

Portal Hypertension and Variceal Bleeding—Unresolved Issues. Summary of an American Association for the Study of Liver Diseases and European Association for the Study of the Liver Single-Topic Conference

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Many randomized controlled trials (RCTs) have advanced the knowledge of the complications of portal hypertension, specifically in the management of varices and variceal hemorrhage. The endpoints in most of these trials have used definitions attained at international consensus workshops that have been published in medical journals since the first Baveno conference in 1992.¹ Three more international consensus conferences have helped further define clinical endpoints and practice recommendations.²⁻⁵ This article summarizes the results of an Endpoints Single Topic Conference on “Portal Hypertension and Variceal Bleeding—Unresolved Issues” that took place in Atlanta, GA, in June 4-6, 2007 and that was sponsored jointly by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver and constitutes the 6th international consensus conference in the area of varices and variceal hemorrhage. As outcomes have improved and knowledge has been gained, it is necessary to prioritize areas that require further research, to define surrogate markers of outcome and to stratify patients in different risk groups. These were the objectives of

this single-topic conference. For areas in the management of varices and variceal hemorrhage in which it was decided that no further trials were necessary or plausible, practice recommendations were put forward. In some instances, these differed from recommendations put forward at the most recent consensus conference in Baveno 2004⁵ and were incorporated into the recently published AASLD/American College of Gastroenterology (ACG)-sponsored recommendations.^{6,7} Recommendations were obtained by majority agreement defined as agreement by greater than 70% of 23 expert participants (listed at the end of the article).

A. Natural History of Varices/Variceal Hemorrhage

There are two main stages in the natural history of cirrhosis: *compensated* and *decompensated* cirrhosis, defined by the absence or presence of ascites, variceal hemorrhage, encephalopathy, or jaundice.^{8,9} Both entities differ in clinical presentation, outcome, mortality, and predictors of death.

Compensated cirrhosis has a median survival of more than 12 years (while remaining in the compensated stage), which is significantly longer than that of decompensated patients (approximately 2 years). Compensated patients die mostly after decompensation or of causes unrelated to liver disease, whereas in patients with decompensated cirrhosis mortality is mostly liver-related. Transition from a compensated to a decompensated stage is the most common outcome in patients with compensated cirrhosis and occurs at a rate of 5%-7% per year.^{8,10} Although the Child-Turcotte-Pugh (CTP) score (or its components) is the most robust predictor of death in cirrhosis (compensated or decompensated), other prognostic markers differ, depending on the stage of cirrhosis.⁹ In compensated cirrhosis, markers of portal hypertension (varices, platelet count, spleen size, gamma-globulins) are predictive of death, whereas in decompensated cirrhosis, markers of

Abbreviations: ACG, American College of Gastroenterology; AASLD, American Association for the Study of Liver Diseases; CE, capsule endoscopy; CTP, Child-Turcotte-Pugh; EGD, esophagogastroduodenoscopy; EVO, endoscopic variceal obturation; HVP, hepatic venous pressure gradient; LS, liver stiffness; NSBB, nonselective beta-blockers; RCT, randomized controlled trials; TIPS, Transjugular intrahepatic portosystemic shunt.

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Received October 2, 2007; accepted January 30, 2008.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22273

Potential conflict of interest: Nothing to report.

circulatory dysfunction (such as renal dysfunction) and hepatocellular carcinoma are more predictive.

More recently, four different stages have been proposed based on 1-year mortality data in a large cohort of untreated patients.¹¹ The first two stages occur in compensated cirrhosis and are defined by the absence (stage 1) or presence of varices (stage 2). The other two stages occur in decompensated cirrhosis and are defined by the presence of ascites (with or without varices, stage 3) and by variceal hemorrhage (with or without ascites; stage 4). The 1-year mortality in these four stages is 1%, 3%, 20%, and 57%, respectively.

Hepatic Venous Pressure Gradient in the Natural History of Portal Hypertension

Assessment of portal pressure by the hepatic venous pressure gradient (HVPG) has been a useful predictor of outcomes in both stages. In patients with compensated cirrhosis, an HVPG greater or equal to 10 mmHg is the most important predictor of the development of varices¹² and clinical decompensation.¹³ This HVPG level has been designated “clinically significant portal hypertension.”¹⁴ Furthermore, in posttransplantation recurrent hepatitis C, HVPG has a higher diagnostic accuracy than liver biopsy in predicting decompensation.¹⁵ In decompensated cirrhosis, HVPG obtained at the time of variceal hemorrhage predicts outcome¹⁶ and is an independent predictor of death in a model adjusted by MELD (model for end-stage liver disease), ascites, and age.¹⁷ An HVPG of 20 mmHg appears to be the best cutoff in this patient population.

Recommendations:

- ***Compensated and decompensated cirrhosis should be considered two separate entities both in clinical practice and in clinical research***
- ***Studies in cirrhosis should consider and analyze these entities separately***
- ***HVPG >10 mmHg is the best predictor of variceal development and decompensation and should be used to stratify patients with compensated cirrhosis in clinical trials***
- ***Substaging of patients with cirrhosis requires validation in prospective cohort studies***

B. Screening for Varices

Current guidelines recommend screening esophago-gastroduodenoscopy (EGD) when the diagnosis of cirrhosis is made so that effective prophylaxis of variceal hemorrhage can be applied.⁵⁻⁷

Noninvasive Assessment of Gastroesophageal Varices

An alternative to EGD is capsule endoscopy (CE), which, in pilot studies, had a negative predictive value of 57%-100%¹⁸⁻²⁰ and may have an acceptable budget impact.²¹ Preliminary results of a multicenter study comparing CE versus EGD in 288 patients (180 with varices by EGD), showed a good agreement in detecting both the presence (86%) and size (77%) of esophageal varices.²² However, 23% of patients with negative CE had varices on EGD and, of 79 patients with medium/large varices on EGD, 17 (22%) were diagnosed as having no or small varices on CE. There was greater preprocedure acceptance and postprocedure satisfaction for CE.

Recommendations:

- ***Capsule endoscopy requires further study to better define its reproducibility, reliability, and accuracy, as well as patient preference and cost-effectiveness, but may be a reasonable alternative to EGD in patients unable or unwilling to undergo EGD***

C. Prevention of First Variceal Hemorrhage

Prevention of Varices

A large multicenter placebo-controlled study showed that nonselective beta-blockers (NSBBs) are not effective in preventing the development of varices in patients with portal hypertension (HVPG > 6 mmHg), and its use is associated with a higher rate of side effects.¹² Most agreed that it is currently unnecessary to perform similar trials.

Prevention of First Variceal Hemorrhage in Patients With Small Varices

RCTs aimed at preventing first variceal hemorrhage in patients with small varices will require a huge sample size and therefore should be discouraged. Because NSBBs may have other beneficial effects via reduction in portal pressure, RCTs combining endpoints such as an increase in HVPG, variceal growth, cirrhosis decompensation, and death may be more appropriate. RCTs of endoscopic variceal ligation (EVL) in this setting also should be explored.

Given that high-risk small varices bleed at a similar rate to large varices and that growth of non-high-risk small varices has been shown in an RCT to be slower in patients treated with nadolol,²³ there was majority agreement in recommending that patients with small varices and a high risk of bleeding (CTP class C or red signs) should receive NSBB and that in other patients with small varices NSBB are optional; if NSBB are given, repeat EGD is not necessary, whereas if NSBB are not given, EGD should be repeated in 2 years. These recommendations are different from those proposed in the last Baveno conference⁵ and were incorporated in the AASLD/ACG guidelines.^{6,7}

Prevention of First Variceal Hemorrhage in Patients With Medium/Large Varices

Two therapies are effective in these patients: NSBB and EVL. Two published meta-analyses of 12 trials comparing them show that EVL is associated with a significantly lower incidence of first variceal hemorrhage but without differences in mortality.^{24,25} The results of a third Cochrane meta-analysis are awaited. The most recent Baveno conference considered that, given a lack of survival benefit and uncertainty regarding the long-term benefits of EVL, NSBB should be first-line therapy and that EVL should be offered to patients who have contraindications or intolerance to NSBB.⁵

Data beyond these meta-analyses were reviewed at the single-topic conference, showing that analysis of six high-quality RCTs show no difference in first hemorrhage between therapies²⁶; that side effects are more severe with EVL, as there have been three reported deaths secondary to bleeding from post-EVL ulcers^{27,28}; that EVL was cost-effective when cost per quality-adjusted life-year is considered²⁹; and that predicted preferences are higher for EVL in both patients and physicians.³⁰ Advantages of NSBB such as prevention of bleeding from other portal hypertension sources (portal hypertensive gastropathy and gastric varices) and possible reduction in the incidence of spontaneous bacterial peritonitis,³¹ and other complications of portal hypertension, were also discussed. Nevertheless, most agreed that both NSBB and EVL are effective therapies and that the clinical decision depends on patient characteristics and preferences, local resources, and expertise. These recommendations differ from those put forward in the Baveno conference and were incorporated in the AASLD/ACG guidelines.^{6,7}

Further studies comparing NSBB versus EVL are not justified. If a new treatment becomes available, it should be compared with either NSBB or EVL and not with a placebo or an untreated group. Studies of NSBB plus EVL have been inconclusive,^{32,33} and, given a perceived unacceptable risk–benefit ratio with combined therapy, most agreed that combination EVL + NSBB is not recommended in this setting.^{6,7}

HVPG Measurements in the Prevention of Varices/Variceal Hemorrhage

In patients with no varices and portal hypertension (HVPG ≥ 6 mmHg), the best predictor of the development of varices is a baseline HVPG greater than 10 mmHg.¹² Furthermore, an HVPG reduction greater than 10% at 1 year was associated with a significantly lower incidence of varices.¹² Interestingly, even though there was no overall difference in the development of varices between patients treated with NSBB and with pla-

cebo, a greater proportion of patients randomized to NSBB achieved a reduction in HVPG greater than 10% (53% on NSBB vs. 38% on placebo), indicating that a drug that could increase the proportion of patients that achieve this HVPG reduction would probably be effective in preventing varices.

In patients with varices (mostly medium/large) that have never bled, reductions greater than 10%-20% reduce the incidence of first variceal hemorrhage, and patients in whom the HVPG decreases below 12 mmHg are essentially protected from bleeding.³⁴⁻³⁶ In this patient population, a reduction in HVPG of more than 15% has been associated with a reduction in spontaneous bacterial peritonitis.³¹

Recommendations:

- ***Unless a new and effective therapy becomes available, further trials of preprimary or primary prophylaxis with existing therapies are unnecessary***
- ***In studies of prevention of varices (preprimary prophylaxis), only patients with an HVPG greater than 10 mmHg should be included***
- ***In studies of prevention of variceal hemorrhage (primary prophylaxis), new pharmacological treatments should be compared with NSBB in a double-blind design and should include HVPG measurements. In patients with small varices, combining endpoints will be necessary***
- ***In RCTs using EVL, because blinding is not applicable, treatment outcome and adverse events should be predefined and assessed by physicians blinded to trial treatment***

D. Treatment of Acute Hemorrhage

Currently, it is recommended that short-term antibiotic prophylaxis, a measure that reduces bacterial infections,³⁷ variceal rebleeding,³⁸ and death³⁷ be used in every patient with cirrhosis admitted with gastrointestinal hemorrhage.⁵⁻⁷ Different antibiotics have been used in different trials and, given different local antibiotic susceptibility patterns and different availability it is unlikely that a definitive trial in this area will be performed.

Specific therapy is based on the combination of pharmacological and endoscopic therapy, which is better than either treatment alone,³⁹⁻⁴¹ particularly with early administration of pharmacological therapy.^{42,43}

No RCTs compare different combinations of endoscopic/pharmacological therapy. RCTs comparing different pharmacological agents (vasopressin, somatostatin, terlipressin, octreotide) demonstrate no differences among them regarding control of hemorrhage and early rebleeding, although vasopressin is associated with more

adverse events.⁴⁰ In practice, the choice of pharmacological agent is usually based on availability and cost.

The optimal duration of pharmacological therapy has not been well established. In RCTs, the duration of vasoactive treatment has varied between 8 hours⁴² and 6 days. Trials aimed at determining the best duration of therapy are impractical and costly. There was majority agreement that an appropriate length of therapy would be anywhere between 2 and 5 days,^{6,7} depending on control of hemorrhage and the presence or absence of predictors of rebleeding (for example, CTP class, HVPG).

EVL is more effective than endoscopic variceal sclerotherapy (EVS) with greater control of hemorrhage, lower rebleeding, and lower adverse events but without differences in mortality.^{44,45} No further trials are necessary to determine the best endoscopic therapy.

HVPG Measurements in Acute Variceal Hemorrhage

Prospective cohort studies in which HVPG has been measured within 48 hours of admission for hemorrhage show that levels greater than 20 mmHg are associated with increased rebleeding and mortality.^{16,44,46-48} A more recent study performed in the era of combined vasoactive drug plus endoscopic therapy confirms this HVPG cutoff and shows that an index including CTP score and blood pressure at admission has similar prognostic value.⁴⁹ Furthermore, a drug-induced HVPG reduction of less than 10% predicts 5-day failure. This response may improve by doubling the dose of somatostatin or switching to another agent (such as terlipressin).⁵⁰

Transjugular Intrahepatic Portosystemic Shunt in Acute Variceal Hemorrhage

Transjugular intrahepatic portosystemic shunt (TIPS) is a reasonable alternative in the face of failure of combined pharmacologic plus endoscopic therapy. In the Baveno conference, it was considered that a second attempt at endoscopic therapy was one possibility but that one could perform TIPS after failure of the first endoscopic therapy.⁵

A small study suggests that early TIPS placement (within 24 hours of hemorrhage) is associated with a significant improvement in survival in patients with an HVPG greater than 20 mmHg.⁴⁸ Therefore, HVPG can provide useful information that allows for risk stratification and more aggressive treatment in high-risk patients.

Consensus Recommendations:

- ***Risk-stratification of patients presenting with acute variceal hemorrhage is necessary to better assess duration of pharmacological therapy and to determine whether different treatment strategies (such as early TIPS in high-risk patients) are warranted***

- ***HVPG greater than 20 mmHg measured within 48 hours of presentation is the best predictor of poor outcome***

- ***Noninvasive markers of a poor outcome have been identified and require validation***

- ***Early TIPS therapy in high-risk patients should be further investigated***

E. Prevention of Recurrent Variceal Hemorrhage

The most recent Baveno consensus conference recommended that patients with cirrhosis who had not received primary prophylaxis could receive NSBB, EVL, or both.⁵ Although it was recognized that combination of NSBB plus EVL was probably the best alternative, it concluded that more trials were needed before a recommendation could be made.

Combination EVL plus NSBB is a rational approach because NSBB will theoretically protect against rebleeding before variceal obliteration and can prevent variceal recurrence. In fact, two small RCTs demonstrate the superiority of combined therapy versus EVL alone.^{51,52} Based on this information, there was majority agreement that, as incorporated in AASLD/ACG guidelines, the best approach in the prevention of recurrent esophageal variceal hemorrhage is the combination of NSBB plus EVL.^{6,7}

Trials of combination pharmacological therapy (NSBB plus isosorbide mononitrate) versus EVL have shown no differences in rebleeding or death. A recent RCT comparing EVL + combination drug therapy (NSBB + isosorbide mononitrate) versus combination drug therapy alone showed no differences in overall rebleeding or survival but a lower incidence of variceal rebleeding in the EVL group, indicating that the benefit of EVL in decreasing variceal hemorrhage was offset by an increase in bleeding from EVL-induced ulcers.⁵³

HVPG in the Prevention of Recurrent Hemorrhage

Patients who experience a reduction of HVPG below 12 mmHg are protected from bleeding, whereas those that reduce it by more than 20% from baseline have a very low risk of rebleeding compared with nonresponders,^{35,54} provided that repeat measurements are performed within 120 days from baseline, preferably within 1 month. Approximately 30% to 40% of patients treated with NSBB ± nitrates are HVPG responders. Therefore, and until a therapy becomes available that will significantly increase the proportion of HVPG responders, it would appear rational that HVPG measurements should guide this therapy.^{55,56} In a study evaluating the cost-effectiveness of three different prophylactic strategies in the setting of secondary prophylaxis,⁵⁷ combination pharmacologi-

cal therapy with HVPG monitoring was more cost-effective than EVL or combination drug therapy without HVPG, and its cost-effectiveness improved with increasing probabilities of achieving a hemodynamic response. Unfortunately, there have been no RCTs comparing an HVPG-guided therapy versus standard therapy, and such a trial is necessary.

Practical Issues Regarding EVL in the Prevention of Recurrent Variceal Hemorrhage

The timing between EVL sessions and the subsequent EGD surveillance schedule is uncertain, and it is considered unnecessary to perform RCTs to clarify these issues. Given available data from RCTs of EVS and EVL cohorts in RCTs of EVS versus EVL, it appears that the smaller the interval between EVL sessions, the faster the eradication of varices. Regarding surveillance EGD, 3-month intervals were used initially in 11 RCTs (in two of them EGD was also performed 1 month after eradication), and in a number of them, it was switched to 6-month intervals at 6 months without differences in recurrent bleeding compared with trials that continued 3-month interval surveillance. Most experts will do the first surveillance EGD 1-3 months after eradication, the second 3 months later, and then at 6-month to 12-month intervals, depending on variceal recurrence. This majority recommendation was incorporated into the AASLD/ACG guidelines.^{6,7}

Practical Issues Regarding Shunt Surgery

TIPS has superseded shunt surgery in most patients and is the main option in patients in whom first-line therapy has failed in most centers. However, a large multicenter trial of TIPS versus distal splenorenal shunt shows similar rates of rebleeding, encephalopathy, and mortality in patients with CTP class A/B cirrhosis who had failed pharmacological/endoscopic therapy, with a higher rate of shunt dysfunction in the TIPS group (perhaps because bare TIPS stents were used).⁵⁸ Because both procedures have equivalent outcomes, surgery is still an option in good-risk patients, when surgical expertise is available. Given this information, and the fact that there are still centers or countries where there is poor access to care, inadequate TIPS expertise, and lower availability of transplantations, most agreed that surgical training in shunt surgery is still warranted but that further trials are not required.

Recommendations:

- ***HVPG-guided therapy should be further investigated, evaluating its effect on decision-making and on outcomes***

- ***New pharmacological treatments should be compared with NSBB in a double-blind design and should include HVPG measurements***

F. HVPG as a Surrogate Endpoint

A surrogate outcome measure is a laboratory measurement, a physical sign, or another intermediate substitute that is able to predict an intervention's effect on a clinically meaningful outcome. Surrogate outcome measures occur faster or more often, are cheaper, and are achieved less invasively than the clinical outcome. Surrogate outcomes must be validated before use. The first step in validation is to demonstrate a correlation between the putative surrogate and the clinical outcome. The second step is to establish whether the intervention's effect on the surrogate outcome accurately predicts the intervention's effect on the clinical outcome.⁵⁹

As shown, HVPG predicts decompensation¹³ and death.⁹ Reductions in HVPG that occur over time are negative predictors of development of varices,¹² the risk of variceal hemorrhage,^{34,35,60} the development of nonvariceal complications of portal hypertension,^{34,61,62} and death.^{9,35,62,63} Portal pressure measured by the HVPG may be as close as we can come to a validated surrogate outcome measure in hepatology.⁵⁹ In fact, HVPG could be a surrogate marker not only in clinical trials for portal hypertension but also in trials assessing progression of chronic liver disease (viral and metabolic liver disease), as in a recent study performed in posttransplantation recurrent hepatitis C in which HVPG was more accurate in predicting the development of decompensated cirrhosis than was liver biopsy.¹⁵

The cutoff levels that would define success in RCTs on prevention of varices would be to achieve a decrease in HVPG of greater than 10% from baseline, preferably to less than 10 mmHg. In trials of prevention of variceal hemorrhage, the outcome would be to decrease the HVPG to less than 12 mmHg or to achieve a decrease of greater than 20% from baseline, although it would appear that for studies of primary prophylaxis of variceal bleeding a decrease of greater than 10% from baseline would be adequate. In secondary prophylaxis, the second measurement should be performed as soon as possible after achieving an optimal dose and no later than 1 month after the first measurement, because one third of rebleeding episodes will occur within this time frame. Recent studies have suggested that an acute assessment of HVPG response to intravenous propranolol at the time of the first HVPG measurement is predictive of long-term response and outcome,^{64,65} but this will require further assessment.

The HVPG Technique

The method is accurate, reproducible, and safe, provided guidelines are followed.⁶⁶ Its reproducibility has been assessed indirectly through the analysis of studies in which baseline and repeat HVPG measurement were performed between 20 and 720 minutes from baseline, showing a mean change of only 0.4% between measurements. In addition, a recent study showed an excellent interobserver agreement ($r = 0.98$) in tracing interpretation.⁶⁷ The overall complication rate in 2,364 measurements performed in a Spanish hospital between 1995 and 2006 was only 2.3%, with large neck or groin hematomas being the most common. There appears to be a learning curve; complication rates were 4.9% before 2000 and approximately 1% after 2000. No procedure-related deaths have been observed.

Important differences are noted between investigators in the United States and those in Europe, where the technique is widely used and is performed by hepatologists. In the United States, HVPG measurements are performed by interventional radiologists mostly for clinical purposes, with a variable frequency (median, 40 procedures/year; range, 0-160) and a variable and suboptimal technique (against current recommendations, a balloon catheter is used by only 33%, and 83% use monitor readouts and do not record tracings). Most agreed that there is a need for standardization of the technique, through the creation of multisociety guidelines as well as proactive assessment through certification and surveillance of the quality of HVPG measurements.

Noninvasive Assessment of HVPG

Transient elastography (FibroScan) is a novel, rapid, noninvasive, and reproducible method for measuring liver stiffness (LS).^{68,69} Prospective studies show that LS measurements are useful in the identification of portal hypertension (HVPG ≥ 6 mmHg).⁷⁰ LS has been shown to correlate with HVPG in chronic hepatitis C^{70,71} and in alcoholic cirrhosis.⁷² However, although this correlation is excellent for HVPG, values less than 10 or less than 12 mmHg ($r^2 = 0.72$ and $r^2 = 0.67$, respectively), for values ≥ 10 mmHg or ≥ 12 mmHg (clinically significant portal hypertension), the correlation is not optimal ($r^2 = 0.35$ and $r^2 = 0.17$, respectively).⁷¹ Also, the correlation between HVPG and LS seems to differ depending on the cause of cirrhosis,⁷² and the LS cutoff value that best identifies clinically significant portal hypertension is not yet well established. Larger blinded prospective studies in unselected consecutive patients with cirrhosis of all causes are needed.

Recommendations:

- ***HVPG is the best surrogate marker in portal hypertension trials and should be measured in every trial involving pharmacological therapy***
- ***HVPG reflects fibrogenesis and progression of chronic liver disease and should be measured in trials assessing therapies in which progression of fibrosis is an endpoint***
- ***Although its prognostic value in alcoholic/viral cirrhosis has been established, prognostic studies of HVPG in other causes of cirrhosis are encouraged***
- ***Transient elastography is a promising method to detect clinically significant portal hypertension***
- ***Noninvasive techniques to assess hemodynamic response are necessary***

G. Gastric Varices

Gastric varices occur in approximately 20% of patients with portal hypertension. Fundal varices are the subtype of gastric varices with highest bleeding and rebleeding rates.⁷³ Remarkably, large fundal varices may occasionally bleed despite HVPG values less than 12 mmHg.^{74,75} NSBB are recommended as primary prophylaxis against gastric variceal bleeding. Therapies to control hemorrhage and prevent recurrent hemorrhage include endoscopic (EVL, glue, thrombin) and radiological (TIPS, balloon-occluded retrograde transvenous obliteration) options. Uncontrolled data comparing these therapies in bleeding fundal varices show that the best control of initial hemorrhage (90%-100%) is achieved with glue, TIPS, or balloon-occluded retrograde transvenous obliteration.⁷⁶

Three small single-center RCTs compare endoscopic variceal obturation (EVO) with glue versus EVS⁷⁷ or EVL in bleeding gastric varices.^{78,79} All three RCTs are favorable for EVO regarding control of acute hemorrhage,^{77,78} rebleeding,⁷⁹ or complication rate.⁷⁸ Unfortunately, less than 50% of the patients included in these studies had fundal varices, and a separate analysis was not performed. It is recommended that TIPS be used in acute bleeding from fundal varices when EVO is unavailable or if rebleeding occurs after EVO; however, this has not been evaluated prospectively. A small single-center study comparing EVO versus TIPS in the prevention of recurrent hemorrhage in patients in whom acute gastric variceal hemorrhage was controlled with EVO showed similar rebleeding rates, but again fewer than 50% of the patients were bleeding from fundal varices.⁸⁰

Recommendations:

- ***Studies on gastric varices should focus on patients with fundal varices***

- *Trials of TIPS versus EVO are encouraged*

H. Pediatric Portal Hypertension and Varices/Variceal Hemorrhage

The most common causes of portal hypertension in children are biliary atresia and portal vein thrombosis. Recommendations from adults with cirrhosis cannot be generally extended to pediatric patients. Children may require different treatments, depending on the cause of the portal hypertension. Inherent characteristics of children such as chronological differences in heart rate and need for general anesthesia for procedures such as EGD and HVPG measurements complicate the performance of RCTs in children. There are limited data from studies using NSBB in cirrhosis⁸¹ or endoscopic therapy (EVL versus EVS) in portal vein thrombosis⁸² that have, unfortunately, included heterogeneous patient populations. EVL appears to be a reasonable option in acute variceal hemorrhage and for preventing hemorrhage recurrence, but it has not been compared with NSBB. However, EVL is not feasible in children younger than 1 year old. In children with portal vein thrombosis, meso-Rex bypass would appear to be the best option for secondary prophylaxis.

Recommendations:

- *Although RCTs are challenging in children, prospective cohort studies in carefully defined risk groups (compensated or decompensated, with or without prior variceal hemorrhage) are warranted*
- *Noninvasive therapies such as NSBB require further investigation*

I. Extrahepatic Portal Hypertension in Noncirrhotic Adults

This type of portal hypertension is mostly attributable to portal vein thrombosis and occurs mostly in patients with an underlying prothrombotic disorder.⁸³ There are few RCTs on therapies and they inappropriately combine primary and secondary prophylaxis as well as children and adults. Given the large numbers of patients required for an RCT of this relatively rare entity, most agreed that useful therapies appear to be those identified in adults with cirrhosis, specifically NSBB⁸⁴ and endoscopic therapy,⁸³ with shunt surgery (splenorenal or mesocaval shunts) and TIPS (when feasible) as second-line therapies. Based on retrospective cohort studies, the use of anticoagulation (indicated in patients with a prothrombotic disorder, personal history of idiopathic thrombosis, family history of more than one thrombotic episode, history of intestinal ischemia or superior mesenteric vein involve-

ment) has been associated with a reduction in thrombotic complications and bleeding^{83,85} and improved survival.⁸⁴

Recommendations:

- *Prospective cohort studies in this area are encouraged*

The authors were the course directors of this Single-Topic Conference. In addition, the expert panel that, together with the course directors, participated in providing the background and the recommendations consisted of: Rafael Bañares (Hospital Gregorio Marañón, Madrid, Spain), Michel Beaugrand (Université Paris XIII, Bondy, France), Thomas Boyer (University of Arizona), Andy Burroughs (Royal Free Hospital, London, UK), Naga Chalasani (Indiana University), Gennaro D'Amico (Ospedale Cervello, Palermo, Italy), Roberto de Franchis (University of Milan, Italy), Liana Fraenkel (Yale University), Juan Carlos Garcia-Pagán (Hospital Clinic, Barcelona, Spain), Norman Grace (Brigham and Women's Hospital), Michael Henderson (Cleveland Clinic), Patrick Kamath (Mayo Clinic), Hetal Karsan (Emory University), David Kravetz (University of California San Diego), Jeanne LaBerge (University of California San Francisco), Loren Laine (University of Southern California), Carlo Merkel (University of Padova, Italy), Cristina Ripoll (Hospital Gregorio Marañón, Madrid, Spain), Arun Sanyal (Virginia Commonwealth University), Ben Shneider (Children's Hospital of Pittsburgh), Dominique Valla (Hôpital Beaujon, Clichy, France).

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