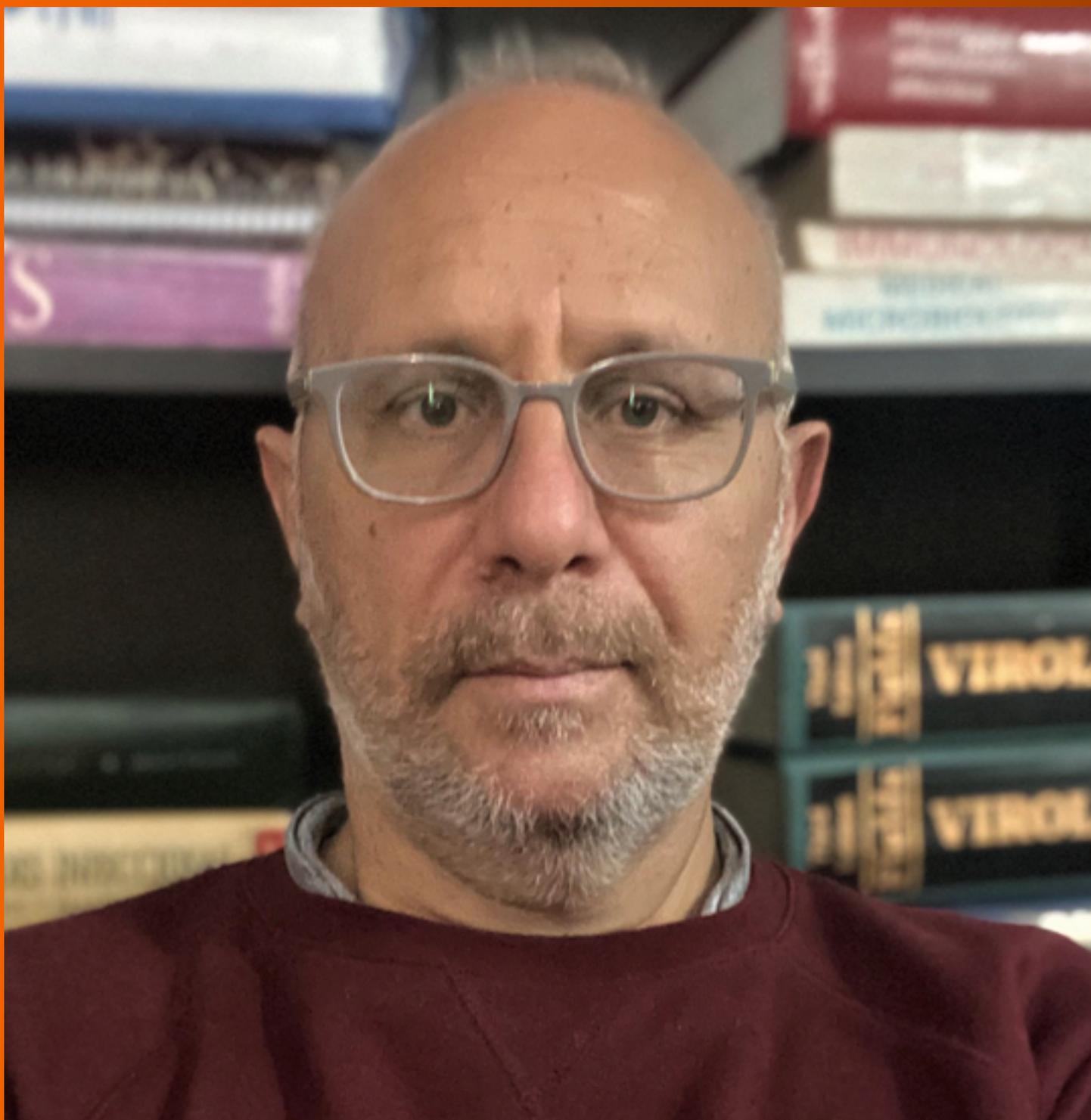


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## Clinical algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis

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### Abstract

Portal hypertension (PH), a common complication of liver cirrhosis, results in development of esophageal varices. When esophageal varices rupture, they cause significant upper gastrointestinal bleeding with mortality rates up to 20% despite state-of-the-art treatment. Thus, prophylactic measures are of utmost importance to improve outcomes of patients with PH. Several high-quality studies have demonstrated that non-selective beta blockers (NSBBs) or endoscopic band ligation (EBL) are effective for primary prophylaxis of variceal bleeding. In secondary prophylaxis, a combination of NSBB + EBL should be routinely used. Once esophageal varices develop and variceal bleeding occurs, standardized treatment algorithms should be followed to minimize bleeding-associated mortality. Special attention should be paid to avoidance of overtransfusion, early initiation of vasoconstrictive therapy, prophylactic antibiotics and early endoscopic therapy. Pre-emptive transjugular intrahepatic portosystemic shunt should be used in all Child C10-C13 patients experiencing variceal bleeding, and potentially in Child B patients with active bleeding at endoscopy. The use of

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carvedilol, safety of NSBBs in advanced cirrhosis (*i.e.* with refractory ascites) and assessment of hepatic venous pressure gradient response to NSBB is discussed. In the present review, we give an overview on the rationale behind the latest guidelines and summarize key papers that have led to significant advances in the field.

**Key Words:** Portal hypertension; Endoscopy; Non-selective betablockers; Transjugular intrahepatic portosystemic shunt

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**Core Tip:** Variceal bleeding is a severe, and often deadly, complication of portal hypertension. Screening for varices, effective bleeding prophylaxis and standardized management of bleeding is critical to improve clinical outcomes. While carvedilol seems to be the treatment of choice for primary prophylaxis in compensated cirrhosis, the use of hepatic venous pressure gradient measurements and safety of non-selective betablockers in advanced cirrhosis with refractory ascites is controversial. The pre-emptive use of transjugular intrahepatic portosystemic shunt within 72 h after variceal bleeding prevents rebleeding and mortality in Child C10-C13 patients.

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## INTRODUCTION

Chronic liver diseases cause recurrent liver damage and can result in the development of liver fibrosis and, ultimately, liver cirrhosis[1]. Fibrosis and cirrhosis lead to gradually increased intrahepatic vascular resistance, splanchnic vasodilatation and increased portal blood flow, which subsequently results in increased portal pressure and the development of collaterals[2]. To allow risk stratification, evidence-based guidelines have been developed to grade portal hypertension severity, and the term clinically significant portal hypertension (CSPH) has been defined to indicate a high risk of complications[3]. CSPH is defined as a hepatic venous pressure gradient (HVPG), an invasive surrogate parameter of portal venous pressure, of  $\geq 10$  mmHg[4]. This definition is based on studies demonstrating that esophageal varices (EV) develop above the 10 mmHg HVPG threshold, subsequently increasing the risk of bleeding[5]. In cross sectional studies, between 40%-60% of patients with liver cirrhosis show EV, highlighting the clinical importance of this condition[6,7]. Variceal bleeding is, next to liver failure, hepatocellular carcinoma, infections and the hepatorenal syndrome, one of the main causes of mortality in patients with CSPH and adequate diagnosis as well as treatment is of utmost importance, given that variceal bleeding episodes are still associated with a high mortality rate of up to 20% [8-12]. Thus, to avoid unnecessary fatal outcomes, variceal bleeding and re-bleeding must be prevented, ideally by (primary or secondary) prophylactic treatment of portal hypertension *per se*. Therefore, this review focusses on clinical algorithms and summarizes the available evidence on prevention and treatment of variceal bleeding.

## PREVENTION OF ESOPHAGEAL VARICEAL BLEEDING

### Screening for gastroesophageal varices in patients with portal hypertension

In patients with cirrhosis but without EVs at baseline, the incidence of developing EV rises from 5% after one year to 28% after three years, independently of liver function or compensated/decompensated liver cirrhosis[13]. In a cross-sectional study of 494 patients of which 48% had decompensated liver cirrhosis, 38% of patients had EV at the time of screening[14]. Thus, EV are common in patients with advanced chronic

liver disease, and it was shown that patients with EV suffer from significantly higher mortality rates and decompensating events than patients without[14]. Of note, however, bleeding risk is correlated with HVPG values, and patients with a HVPG of  $\geq 12$  mmHg are at significantly higher bleeding risk than patients with  $< 12$  mmHg, despite the diagnostic CSPH cutoff value of 10 mmHg[15,16]. Although HVPG is considered the gold standard, measurement requires specific expertise and equipment, comes at relatively high cost and is invasive. Thus, it is not considered as standard of care and not available to most centers[17]. As an alternative, transient elastography (TE) has been established as a well-validated cheap, non-invasive tool to measure liver stiffness, as fibrosis/cirrhosis severity and portal pressure directly correlate[18,19]. TE allows to classify patients with liver cirrhosis, defined as a liver stiffness measurement value  $> 15$  kPa and can be used as screening tool[3,20]. Efforts to establish clear cutoff values have been made[21], and evidence indicates that patients with TE values  $< 20$  kPa and platelet count  $> 150$  G/L are unlikely to have varices ( $< 5\%$ )[22]. These values can be used to avoid screening gastroscopies for EV, and the next TE screening for EV can be postponed for another year[22]. Screening gastroscopy is, however, required in patients with diagnosed liver cirrhosis who do not meet these mentioned criteria[3,17,22] and allows to identify “high risk” varices, which are referred to as “varices needing treatment” (VNT) in recent guidelines[22]. VNT are varices of large size ( $> 5$  mm diameter) or small varices ( $< 5$  mm diameter) with red spot signs/red wale markings, as both of them are at high risk of bleeding[22]. When VNT are detected, treatment with non-selective betablockers (NSBB) or endoscopic band ligation (EBL) should be initiated for primary prophylaxis of variceal bleeding[3,17,22].

While evidence is clear on these VNTs, current guidelines are less validated whether endoscopic screening is indicated for small varices[23]. Augustin *et al*[24] found that following the current Baveno VI criteria spared more screening endoscopies with a minimal risk of missing VNT, but when guidelines are followed strictly, small varices would be missed in a significant number of patients. Thus, treatment decisions in these cases should be made on a case-to-case basis until further evidence is available.

### **Preprimary and primary prophylaxis for patients with small esophageal varices**

When patients with high risk EV are identified, treatment should aim to prevent variceal bleeding as primary prophylaxis. Current guidelines recommend either NSBB or EBL for prevention of first EV bleeding in patients with medium to large varices, while they do not specifically recommend treatment for small varices due to above mentioned lack of decisive studies[3,17].

While available evidence uniformly demonstrated that NSBB therapy effectively prevents first, as well as recurrent, EV bleeding and reduces mortality when EV are diagnosed[25,26], it is under debate whether NSBB should be prescribed without signs of EV. One large randomized multicenter study assigned patients with CSPH without EV to timolol or placebo and found that although HVPG was lower in timolol-treated patients, the subsequent development of EV or variceal bleeding rate did not differ between timolol or placebo treated patients[27]. Although the HVPG-response to NSBB differs in patients with or without CSPH, the results were relatively unexpected [27].

Little high-quality evidence is available regarding treatment of patients with small and low risk varices in primary prophylaxis[22,28]. It seems as if some trials were underpowered to see sufficient effects of NSBB on the incidence of first variceal bleeding in patients with small varices[23] while others demonstrated that NSBB effectively prevented the progression from small to large varices, especially in patients assigned to carvedilol[29,30]. The recently published PREDESCI trial showed that NSBB were associated with a decreased risk of decompensation [hazard ratio: 0.51 (95%CI: 0.26-0.97),  $P = 0.041$ ] in patients with CSPH and low risk varices, potentially resulting in longer decompensation-free survival[31]. Taken together, the conflicting evidence led the authors of the current international guidelines to not recommend NSBB treatment for patients with no EV or for prevention of varix progression. However, some experts still recommend using NSBB in patients with cirrhosis as soon as CSPH is evident (*e.g.* by HVPG  $\geq 10$  mmHg or by any size of varices) to prevent clinical decompensation.

### **Beta blocker therapy for primary prophylaxis in patients with medium and large esophageal varices**

Prescribing NSBB for primary prophylaxis is less expensive, has no procedural risk, does not require repetition of esophageal gastroscopy after initiation of NSBB for prevention of variceal bleeding and saves time for gastroenterologists[3,17]. Therefore,

NSBB are sometimes favorable compared to EBL, with dosing intensities summarized in [Table 1](#). Beside the positive effect of NSBB on variceal bleeding (absolute risk reduction of up to -16%, NNT = 6), several studies have also demonstrated benefits that are likely mediated by their additional non-hemodynamic effects[32-35]. With regards to beta blocker selection, some trials showed a better or comparable efficacy in primary prophylaxis of carvedilol in comparison to other NSBBs, probably as carvedilol has additional anti- $\alpha$ -1-adrenergic activity and does therefore result in a more potent decrease of portal pressure[36-38]. Thus, carvedilol is recommended as first line therapy in some national guidelines[3,39-41]. However, carvedilol for the sole indication of portal hypertension should not be prescribed in doses above 12.5 mg per day, as higher doses (> 12.5 mg/d) do not lead to further reductions of portal pressure [36,37]. Importantly, carvedilol may be prescribed when NSBB have already failed, as our group could show that in 58% of patients who did not respond to propranolol, carvedilol still resulted in a significant HVPG response (defined as reduction of HVPG of more than 20% or reduction to a HVPG value < 12 mmHg)[36].

Despite the easy handling of NSBB or carvedilol, up to 15% of patients require a dose reduction or discontinuation due to common and severe side effects such as hypotension, shortness of breath and/or fatigue[42], and 15% to 25% of patients have absolute or relative contraindications for NSBB initiation[35,42]. In addition, there is a great abundance of studies comparing NSBB to EBL in primary prophylaxis, and there is no clear outcome benefit for one or the other. In a Cochrane analysis from 2012, patients who underwent EBL as primary prophylaxis showed reduced variceal bleeding rates compared to patients using NSBB alone, while bleeding did not impact on mortality[43]. Another meta-analysis demonstrated that there was no difference in bleeding rates when high-quality studies were assessed[44]. In contrast to these meta-analyses, one large multicenter study showed better efficacy of carvedilol for primary prophylaxis compared to EBL alone[41], and another meta-analysis of 32 randomized controlled trials and a total number of 3362 patients with large varices in primary prophylaxis found that NSBB monotherapy was associated with a decrease of all-cause mortality, decrease risk of first variceal bleeding and a better safety profile compare to patients treated with EBL[45]. Overall, bleeding rates in primary prophylaxis greatly vary between studies and no reproducible differences between the overall effectiveness, especially the overall- or bleeding-related mortality, could be established so far[46-49]. To address certain limitations of previous studies, another large randomized controlled open-label multicenter study, CALIBRE, is currently recruiting patients with liver cirrhosis and medium to large EV, and will investigate the effect of carvedilol or EBL on the incidence of variceal bleeding within 1 year of treatment initiation[50], potentially impacting on treatment regimes in the future.

### ***NSBB in patients with complicated ascites and/or spontaneous bacterial peritonitis***

Due to vasodilating effects, sympathetic activation, increased left ventricle systolic function and, therefore, impairment of renal perfusion, several studies questioned the safety of NSBB and carvedilol in patients with decompensated cirrhosis[51-59]. This is in line with evidence that NSBBs were associated with higher mortality in patients with refractory ascites[51,60,61]. However, these findings were not uniformly confirmed and some studies report no impact on outcome[62-64]. As a result of this conflicting evidence, current guidelines suggest to monitor blood pressure, serum sodium levels and kidney function in patients with decompensated cirrhosis[3,17,22], but do not state that NSBB are contraindicated[17,22]. Nevertheless, high doses of NSBB (*e.g.* propranolol > 160 mg/day) should be avoided as they seem to be associated with worse outcome[65]. In addition, there is limited evidence supporting a switching strategy from carvedilol to propranolol in patients with ascites and/or renal impairment[56]. Thus, carvedilol should not be used in patient with severe ascites[3].

Similar conflicting results were reported for NSBB use in patients with spontaneous bacterial peritonitis (SBP) and/or acute kidney injury[56]. In one retrospective study, NSBB use was associated with a higher risk for the development of a hepatorenal syndrome in patients with newly diagnosed SBP, resulting in impaired survival[59]. However, a more recent study suggests that NSBB maintenance during an SBP-episode is not associated with increased mortality as long as there is no severe arterial hypotension, highlighting the importance of the guideline's recommendations to monitor blood pressure[66].

### ***EBL for patients in primary prophylaxis with medium or large esophageal varices***

EBL has a very low procedural risk and is the most effective endoscopic choice for EV [3,17,22,67,68]. When EBL is chosen for primary prophylaxis, it should be repeated every two to four weeks until varices are completely eradicated (small "remnant"

**Table 1 Recommended use of non-selective betablockers in patients with primary and secondary prophylaxis [adapted from the Austrian (Billroth III), European (Baveno VI) and American (Guidance by the AASLD 2017) guidelines][3,17,22]**

Beta blocker	Initial dose	Goal	Treatment duration	Further guidance
Propranolol	20–40 mg twice daily	Maximum dosage of 160 mg/day; Or until the resting heart rate of 55–60 beats/min; Maximum dosage of 80 mg/day in patients with ascites	Indefinite	Adapt every 2–3 d until optimal dose is reached; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125 mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed
Carvedilol	6.25 mg once daily	Maximum dosage of 12.5 mg/day	Indefinite	Adapt dose after 3 d and increase to 6.25 mg twice daily; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed; Potential switch from carvedilol to propranolol in case of new onset of ascites
Nadolol	20–40 mg once daily	Maximum dosage of 160 mg/day; Or until the resting heart rate of 55–60 beats/min; Maximum dosage of 80 mg/day in patients with ascites	Indefinite	Adapt every 2–3 d until optimal dose is reached; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed

EGD: Esophagogastroduodenoscopy

varices can be tolerated) and endoscopy should subsequently be repeated after six and twelve months[3]. If EV reappear, the treatment algorithm has to be restarted in the same intervals[3]. Compared to NSBB, EBL for primary prophylaxis has a lower overall rate of adverse events, but if adverse events occur they are more severe and life-threatening (e.g. EBL-related ulcer bleeding)[47,49,69]. Procedure related bleeding as a potential complication after EBL has been described to occur in 2%-6% of interventions[68,70-72]. In addition to potential esophageal injuries, EBL induces/accelerates the development of gastric collaterals[73] as it does not affect the underlying cause of increased portal pressure and thus has no disease-modifying effects. In summary, however, both treatments, namely NSBB or EBL, are effective and physicians should choose individually which primary prophylaxis is used, based on patients' concomitant risk factors and local availability. As a brief overview, we have summarized the recommended clinical algorithms in [Figure 1](#).

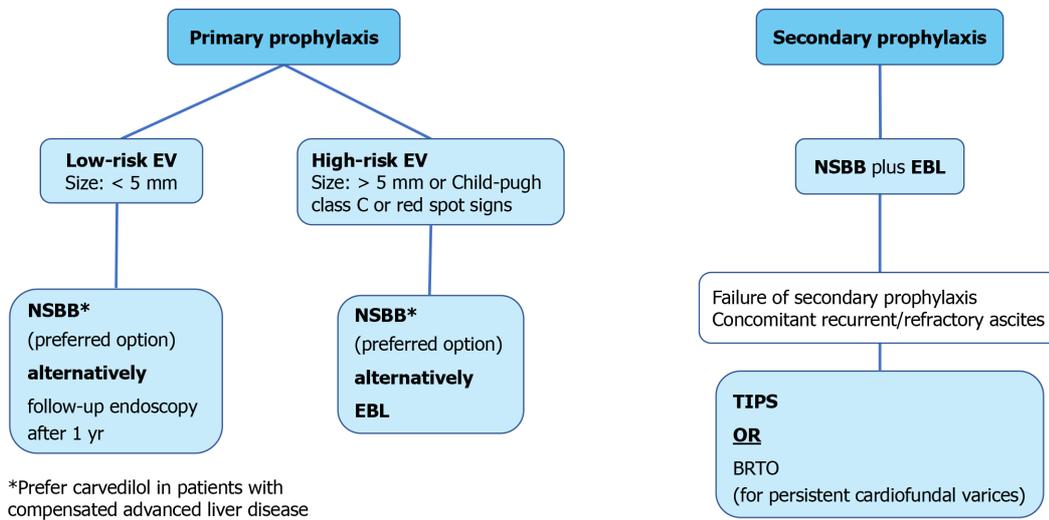
## ACUTE ESOPHAGEAL VARICEAL BLEEDING

### Management of acute variceal bleeding

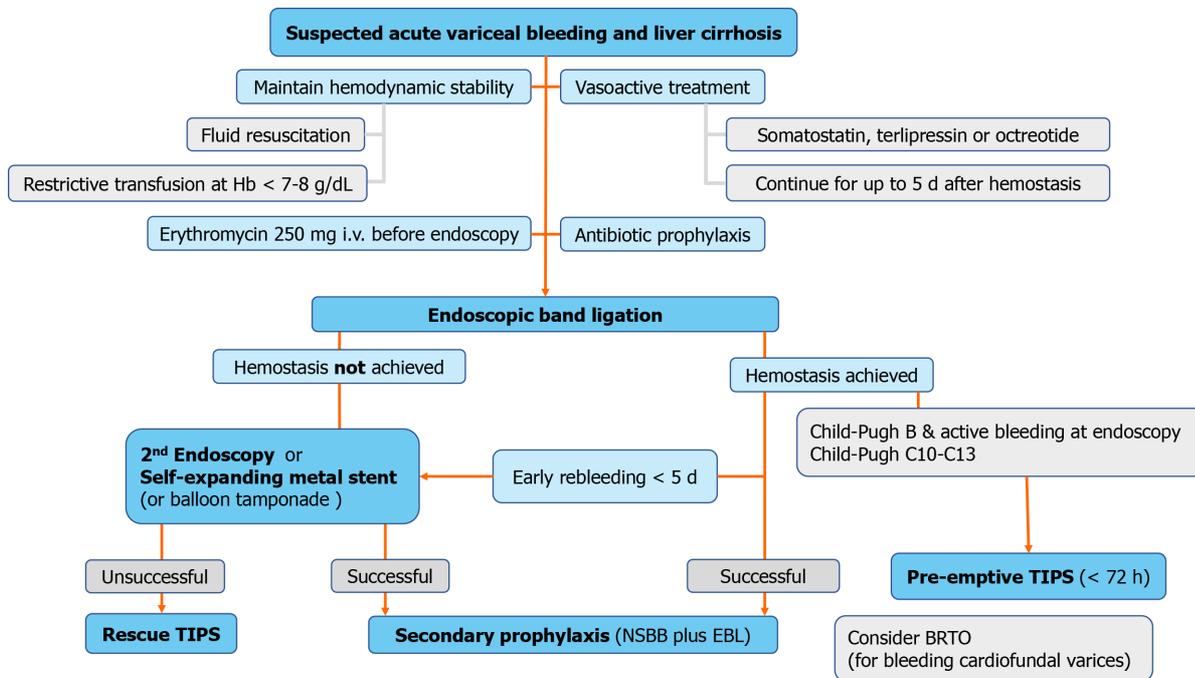
When EV are not detected in time, or if primary prophylaxis fails and acute variceal bleeding cannot be prevented, a determined and rapid treatment initiation as well as intensive care are required to optimize outcome. Despite improved mortality rates in the past decades, bleeding-related mortality remains as high as 15%-20% [9,10,12,74]. Patients presenting with acute variceal bleeding are classified as "decompensated cirrhosis", irrespective of fibrosis severity[5,17]. Despite this classification, 5 year mortality rates are affected by the underlying fibrosis severity as complications such as ascites and/or hepatic encephalopathy also impact on overall survival[14]. Fluid resuscitation, pharmacological treatment and endoscopy/EBL are the three main pillars for acute variceal bleeding treatment (see [Figure 2](#))[3,17,22].

Initial fluid resuscitation to counteract hemorrhagic shock is the first important step in patients with acute variceal bleeding, and packed red blood cell (PRBC) transfusions are indicated when hemoglobin levels are below 7 to 8 g/dL, as too liberal administration of PRBCs has been shown to impair outcome[3,75]. In the randomized controlled study by Villanueva *et al*[75], patients with "liberal" use of PRBC transfusion showed significantly increased mortality rates compared to patients in which PRBCs were only transfused at a threshold of 7 g/dL, maintaining hemoglobin levels of 7-9 g/dL. Thus, the threshold of 7 g/dL is still recommended by current guidelines [3,17,22].

In contrast to PRBCs, transfusion of platelets, the use of fresh frozen plasma or administration of recombinant factor VIIa to correct platelet count or international normalized ratio (INR), respectively, did not demonstrate a clear benefit and is therefore not recommended[3,17,22,76,77].



**Figure 1 Clinical algorithms recommended for cirrhotic patients in primary prophylaxis and secondary prophylaxis (adapted from the Austrian Billroth-III guidelines)[3].** EV: Esophageal varices; NSBB: Non-selective betablocker; EBL: Endoscopic band ligation; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon occluded retrograde transvenous variceal obliteration.



**Figure 2 Clinical algorithm for treatment of patients with acute variceal bleeding (adapted from the Austrian Billroth-III guidelines)[3].** TIPS: Transjugular portosystemic shunt; i.v: Intravenous; NSBB: Non selective betablocker; EBL: Endoscopic band ligation; BRTO: Balloon occluded retrograde transvenous variceal obliteration.

To counteract active bleeding, vasoactive drugs (vasopressin, terlipressin, somatostatin or octreotide, dosing regimens summarized in Table 2) have been shown to reduce portal pressure by reducing portal systemic collateral blood flow, portal blood flow and intravariceal pressure *via* systemic and splanchnic vasoconstriction[17, 78,79]. Thus, they are recommended for use in patients with acute variceal bleeding, while none of the vasoactive treatments has been shown to be superior to the others in terms of bleeding control and impact on mortality[3,17,22,80,81]. Of note, however, terlipressin has been associated with hyponatremia, especially in patients with preserved liver function and sodium levels should therefore be monitored, although these systemic sodium alterations did not translate to any outcome difference[80].

In addition to fluid resuscitation and administration of vasoactive drugs, antibiotic treatment is indicated as patients with acute variceal bleeding suffer from a significant risk of infection[82]. Thus, intravenous broad spectrum antibiotics (*e.g.* ceftriaxone at a

**Table 2 Recommended vasoactive agents for management of acute variceal bleeding [adapted from the Austrian (Bilroth III), European (Baveno VI) and American (Guidance by the AASLD 2017) guidelines][3,17,22]**

Regimen	Dosing	Duration of regimen	Further guidance
Somatostatin	Bolus of 500 µg, followed by 500 µg/h <i>via</i> continuous infusion (6 mg/50 mL, infusion rate of 4.2 mL/h)	2-5 d	Bolus can be repeated in case of uncontrolled bleeding
Terlipressin	Bolus of 2mg every 4 h for the first 24-48 h, followed by giving bolus of 1mg every 4 h; Or continuous infusion 2 mg/d; maximum 12 mg/d	2-5 d	Be caution in patients with coronary artery disease, peripheral arterial occlusive disease hyponatremia (< 125 mmol/L), cardiac arrhythmia and severe asthma or chronic occlusive pulmonary disease
Octreotide (somatostatin analogue)	Bolus of 50 µg, followed by 50 µg <i>via</i> continuous infusion	2-5 d	Bolus can be repeated in case of uncontrolled bleeding

dose of 1g every 24 h with a duration for 7 d or less) should be administered before endoscopic therapy is initiated[3,17,22]. In addition, erythromycin should be administered ideally 30-120 min before endoscopy to improve sight during the procedure *via* facilitation of gastric emptying[3,17,22,83].

Finally, EBL is the gold standard of endoscopic treatment after hemodynamic stabilization and should ideally be performed within the first six to twelve hours of admission when EV bleeding is suspected or detected[3,17,22,84,85]. Performing endoscopists should be adequately trained, and EBL has been proven to be the best available treatment in terms of rebleeding, further development of esophageal strictures, and associated mortality[86].

Recently, however, data suggests that instead of vasoactive drugs and endoscopic therapy, preemptive implantation of a transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressure can be effective. An international multicenter observational study compared pre-emptive TIPS to endoscopy plus vasoactive drugs in patients with Child-Pugh C or Child Pugh B cirrhosis with active bleeding at the time of endoscopy[87]. The authors found that pre-emptive TIPS implantation, compared to standard of care with medication and endoscopic treatment, significantly reduced treatment failure and rebleeding in Child-Pugh C, and Child-Pugh B patients with active bleeding. This translated into a significantly lower mortality rate in Child-Pugh C patients, while mortality in Child-Pugh B patients with active bleeding were low in both, EBL/medication and TIPS, groups and did not improve by pre-emptive TIPS implantation[87]. Thus, pre-emptive TIPS implantation emerges as a valid option in patients with high risk of rebleeding, especially in Child-Pugh C patients.

### Therapy-refractory variceal bleeding

These favorable results are in line with findings in patients with therapy refractory acute variceal bleeding in which rescue-TIPS implantation is the best choice when standard treatment fails[3,17,22]. Rescue-TIPS, *e.g.* TIPS implantation after EBL failure to control bleeding, achieves bleeding control in 90%-100% and results in very low rebleeding rates of approximately 15% [88]. However, despite the available encouraging results, use of TIPS in acute settings is limited by technical challenges and availability[89,90]. Therefore, balloon tamponade (Sengstaken tube and Linton-Nachlas tube) is the most commonly used treatment for uncontrolled bleeding in real-world settings. By compressing bleeding varices, it controls EV bleeding in up to 90%, but half of the patients suffer from rebleeding events after deflation of balloon tamponade[91-95]. Furthermore, it is associated with often life-threatening complications in 60% of patients, such as perforation, esophageal ulceration and aspiration pneumonia[91-94,96,97]. Additionally, balloon tamponade can only be left *in situ* for 24-48 h due to the high risk of pressure-induced necrosis[98].

As these high complication rates are considered unacceptable in modern medicine, a self-expanding metal stent (SEMS), SX-ELLA Stent Danis, has been developed to improve procedure related complication rates. It can easily be deployed without endoscopic guidance and can be left *in situ* for up to seven days. Several studies showed successful bleeding control in 70%-100% of patients[99-101] with lower complication rates than balloon tamponade, although this did not improve mortality rates[102,103]. Current guidelines nevertheless recommend the use of SEMS because of its better safety profile[3,17,22].

On the basis of these poor outcome data, balloon tamponade and SEMS are usually only used as a bridging to further definitive therapy, such as TIPS implantation. Despite this large body of favorable evidence, however, we recently reported a lack of systematic use of TIPS implantation after SEMS in acute variceal bleeding[101]. This is in line with recently published real-life data from France which showed that approximately 1/3 of patients with variceal bleeding fulfilled the criteria for early TIPS, but only 7% underwent subsequent early TIPS implantation[90]. This knowledge gap on TIPS indication criteria was also evident in our recently published survey in which only 20% of the respondents could report TIPS criteria correctly[104]. Therefore, knowledge on early TIPS implantation must be improved among all specialists.

Furthermore, in case of additional cardiofundal variceal bleeding and/or ongoing variceal bleeding after TIPS implantation, balloon occluded retrograde transvenous variceal obliteration (BRTO) should be considered[3,105-107]. A recently published meta-analysis showed improved outcome in terms of rebleeding, mortality and hepatic encephalopathy in patients who also underwent BRTO as compared to patients who only underwent TIPS implantation[106].

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## PREVENTION OF ESOPHAGEAL VARICEAL REBLEEDING

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### **Secondary prophylaxis of EV bleeding**

Secondary prophylaxis is defined as the prevention of recurrent variceal bleeding. Patients who survive and recover from an episode of acute variceal bleeding are at high risk of rebleeding and death, which is 60% and 33% in the first year, respectively [17,108]. Older studies found that HVPG measurement at the time of the first bleeding episode can predict rebleeding risk, and a HVPG of  $\geq 20$  mmHg was associated with a significantly increased risk for rebleeding and death[109]. Despite several non-invasive scores (APRI, FIB-4, AST/ALT, King's score) are available, their role as non-invasive predictors for the presence of esophageal varices in patients with cirrhosis is not established. Kraja *et al*[110] showed that the FIB-4 is a powerful predictor of EV (cut off value: 3.23; AUC: 0.66, 95%CI: 0.54-0.78) but a poor predictor for EV bleeding (AUC: 0.42, 95%CI: 0.28-0.56) and that all other non-invasive biomarkers were not useful. This is in line with several other available studies that showed great variation in accuracy in different populations and etiologies of liver cirrhosis[111-113]. Recently, Drolz *et al*[68] reported high bilirubin and larger size varices as risk factors for rebleeding within 30 d of prophylactic EBL, while reduced platelet counts, elevated INR, and decreased fibrinogen levels were associated with procedure-related bleeding in other studies [113-115]. Another study showed an adequate prediction value for predicting in-hospital rebleeding using Child-Turcotte-Pugh score (cut off  $> 7$ ) and Clinical Rockall score (cut off  $> 2$ )[116], while the well-established MELD and MELD-Na scores showed good results for predicting in-hospital mortality[116]. Thus, non-invasive prognostic scoring systems cannot be recommended to predict risk for recurrent variceal bleeding but are useful tools to estimate overall mortality rates[116-118].

In terms of secondary prophylaxis to avoid rebleeding, monotherapy of NSBB or EBL are associated with higher mortality in secondary prophylaxis than combined NSBB + EBL therapy, which is in contrast to studies in the primary prophylaxis setting [35]. Thus, current guidelines recommend the combination of EBL + NSBBs[3,17,22, 119,120], while the combined treatment of NSBB and low-dose isosorbide mononitrate, a combination used in the past, is no longer recommended due to high rates of adverse events[3,17,22].

With regard to NSBB choice, propranolol is recommended at a daily dosage of 80-160 mg/day in most guidelines, with a maximum dosing of 80 mg/day in patients with ascites[3]. Similar to primary prophylaxis, some guidelines also recommend carvedilol, while others do not (yet) recommend its general use[17,22]. Guidelines that do recommend carvedilol suggest to use it at a concentration of 6.25-12.5 mg/day and only in patients without ascites[3]. Finally, with regards to EBL for secondary prophylaxis, endoscopy and banding intervals are equal to the intervals in primary prophylaxis (complete eradication, re-endoscopy after 6 and 12 mo).

Similarly, when first-line therapy with EBL + NSBB to prevent rebleeding fails, TIPS implantation is the best choice for further treatment[3,17,22], as it decreases portal pressure and therefore targets the underlying cause of EV bleeding. Of note, however, no significant benefit on survival rates was found despite the better outcomes in terms of rebleeding rates[15,126,122]. In patients with gastric varices and contraindications for TIPS implantation such as spontaneous episodes of hepatic encephalopathy, BRTO can be considered as treatment option in selected patients, as it may even decrease

portosystemic shunting through the collaterals that are scheduled for occlusion[3]. Furthermore, surgical shunts, devascularization, splenectomy or (partial) splenic embolization may be considered if first-line treatments fail[3].

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## CONCLUSION

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The continuous efforts of hepatologists and gastroenterologists around the world, as well as initiatives of international collaborations to generate high-quality evidence has translated to improved survival in patients with EV bleeding in the last decades. Thus, we have summarized recent advances and highlighted the rationale for specific treatments now recommended by several national and international guidelines.

In primary prophylaxis, NSBB or EBL are equal in outcomes and are therefore both recommended as monotherapies to prevent a first variceal bleeding event[3,17,22]. However, carvedilol – due to its higher potency to lower portal pressure[36] resulting in higher proportions of HVPG responders – may be the treatment of choice for primary prophylaxis in compensated cirrhosis. No clear recommendation for the use of betablockers can be made for patients with small varices (even with additional risk factors), as their efficacy in this setting remains unclear. Importantly, due to non-hemodynamic effects of NSBBs on intestinal permeability[34], systemic inflammation [124] and considering the results of the recent PREDESCI trial[31] showing reduced risk of decompensation and mortality, NSBB may already be recommended for small varices.

To monitor NSBB treatment response, invasive HVPG measurement is still considered as gold standard, but other non-invasive surrogates to monitor NSBB response to prevent variceal bleeding such as ultrasound-based elastography or transient elastography assessment of the spleen are currently under consideration as HVPG measurement is not widely available[125,126].

When acute variceal bleeding occurs, standardized treatment algorithms recommend conservative transfusion strategies, early initiation of vasoactive drugs, prophylactic antibiotics, and EBL[3,17,22]. More recently, the pre-emptive use of TIPS implantation in selected high-risk patients with variceal bleeding has been demonstrated to not only decrease rebleeding rates but also mortality[3,17,22,127,128].

Due to logistic challenges with the “time-critical” use of pre-emptive TIPS implantation, specialist should be familiar with this concept and infrastructure and networks need to be developed in order to improve the outcomes of patients with variceal bleeding.

In secondary prophylaxis, the combination of NSBB and EBL has proven to be superior to either monotherapy[3,17,22].

In conclusion, NSBBs remain the cornerstone of medical therapy of portal hypertension and are still used for pharmacological bleeding prophylaxis. EBL may also be used for primary prophylaxis, but its main role is in effective control of acute variceal bleeding and variceal eradication in secondary prophylaxis. Standardized concepts and the infrastructure for the general use of pre-emptive TIPS in selected patients with high-risk variceal bleeding need to be developed. This review should have provided clinicians with valuable concepts for the management of PH, including variceal screening, primary bleeding prophylaxis, management of acute variceal bleeding and finally effective secondary prevention of variceal rebleeding.

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