	Every 2-4 wk until the obliteration of varices	Obliteration of varices; Eradication of new varices following initial obliteration	First EGD performed 1-3 mo after obliteration and every 6-12 mo thereafter

Either one of the three therapies shown in the table are recommended. EGD: Esophagogastroduodenoscopy; EVL: Endoscopic variceal ligation; ISMN: Isosorbide-5-mononitrate.

ly for a target hemoglobin level between 7-8 g/dL[41], because excessive blood volume restitution can increase portal pressure[42,43]. There are no definite recommendations on management of coagulopathy and thrombocytopenia, as randomized controlled trials of recombinant factor Ⅶa have not shown any advantages[44,45]. Antibiotic prophylaxis is provided by quinolones with consideration of iv ceftriaxone in patients with advanced cirrhosis or previous therapy with quinolones[12,46]. Safe vasoactive drugs are started as soon as possible, prior to diagnostic endoscopy. Endoscopy is done as soon as possible and not more than 12 h after presentation. If a variceal source is confirmed, EVL is the procedure of choice, but sclerotherapy is an option when EVL is technically difficult. TIPS is recommended in patients who fail standard combination therapy with endoscopic and pharmacological therapy, however salvage TIPS is accompanied by a very high mortality. Predictors of failure are Child class C, HVPG > 20 mmHg and active bleeding at endoscopy[47]. The use of early (pre-emptive) TIPS (within about 48 h of admission) in patients at high risk of failing standard therapy has been shown to reduce mortality[28]. These patients are specifically those who are Child C (score of 10-13 points) or are Child B with active hemorrhage (at the time of diagnostic endoscopy), and constitute < 20% of the patients admitted for variceal hemorrhage. In these patients it is recommended to consider early preemptive TIPS. All others should continue standard therapy with vasoactive drugs continued for 2-5 d depending on control of bleeding and severity of liver disease. Vasoactive drugs can be discontinued once the patient has been free of bleeding for at least 24 h. Balloon tamponade is only used as a temporary measure (inflated for 12 h or less) to control bleeding while a definitive therapy (TIPS or endoscopic therapy) is planned. A new self-expanding esophageal stent is being tested that may replace balloon tamponade[48].

Although there are pros and cons for each of these first-line therapies (pharmacological and endoscopic), the current recommendation is to use them jointly in the control of acute hemorrhage.

Pros

Vasoactive agents improve the control of variceal hemorrhage when combined with endoscopic therapy and when compared to endoscopic therapy alone[49]. However there appears to be no significant difference among the different vasoactive agents regarding control of hemorrhage and early rebleeding. Vasopressin, a powerful vasoconstrictor, is associated with more adverse events[50], and should not be considered a first-line vasoactive drug. Terlipressin is the only agent that, in small studies and when compared to no treatment, improved survival[50]. In practice, the choice of pharmacological agent is usually based on availability and cost. Octreotide, a somatostatin analogue, is the only safe vasoactive drug available in the United States. Doses and schedules for the different vasoconstrictors are shown in Table 3. Except for vasopressin that must be administered with nitroglycerin, the administration of these agents does not require any special procedure or expertise and can be started in the emergency room setting.

Endoscopic therapy in the acute setting is very effective in controlling variceal hemorrhage, particularly when

Table 3 Vasoactive agents used in the management of acute hemorrhage

Drug	Standard dosing	Duration	Mechanism of action
Somatostatin	Initial iv bolus 250 μg (can be repeated in the first hour if ongoing bleeding); continuous iv infusion of 250 to 500 μg/h	Up to 5 d	Inhibits vasodilator hormones like glucagon causing splanchnic vasoconstriction and reduced portal blood flow
Octreotide (somatostatin analogue)	Initial iv bolus of 50 μg (can be repeated in first hour if ongoing bleeding); continuous iv infusion of 50 μg/h	Up to 5 d	Same as somatostatin, longer duration of action
Vapreotide (somatostatin analogue)	Bolus: 50 μg; continuous iv infusion of 50 μg/h	Up to 5 d	Similar to somatostatin with higher metabolic stability
Vasopressin + nitroglycerine	0.2-0.4 units/min continuous iv infusion intravenously, may titrate to a maximum of 0.8 units/min; always use in combination with nitroglycerine	Maximum of 24 h at lowest effective dose	Causes direct vasoconstriction on splanchnic circulation resulting in decreased portal blood flow
Terlipressin (vasopressin analogue)	Initial 48 h: 2 mg iv every 4 h until control of bleeding; maintenance: 1 mg iv every 4 h to prevent re-bleeding	Up to 5 d	Splanchnic vasoconstriction; the active metabolite lysine-vasopressin is gradually released over several hours thus decreasing typical vasopressin side effects

a spurting varix is observed. However, in a meta-analysis comparing sclerotherapy *vs* vasoactive drugs, no differences in efficacy were observed between treatments, with more side-effects with sclerotherapy[51]. EVL has replaced sclerotherapy as the endoscopic procedure of choice due to more effective control of bleeding, obliteration of varices in fewer treatment sessions, a lower rebleeding rate, and lower mortality[19,33]. How EVL compares with vasoactive drugs alone remains to be determined. There is no added benefit of a combination of EVL and sclerotherapy over band ligation alone.

Cons

Vasoactive drugs often require placement of central lines and require close monitoring for ischemic complications. Vasopressin is the most potent vasoconstrictor, but its use is limited by multiple side-effects related to splanchnic vasoconstriction (e.g., bowel ischemia) and systemic vasoconstriction (e.g., hypertension, myocardial ischemia). Terlipressin is an analogue of vasopressin that, although safer, is still accompanied by more side-effects than somatostatin[52]. The main side effects of the somatostatin analogs octreotide and vapreotide are sinus bradycardia, hypertension, arrhythmia, and abdominal pain.

Endoscopic therapy during acute hemorrhage carries the usual risks of endoscopic procedures, with increased risk of aspiration due to active bleeding and the emergency nature of the procedure. In the setting of active hemorrhage, the band ligator limits the visibility, and it becomes technically difficult to maneuver the endoscope back into the stomach. Elastic bands can slip or can cause ulcers that can result in rebleeding. As mentioned previously, EVL has less side-effects than sclerotherapy and is the endoscopic therapy of choice.

Recommendation

The specific treatment of choice for acute variceal hemorrhage is the combination of vasoactive drugs (started prior to EGD) and emergency endoscopic therapy (at the time of initial diagnostic EGD). The pharmacological therapy of choice is terlipressin (lower mortality in small placebo-controlled studies) or somatostatin (fewer side-effects), however the choice is dependent on availability and cost. Octreotide is the only vasoactive drug available in the United States. The endoscopic therapy of choice is EVL.

Recommendations may vary depending on the severity of liver disease. In patients who are Child C (or Child B with active hemorrhage), the risk of failing recommended treatment (vasoactive drugs and EVL) is high and therefore proceeding to a "rescue" therapy (i.e., TIPS) before failure occurs should be considered. In patients who are Child A, mortality with the treatment of choice is essentially nil[32,34], and these patients may respond to vasoactive therapy alone, although this requires further exploration.

PREVENTION OF RECURRENT VARICEAL HEMORRHAGE (SECONDARY PROPHYLAXIS)

The risk of rebleeding in patients who survive an episode of variceal hemorrhage is high (median rebleeding rate 60%), with a mortality of up to 33%. Prevention of rebleeding is therefore an essential part of the management of the patient with variceal hemorrhage. Patients who had a TIPS performed during the acute episode do not require specific therapy for portal hypertension or for varices but should be referred for transplant evaluation. TIPS patency should be checked through Doppler ultrasound every 6 mo. For the majority (patients who do not have a TIPS performed during the acute episode), secondary prophylaxis with NSBB should be started as soon as the intravenous vasoactive drug is discontinued. NSBB significantly reduce the risk of recurrent hemorrhage[13]. Although the addition of ISMN to NSBB has a greater portal pressure-reducing effect[53], in clinical trials the combination of NSBB and ISMN is no different from NSBB alone regarding the rate of overall rebleeding or mortality, but has a higher rate of side-effects[54]. Sclerotherapy decreases rebleeding rates and mortality, but is associated with serious complications (e.g., esophageal strictures, bleeding from ulcers). Sclerotherapy has been replaced by EVL, since it has significantly better outcomes

(rebleeding, mortality and side-effects) compared with sclerotherapy. Studies comparing pharmacological therapy (NSBB plus ISMN) *vs* EVL show no differences in recurrent hemorrhage, but there is a suggestion of a beneficial effect on survival with pharmacological therapy in the long term[54,55]. The combination of pharmacological (NSBB alone or NSBB + ISMN) plus EVL is associated with lower rebleeding rates than either therapy alone[31,56], and constitutes the treatment of choice.

In patients who experience recurrent variceal hemorrhage despite the combination of pharmacologic and endoscopic treatment, TIPS with polytetrafluoroethylene-covered stents[57] or, where expertise is available, surgical shunts[58] should be provided.

Table 2 presents the doses, therapeutic goals and follow-up procedures for the recommended therapies. The pros and cons of each of these first-line therapies (pharmacological and endoscopic) are the same as those described for primary prophylaxis, with some additional considerations described below.

Pros

Pharmacologic agents provide protection against rebleeding during the initial phase after index hemorrhage while esophageal varices are being obliterated by EVL. NSBB alone or in combination with ISMN should be used. The choice will depend on patient tolerability. Patients who are not candidates for EVL should receive combination NSBB + ISMN.

The lowest rates of recurrent variceal hemorrhage (approximately 10%) are observed in individuals who have a hemodynamic response to pharmacologic therapy, defined as a decrease in HVPG to < 12 mmHg or a decrease of > 20% from baseline levels[39,59]. The more rational approach would thus be to guide therapy based on hemodynamic response and, in those who achieve a hemodynamic response, endoscopic therapy would not be necessary. However there are cons (see below) to this approach.

Patients who are intolerant or have contraindications to pharmacological therapy should receive EVL alone.

Cons

A recent study suggests that NSBB are associated with a poorer survival in patients with refractory ascites[60], a condition that may be present in patients in this clinical stage. However, the study is retrospective and the groups were disparate at baseline, with patients on NSBB having more advanced disease as shown by a higher prevalence of varices and variceal hemorrhage, and there is evidence that indicates the contrary, that is, that NSBB may be beneficial for these patients[13,61]. Therefore, unless stronger evidence arises, the use of NSBB in patients with refractory ascites should not be contraindicated.

The combination of NSBB + ISMN has a higher incidence of side effects because of the added ones associated with ISMN, specifically headache and lightheadedness. As mentioned above, the lowest rebleeding rates are in patients who experience a hemodynamic response. Although HVPG-guided therapy would appear rational, a small trial showed that outcomes with HVPG-guided therapy are no different from those in patients treated with combined pharmacological and endoscopic therapy[62]. Until the best treatment for non-responders is settled, larger clinical trials are performed, and HVPG measurements are standardized across centers, HVPG-guided therapy cannot be currently recommended[63].

As mentioned above, EVL is associated with bleeding from EVL-induced ulcers. Treatment with proton pump inhibitors post ligation reduces the size of these ulcers, with a trend towards a lower risk of bleeding[64], and can be considered in this setting.

Recommendation

The treatment of choice to prevent rebleeding is the combination of pharmacological therapy (NSBB ± ISMN) and EVL. Contrary to other clinical stages, risk stratification has not been tested in this setting. The main predictor of recurrent bleeding and death is the Child classification. It is conceivable that patients who are Child A would only require one or other therapy, while patients who have more advanced disease require the combination therapy. Patients who fail this therapy should be considered for TIPS placement and, in centers where expertise is available, for a surgical shunt. Patients with recurrent variceal hemorrhage are in a category of "further decompensation" of cirrhosis and, as such, should be evaluated for liver transplantation.

CURRENT STANDARD TREATMENT OF PORTAL HYPERTENSION IN CHILDREN

The most common causes of portal hypertension in children are biliary atresia and portal vein thrombosis. Data regarding the prevalence of esophageal varices in children with portal hypertension is very limited and to date there have been no randomized controlled trials comparing different treatments for primary and secondary prophylaxis[65].

Regarding primary prophylaxis, there is currently no recommended treatment[22,66]. In a recent gathering of experts at the AASLD annual meeting, it was concluded that, before a randomized trial could be performed in children, pediatric research should focus on addressing questions of the natural history and diagnosis of varices, prediction of variceal bleeding, optimal approaches to β-blocker and ligation therapy, and alternative study designs to explore therapeutic efficacy in children[65].

Regarding acute variceal hemorrhage, management in children is based on limited data comparing EVL and sclerotherapy[67], and expert pediatric opinion based on adult Baveno Ⅳ guidelines[66]. These include vasoactive agents, antibiotic prophylaxis and endoscopic variceal ligation.

EVL is also recommended for secondary prophylaxis of variceal hemorrhage but it has not been compared with β-blockers[22,66]. In children with portal vein throm-

bosis, meso-rex bypass appears to be the best option for secondary prophylaxis[22,66].

CONCLUSION

In the last two decades significant advances in the field of portal hypertension have improved the clinical care and survival of patients with cirrhosis and portal hypertension. In addition to better treatment strategies and improved therapeutic options, the issue of risk stratification has become more important so that, within each clinical stage, different patient subpopulations have been identified that require a different management. Clearly, further research is necessary to explore new pharmacological options that would allow a majority of patients to be hemodynamic responders, thereby foregoing the need for HVPG measurements and even the need for endoscopic therapy. The identification of different risk populations within each stage also requires further definition. It is expected that future trials and Baveno and AASLD conferences will continue to advance the field.

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