HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2015 November ; 13(12): 2109–2117. doi:10.1016/j.cgh.2015.07.012.

Varices and Variceal Hemorrhage in Cirrhosis. A new view of an old problem

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Abstract

The management of portal hypertension in cirrhosis has evolved over time leading to improvements in the care and survival of patients with varices and variceal hemorrhage, particularly in those who achieve a significant reduction in portal pressure. In addition to better treatment strategies and improved therapeutic options, the issue of risk stratification has become essential to identify different patient subpopulations that require a different treatment. We now recognize that the management of varices and variceal hemorrhage must be taken in the context of other complications of cirrhosis (ascites, encephalopathy, jaundice) and that the goals of therapy should be based on the presence of such complications. Evolving knowledge of the predominant pathophysiological mechanisms at each of the stages of cirrhosis has also evolved and will continue to lead to improvements in therapy. This review focuses on the management of varices and variceal hemorrhage vis-à-vis refinements in the risk stratification of patients with cirrhosis.

Portal hypertension is a frequent clinical syndrome that is defined by an increase in porto-systemic pressure gradient in any portion of the portal venous system. Although portal hypertension can 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. This review will specifically discuss management of portal hypertension secondary to cirrhosis.

In cirrhosis, the portosystemic gradient is assessed by measuring the hepatic venous pressure gradient (HVPG), the difference between the wedged hepatic venous pressure (a measure of sinusoidal hepatic pressure) and the free hepatic venous pressure [1]. A normal HVPG is 3–5 mmHg. An HVPG above 5 mmHg defines portal hypertension (and heralds the presence of cirrhosis in patients with most chronic liver diseases). When the HVPG reaches 10 mmHg or

above the patient with cirrhosis is at a higher risk of developing varices [2], clinical decompensation (i.e. development of ascites, variceal hemorrhage and hepatic encephalopathy [3] and hepatocellular carcinoma [4]. Therefore, a HVPG equal or above 10 mmHg has been designated "clinically significant portal hypertension" (CSPH).

The complications that directly result from portal hypertension are the development of varices and variceal hemorrhage. The management for varices and variceal hemorrhage in the context of cirrhotic portal hypertension has markedly advanced over the past decades due to research on animal models, introduction of new effective treatments and many randomized clinical trials that have led to our current knowledge. The field has moved forward in large part through consensus conferences among experts where events and endpoints have been defined and the existing knowledge 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 Conferences) and the United States (American Associaton for the Study of Liver diseases or AASLD Single Topic Conferences). Evidence-based guidelines endorsed by the AASLD [5] and the American College of Gastroenterology [6] (30) as well as a more recent comprehensive review [7] on the treatment of portal hypertension have been heavily based on these consensus conferences. The impact of the research and resulting guidelines during these years has been great with a decrease in mortality from acute variceal bleeding from over 40% in 1986 to about 15% at present [89, 10]

The most recent consensus conference was the 6th Baveno Consensus Workshop that took place in Baveno, Italy in April 2015 [11]. Recognizing the different stages of cirrhosis [12], the workshop aimed at stratifying risk and individualizing care for portal hypertension.

This review addresses current recommendations for the management of portal hypertension and the modifications that these recommendations may have undergone vis-à-vis the recent consensus conference [11].

Clinical settings

Therapy of varices and variceal hemorrhage is now stratified depending on the different clinical stages in the natural history of portal hypertension [12, 13]: a) patient with compensated cirrhosis without clinically significant portal hypertension; b) patient with compensated cirrhosis with clinically significant portal hypertension who has not yet developed varices; c) the patient with cirrhosis and clinically significant portal hypertension with gastroesophageal varices that have never bled; d) the patient with cirrhosis that presents with acute variceal hemorrhage; and e) the decompensated patient who has recovered from an episode of variceal hemorrhage.

Per the new consensus conference [11], portal hypertension should not only be considered in the context of varices/variceal hemorrhage but should take into consideration other complications of cirrhosis/portal hypertension such as ascites and hepatic encephalopathy and the status compensated, decompensated or "further" decompensated (as per the Child Pugh classification) [13]. In addition, stratification now incorporates the presence or not of

CSPH (defined by an HVPG equal or greater than 10 mmHg). Although HVPG measurement is not indicated in routine clinical practice, its presence can be established by the presence of collaterals on imaging studies, gastroesophageal varices on endoscopy and, most obviously in the patient with decompensated cirrhosis (presence of ascites by definition denotes the presence of CSPH). Additionally, non-invasive methods may become accurate enough to identify patients with or without CSPH.

Accordingly, the treatment of portal hypertension per Baveno 6 recommendations should be stratified by the different stages and substages of cirrhosis. The goals of therapy and different therapies used are depicted in Table 1.

A) Compensated patients without clinically-significant portal hypertension (CSPH)

Patients with an HVPG >5 but lower than 10 mmHg have cirrhosis but do not have CSPH. The goal of therapy in these patients is to prevent the development of CSPH. Since these patients have not yet reached the threshold portal pressure that predicts development of complications (varices, decompensation), therapy has to be directed towards the etiology of cirrhosis and/or to antifibrogenic therapies. On liver histology, patients without CSPH are more likely to have thin fibrous septa than patients with CSPH who characteristically have thicker septa and small nodules [14], therefore it is precisely in these patients that fibrosis will be more susceptible to resorb and in whom cirrhosis may “reverse” to a non-cirrhotic stage [15].

Although, as mentioned previously, clinical findings and non-invasive methods as liver stiffness measurements may be helpful in ruling in CSPH, they are not that helpful in ruling it out. Therefore, and until non-invasive methods are further developed, the only way of confirming the absence of CSPH is by performing HVPG measurements. This is of particular importance in the setting of clinical trials, particularly in those in which reversibility of fibrosis is considered the main outcome. This is applicable to cirrhosis of all etiologies except for cirrhosis due to cholestatic liver diseases, in which HVPG may underestimate the magnitude of the portal pressure elevation.

In addition to elimination/suppression of specific viruses in viral etiologies of cirrhosis, in which a long term benefit has been documented, other therapies may apply to patients with cirrhosis of any etiology, such as life-style modification (diet and exercise that has been shown to decrease HVPG in overweight or obese cirrhotics) and alcohol abstinence, as obesity and superimposed alcohol-induced liver damage can facilitate progression of disease. In fact, in the recent Baveno conference it was recommended that alcohol abstinence should be encouraged in all patients with cirrhosis irrespective of etiology. Statins may have a benefit in cirrhosis of any etiology as they may decrease fibrogenesis, improve liver microcirculation and decrease portal pressure in cirrhosis [16, 17] and may also facilitate hepatitis C viral suppression [18]. Objective evidence for the efficacy and cost-effectiveness of these nonspecific therapies in cirrhosis require further evaluation.

B) Compensated patients with CSPH but without varices

CSPH is defined as HVPG≥10 mmHg. An increase in portal pressure to this level is a hallmark of advanced compensated chronic liver disease, as it heralds the development of

varices [2], decompensation (variceal haemorrhage, ascites and encephalopathy) [3], as well as hepatocellular carcinoma [4] and predicts poor outcomes with liver resection [19]. Per the recent Baveno conference, in patients with viral cirrhosis non-invasive methods are sufficient to rule-in CSPH, specifically a liver stiffness by transient elastography ≥20–25 kPa; alone or in combination with spleen size and platelet count [20].

The objective of treatment in these patients is to prevent the development of varices ("pre-primary prophylaxis" and clinical decompensation. A large multicenter randomized controlled trial showed no differences between placebo and nonselective beta-blockers in the prevention of varices [2]. Therefore, no specific portal pressure-reducing treatment to prevent the formation of varices is recommended in this setting; the main focus at this stage being to prevent decompensation. Again, the mainstay of treatment is to correct the etiologic factor (whenever possible) and associated aggravating conditions (obesity, alcohol intake), and the use of statins and/or drugs that will have an effect on intrahepatic resistance. A large multicenter placebo-controlled study is being conducted in Spain to examine if decreasing HVPG by means of propranolol/carvedilol can prevent decompensation in these patients.

Every patient with a diagnosis of cirrhosis with CSPH, proven by HVPG measurement, or suspected on the basis of non-invasive tests should have an EGD to look for the presence and size of varices. Possibly, screening endoscopy can be avoided in patients with a liver stiffness < 20 kPa and with a platelet count > 150,000, as their risk of having varices requiring treatment is very low [11]. These patients can be followed up by yearly liver stiffness and platelet count; if liver stiffness increases or platelet count declines, these patients should undergo screening EGD [11].

In patients with no varices on screening endoscopy, intervals at which follow-up endoscopy should be repeated depends on whether the patient has ongoing liver injury or if the etiologic factor has been controlled; 2 year intervals were suggested for the former and 3 year intervals for the latter. Future studies, including cost-effectiveness studies, should explore the possibility of discontinuing surveillance after 2 controls showi no varices.

C) Compensated patients with gastroesophageal varices

This clinical setting was previously described as "primary prophylaxis of variceal hemorrhage". Patients in this group have endoscopically-proven gastroesophageal varices and, by definition, have CSPH [21]. As already mentioned, the recent Baveno workshop stated that prevention of decompensation is probably more appropriate as an end-point in this group as well, since bleeding is not the most frequent decompensating event (it is usually ascites) and patients with varices are more likely to decompensate than those without varices [22]. Considering only the bleeding episodes as relevant outcomes ignores the profound impact that developing ascites or encephalopathy *before* bleeding has on the prognosis of cirrhosis [12, 23, 24]. This new approach implies that treatments for this stage should be able to prevent *all* complications of portal hypertension. While this is achievable with treatments directed at lowering portal pressure, specifically non-selective beta-blockers (NSBB)[2526], it is very unlikely for local treatments such as endoscopic variceal ligation (EVL). As we still do not have results of studies specifically designed to assess the impact of

therapy on decompensation, the following recommendations are only pertinent with regards to prevention of first bleeding.

Size of varices, red wale signs on varices and severity of liver disease (Child class C) identify patients at the highest risk of variceal hemorrhage [27]. Therefore, within this stage, patients need to be stratified by the risk of hemorrhage into a) high-risk patients, i.e. those with medium/large varices or those with small varices that have red signs or occur in a Child C patient, and b) low risk patients, i.e. those with small varices without red signs or occurring in a Child A or B patient.

C.1. Patients with medium/large varices—Recommendations from the Baveno conference remained unchanged, that is, in the prevention of first variceal hemorrhage in these patients either NSBB (propranolol, nadolol) or EVL can be used and the choice of treatment should be based on local resources and expertise, patient preference and characteristics, contra-indications and adverse events. Based on two trials that compare EVL to carvedilol (a NSBB with vasodilatory effect due to intrinsic anti-α_1 adrenergic activity) and that show either a greater efficacy of carvedilol [28] or comparable efficacy [29], carvedilol was added to the list of NSBB that can be used in this setting (Table 2).

Advantages of NSBB include low cost, ease of administration and not requiring specific expertise. As they act by decreasing portal pressure, NSBB may also reduce the development of ascites and decompensation [3026]. Also, once a patient is on NSBB there is no need for repeat EGD [5, 11]. Disadvantages are that approximately 15% of patients may have absolute or relative contraindications to therapy and 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 may discourage patients from using these drugs [31]. There have been concerns on the use of NSBBs in patients with refractory ascites but these are not entirely pertinent in this clinical setting (see below). Per Baveno, patients with refractory ascites that are on NSBB for primary prophylaxis should be closely monitored and dose reduction or discontinuation can be considered in those who develop low blood pressure and impairment in renal function. Patients who are intolerant to propranolol or nadolol could be switched to carvedilol (not recommended in those with refractory ascites) or to EVL.

Advantages of EVL are that it can be done at the same time as screening endoscopy and has few contraindications. The risks are those of conscious sedation plus the risk of causing esophageal ulcerations and bleeding. Although the quantity of side-effects is greater with NSBB than with EVL, the severity of side-effects is greater with EVL with several reports of deaths resulting from EVL-induced bleeding ulcers. Importantly, as this is a local therapy it is unlikely to have a role in preventing other decompensating events.

Interestingly, in a recent survey using best-worst scaling, physicians that spent at least half their time performing endoscopy were more likely to choose EVL and were influenced mostly by the ability to visually confirm disappearance of varices while physicians that had a large Hepatology practice were more likely to choose NSBB and were influenced by the side effects and mechanism of action of NSBB [32].

C.2. Patients with high-risk small varices (red wale marks and/or occurring in a Child C patient)—The recommended treatment is NSBBs because technically performing EVL in these varices may be challenging (although there is no clear evidence for this).

C.3. Patients with small varices without signs of increased risk—There is limited evidence showing that their growth may be slowed by the use of NSBB to prevent bleeding [33], but further studies are required to confirm their benefit. Therefore, the use of NSBB in this setting is considered optional and should be discussed with the patient.

Table 2 shows the doses, therapeutic goals and followup procedures for each of the recommended therapies.

D) Patients presenting with acute variceal haemorrhage

In these patients the goal of therapy is to control acute hemorrhage and to prevent its early recurrence (within 5 days) and death. Per the recent Baveno conference, the main treatment outcome in acute variceal hemorrhage should be six-week mortality. Child-Pugh class C, the recalibrated MELD score, and failure to achieve primary hemostasis are the variables most consistently found to predict 6-week mortality [34, 35].

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. The goal of this resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability. Packed red blood cell transfusion should be done conservatively for a target hemoglobin level between 7–8 g/dL because a more liberal transfusion strategy (i.e transfusing for a target hemoglobin of 9–11 g/dL) has been shown in a RCT to be associated with increased mortality and a significant increase in HVPG [36]. However, transfusion in the individual patient should take into account other factors such as age, cardiovascular disorders, ongoing hemorrhage and hemodynamic status. There are no definite recommendations on management of coagulopathy and thrombocytopenia and randomized controlled trials of recombinant factor VIIa have not shown a clear advantage[37, 38]. Patients with gastrointestinal hemorrhage are at a high risk of developing bacterial infections and it has been shown that antibiotic prophylaxis in this setting leads to a decrease, not only in the development of infections, but also of early recurrence of hemorrhage and death [39]. Although studies have recognized that rates of infection and death are low in Child A cirrhotic patients admitted with GI hemorrhage [4041], the Baveno conference considered that, until prospective studies evaluate the efficacy (or lack thereof) of antibiotic prophylaxis in these patients, it should still be instituted in all patients from admission. The specific antibiotic recommended should be based on individual patient risk characteristics and local antimicrobial susceptibility patterns, with ceftriaxone (1 g/24 h) being the first choice in patients with advanced cirrhosis [42], in those on quinolone prophylaxis and in hospital settings with high prevalence of quinolone-resistant bacterial infections.

Safe vasoactive drugs should be started as soon as possible, together with antibiotics, and prior to diagnostic endoscopy. All vasoactive drugs used in the control of acute hemorrhage

are used in intravenous infusion (Table 3) and overall, their use is associated to a significant effect on control of hemorrhage but also a significant reduction in mortality [43]. A recent study comparing the three most utilized worldwide (somatostatin, octreotide, terlipressin) found no significant differences among them [10]. Octreotide is the only vasoactive drug available in the U.S. and in a meta-analysis of 11 trials was shown to significantly improve control of acute hemorrhage [43]. Table 3 shows the doses, therapeutic goals and followup procedures for the three most commonly used vasoactive drugs.

Endoscopy is done as soon as possible and not more than 12 hours after presentation. If a variceal source is confirmed, EVL should be performed.

Once vasoactive drugs have initiated and EVL performed, placement of early (ideally within 24 hours of admission) TIPS should be considered in patients at a high risk of failure on standard therapy (Child C patients with a score 10–13 and Child B with active hemorrhage at time of endoscopy) since it has been shown to reduce mortality [44, 45]. Notably these patients constitute <20% of those admitted for variceal hemorrhage. All others should continue standard therapy with vasoactive drugs continued for up to 5 days 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 hours at which time the patient should be started on secondary prophylaxis. Persistent bleeding or severe rebleeding despite combined pharmacological and endoscopic therapy is best managed by PTFE-covered TIPS. If rebleeding is modest, a second session of endoscopy therapy can be attempted.

Balloon tamponade should only be used in refractory esophageal bleeding, as a temporary “bridge” (for a maximum of 24 h) with intensive care monitoring and considering intubation, until definitive treatment can be instituted. Self-expandable metal stents may be at least as effective and safer than BT in refractory esophageal variceal bleeding. Endoscopic treatment for patients bleeding from isolated gastric varices should be variceal obturation using tissue adhesives as this is better than EVL. Thrombin injection and endoscopic devices such as endoloops have also been used. Balloon occlusion retrograde transvenous obliteration of the varices (BRTO) has not been evaluated in randomized trials and should not be preferred to TIPS. It can be considered in patents with pre-hepatic portal vein occlusion.

E) Patients who have recovered from an episode of acute variceal hemorrhage

This clinical setting was previously described as “secondary prophylaxis of variceal hemorrhage”. However, variceal hemorrhage can occur in the absence of other decompensating events or may occur in patients who are already decompensated or develop other complications during the admission for variceal hemorrhage. These different scenarios have a different prognosis and should be taken into account in the treatment and investigation of patients with variceal hemorrhage [24]. Moreover, therapies used to prevent recurrent variceal hemorrhage may have an impact (negative or positive) on the course of other complications of cirrhosis. Conversely, therapies used to treat other complications of cirrhosis may have an impact (negative or positive) on the course of a patient that has bled

from varices. Recognizing this, it was concluded at the Baveno conference that in patients with a low risk of death (those with variceal hemorrhage as the sole complication) the endpoints should be the development of an additional complication, including variceal rebleeding, while in patients at a high risk of death (those with variceal hemorrhage and other complications), the endpoint should be death.

As these study design strategies have not been explored, the following recommendations are only pertinent with regards to prevention of recurrent variceal hemorrhage. Patients who survive an episode of variceal hemorrhage have a high rebleeding risk (60% in the first year) with a mortality of up to 33 %. Prevention of rebleeding is therefore an essential part of the management of the patient in whom variceal hemorrhage has been controlled.

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 by Doppler ultrasounds every six months. First line therapy for all other patients (the majority) is the combination of NSBB (propranolol or nadolol) + EVL. A recent meta-analysis comparing combination therapy to monotherapy with EVL or drug therapy has demonstrated that, when compared to EVL, combination therapy is significantly more effective in preventing all-source GI hemorrhage. However, when compared to drug therapy (NSBB + nitrates), combination therapy is only marginally more effective than drug therapy alone with a tendency for an increased survival with drugs alone [46]. This suggests that pharmacological therapy is the cornerstone of combination therapy and therefore EVL should not be used as monotherapy and perhaps TIPS should be considered in patients who cannot tolerate NSBB.

Sersté et al have suggested that patients with refractory ascites on propranolol have a higher mortality than those not on propranolol [47]. Although prospective, the study did not perform matching on factors associated with propranolol use or with prognosis and consequently, at baseline, patients on propranolol were sicker (larger number of patients with varices, variceal hemorrhage and Child C, lower serum sodium) and, notably, had a lower mean arterial pressure. A followup crossover study showed that, while on NSBB, a larger percentage of patients developed post-paracentesis circulatory dysfunction (an defined by an increase in plasma renin activity that may reflect further vasodilatation) than while off NSBB [48]. Two subsequent retrospective unmatched studies could not show a deleterious effect of NSBB in patients with refractory ascites [49, 50], although one of them showed a lower blood pressure and a higher rate of hepatorenal syndrome in patients admitted with SBP [49]. Leithead et al performed a propensity score-matched study in a cohort of patients with cirrhosis on the transplant wait list that showed a survival advantage of patients with refractory ascites on NSBB compared to those not on NSBB [51].

It is possible that, in a subset of patients with refractory ascites who may be more vasodilated, NSBB may lead to worsening in the hyperdynamic circulatory state. Therefore, Baveno recommended that, until further evidence is available, NSBB should be used cautiously in patients with refractory ascites and dose reduced/discontinued in face of a systolic blood pressure <90 mmHg, serum sodium <130 mEq/L or development of acute kidney injury.

The combination of NSBB+ISMN has a higher rate of side-effects because of the added ones associated with ISMN, specifically headache and lightheadedness. Although the addition of ISMN to NSBB has a greater portal pressure-reducing effect, in meta-analysis the combination of NSBB and ISMN is no different than NSBB alone regarding rate of overall rebleeding or mortality, but has a higher rate of side-effects [52].

Carvedilol has only been compared to EVL alone [53] or to NSBB+ISMN [54] in the setting of secondary prophylaxis of variceal hemorrhage but has not been compared to standard of care with the combination of NSBB + EVL. Therefore, Baveno VI could not recommend its use in the setting of prevention of rebleeding. As for nitrates, carvedilol may decrease in mean arterial pressure [55] and should not be used in patients with refractory ascites (even in the setting of primary prophylaxis) particularly since its use had an intermediate survival between those on NSBB (best survival) and those not on NSBB (worst survival) in the Leithead et al study {Leithead, 2015 3370/id.

PTFE-covered TIPS is the treatment of choice in patients that fail first line therapy (NSBB + EVL). Surgical shunts have been largely substituted by TIPS but have a role in centers where TIPS is unavailable.

Table 4 shows the doses, therapeutic goals and followup procedures for each of the first line recommended therapies

CONCLUSIONS

Marked advances in the knowledge of portal hypertension over the last decades have resulted in the introduction of new effective treatments that have led to a significant improvement in the prognosis of portal hypertension. In parallel, major advances in the development of prognostic markers have allowed for risk stratification and re-definition of endpoints.. We now recognize that management of patients at different prognostic stages is different, resulting in a more personalized approach to therapy and a better definition of the clinical end-points of treatment in each stage. These new concepts will require confirmation through specifically designed clinical trials.

General therapy includes treating the cause of cirrhosis, lifestyle modification and avoiding alcohol. New agents such as statins may further improve the results of treatment. Specific long-term treatment is based on the use of NSBB, including carvedilol, and EVL. During acute variceal hemorrhage, prophylactic antibiotics, IV vasoactive drugs and EVL are mainstay of treatment. Pre-emptive TIPS is recommended for high risk patients, and rescue TIPS for treatment failures. Gastric varices are better treated with endoscopic variceal obturation with tissue adhesives. After control of hemorrhage, prevention of recurrent hemorrhage is based on the use of NSBBs plus EVL.

It is expected that future trials and Baveno and AASLD conferences will continue to advance the field. Among others, development of noninvasive tools to monitor HVPG and its response to therapy, as well as the relevance of HVPG-guided therapy will be part of a research agenda.

Acknowledgments

Grant Support: GGT: NIH P-30DK 034989; JB: The CIBERehd is funded by the Instituto de Salud Carlos III. Supported in part by a grant from the Instituto de Salud Carlos III (PI13/00341) in a program co-funded by FEDER, EU.

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Table 1

Stages of portal hypertension in advanced chronic liver disease, goals of therapy, and type of treatment

Stage	HVPG	Varices	Clinical complications of portal hypertension	Goal of therapy	Type of Treatment
Compensated	<10 mmHg	Absent	Absent	Prevent CSPH	E, A
	≥10 mmHg	Absent	Absent	Prevent varices and first decompensation	E, A/Statins? NSBB?
		Present	Absent	Prevent decompensation (1st bleeding episode)	NSBB, Carvedilol, EVL E/A/Statins?
Decompensated *	≥ 12 mmHg	Absent or Present	**Acute Bleeding**	Control bleeding, prevent early rebleeding and death (6-wk)	Transfusion, Antibiotics + Vasoactive drugs ** + EVL, TIPS (tamponade/stents)
			Yes (only bleeding)	Prevent further decompensation (further bleeding)	E/A NSBB + EVL + Statins? (TIPS)
			Yes (bleeding and any other)	Prevent further decompensation and death/OLT	E/A NSBB + EVL + Statins? (TIPS/OLT)

HVPG=hepatic venous pressure gradient; E=etiologic treatment, includes antiviral therapy (HVB, HCV), alcohol abstinence, venesection, inmunosuppression, UDCA and other treatments depending on the etiology; A=antifibrotic drugs; NSBB=non-selective beta-blockers (propranolol, nadolol); EVL=endoscopic variceal ligation; TIPS=transjugular intrahepatic portosystemic shunt; OLT=orthotopic liver transplant

*Patients with decompensated cirrhosis without variceal haemorrhage (past or present) are not considered in this table/review

**Includes terlipressin, somatostatin, octreotide

Table 2

Management of patients with moderate/large varices that have not bled. Only one of the four therapies shown in the table are recommended.

Therapy	Dose	Therapy goals	Maintenance/Followup
Propranolol *	• 20 mg orally twice a day • Adjust every 2–3 days until treatment goal is achieved * • Maximal daily dose should not exceed 320 mg	• Maximum tolerated dose • Aim for resting heart rate of 50–55 beats per minute	• At every outpatient visit make sure that patient is appropriately beta-blocked • Continue indefinitely. • No need for follow-up EGD
Nadolol *	• 40 mg orally once a day • Adjust every 2–3 days until treatment goal is achieved * • Maximal daily dose should not exceed 160 mg	As for propranolol	As for propranolol
Carvedilol	• Start with 6.25 mg once a day • After 3 days increase to 12.5 mg • Maximal dose should not exceed 12.5 mg/day (except in patients with arterial hypertension)	Systolic arterial blood pressure should not decrease < 90 mmHg	
EVL **	• Every 2– 4 weeks until the obliteration of varices	Obliteration varices Eradication of new varices following initial obliteration	First EGD performed 1 – 3 months after obliteration and every 6 – 12 months thereafter.

* Dose titration is feasible in 1–2 weeks in settings where a medical assistant is available to check the patient's heart rate. In the case of carvedilol, the dose is fixed at a maximum of 12.5 mg/day so no titration is necessary.

** EVL is unlikely to prevent other complications of portal hypertension.

Table 3

Most commonly used vasoactive agents used in the management of acute hemorrhage.

Drug	Standard Dosing	Duration	Mechanism of action
Somatostatin	• Initial IV bolus 250 mcg (can be repeated in the first hour if ongoing bleeding) • Continuous IV infusion of 250 to 500 mcg/hr	Up to 5 days	Inhibits vasodilator hormones like glucagon causing splanchnic vasoconstriction and reduces portal blood flow. Facilitates adrenergic vasoconstriction.
Octreotide (somatostatin analogue)	Initial IV bolus of 50 mcg (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50 mcg/hr	Up to 5 days	Same as somatostatin, longer duration of action
Terlipressin (Vasopressin analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding. Maintenance: 1 mg IV every 4 hours to prevent re-bleeding	Up to 5 days	Splanchnic vasoconstriction. The active metabolite lysine-vasopressin is gradually released over several hours in tissue thus decreasing typical systemic vasopressin side effects.

Table 4

Management of patients who have bled from varices and in whom the goal is to prevent recurrence of hemorrhage. Combination of one non-selective beta-blocker (propranolol or nadolol) plus EVL is recommended.

Therapy	Starting dose	Therapy goals	Maintenance/Followup
Propranolol	• 20 mg orally twice a day • Adjust every 2–3 days until treatment goal is achieved • Maximal daily dose should not exceed 320 mg	• Maximum tolerated dose • Aim for resting heart rate of 50–55 beats per minute	• At every outpatient visit make sure that patient is appropriately beta-blocked • Continue indefinitely. • In patients with refractory ascites reduce dose or discontinue if SBP<90 mmHg, serum sodium <130 or with acute kidney injury
Nadolol	• 40 mg orally once a day • Adjust every 2–3 days until treatment goal is achieved • Maximal daily dose should not exceed 160 mg		
Endoscopic variceal ligation (EVL)	Every 2–4 weeks until the obliteration of varices	Obliteration varices Eradication of new varices following initial obliteration	First EGD performed 1 – 3 months after obliteration and every 6 – 12 months thereafter.