

REVIEW

Variceal bleeding in cirrhotic patients

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Abstract

Variceal bleeding is one of the major causes of death in cirrhotic patients. The management during the acute phase and the secondary prophylaxis is well defined. Recent recommendations (2015 Baveno VI expert consensus) are available and should be followed for an optimal management, which must be performed as an emergency in a liver or general intensive-care unit. It is based on the early administration of a vasoactive drug (before endoscopy), an antibiotic prophylaxis and a restrictive transfusion strategy (hemoglobin target of 7 g/dL). The endoscopic treatment is based on band ligations. Sclerotherapy should be abandoned. In the most severe patients (Child Pugh C or B with active bleeding during initial endoscopy), transjugular intrahepatic portosystemic shunt (TIPS) should be performed within 72 hours after admission to minimize the risk of rebleeding. Secondary prophylaxis is based on the association of non-selective beta-blockers (NSBBs) and repeated band ligations. TIPS should be considered when bleeding reoccurs in spite of a well-conducted secondary prophylaxis or when NSBBs are poorly tolerated. It should also be considered when bleeding is refractory. Liver transplantation should be discussed when bleeding is not controlled after TIPS insertion and in all cases when liver function is deteriorated.

Key words: variceal bleeding; cirrhosis; endoscopic treatment; non-selective beta-blockers; transjugular intrahepatic portosystemic shunt; liver transplantation

Introduction

Acute variceal bleeding is one of the major causes of death in cirrhotic patients [1]. It is also the major cause of upper gastrointestinal (GI) bleeding in cirrhotic patients, accounting for 70% of cases [2]. Mortality during the first episode is estimated to 15–20% [3], but is higher in severe patients (Child Pugh C), at around 30%, whereas it is very low in patients with compensated cirrhosis (Child Pugh A) [3]. The main predictors of bleeding in clinical practice are: large versus small varices, red wale marks, Child Pugh C versus Child Pugh A–B [4].

In recent years, significant improvements have been made regarding the management of acute variceal bleeding, leading to a better prognosis [5,6]. Recent recommendations (2015 Baveno VI expert consensus) summarize the most important aspects [6]. In this review, we will discuss Baveno VI conclusions

and more recent data in order to provide guidance for an optimal management of variceal bleeding.

Management of acute bleeding

Unspecific measures

Resuscitation

Restoring mean arterial pressure (MAP) allowing an adequate tissue perfusion is of major importance. Prolonged hypovolemia favors kidney failure and bacterial infections, and increases mortality [7]. Conversely, portal pressure follows a linear correlation with MAP. As such, excessive MAP could promote bleeding [8,9]. The optimal MAP is not well defined in this context, but a target of around 65 mmHg can reasonably be extrapolated from recommendations established for septic or hemorrhagic shock in trauma

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Take home messages:

- Variceal bleeding patients should be managed in emergency in an intensive care unit. A restrictive transfusion strategy should be applied.
- Initial management always includes vasoactive drugs, antibiotic prophylaxis and emergency EBL.
- Secondary prophylaxis depends on the severity of underlying cirrhosis. TIPS placement should be discussed in severe patients.
- Liver transplantation should be discussed when liver function is deteriorated.

patients [10,11]. Transfusion of packed red blood cells should be performed with a restrictive hemoglobin target of 7 g/dL [6,12]. A liberal transfusion strategy (hemoglobin target of 9 g/dL) has been associated with a poorer prognosis in Child Pugh A and B patients. This effect was not observed in the most severe patients (Child Pugh C), either because of a lack of power of the study or because of a more severe hypovolemia in these patients [12]. Transfusion strategy should be adapted to specific situations such as high cardiovascular risk. The effect of fresh frozen plasma administration has never been evaluated during variceal bleeding and no recommendations are available. It is important to note that prothrombin rate and international normalized ratio (INR) should be considered as markers of liver function and not of coagulation disorders [13]. Correcting them is not part of the management of variceal bleeding. Platelet transfusion is usually recommended when platelet count falls below 30 000/mm³. No specific data are available for variceal bleeding patients. Two studies have evaluated the effect of recombinant factor VII administration during variceal bleeding [14,15]. No significant results have been obtained. A potential efficacy in the subgroup of patients with severe cirrhosis (Child Pugh C) with active bleeding was noted in the post-hoc analyses. This therapeutic is not recommended.

Prior to endoscopy

In the absence of contraindications (QT prolongation), infusion of erythromycin 250 mg as a prokinetic agent should be administered in order to improve stomach clearance and thus facilitate endoscopy [6]. Gastric lavage has shown no superiority compared to erythromycin or both therapeutics [16].

Proton pump inhibitors (PPI)

It is not recommended to use PPI during variceal bleeding. A randomized trial has studied the effect of PPI administration after endoscopic band ligation (EBL) [17]. The size of post-banding ulcers was smaller in the PPI group but their number and clinical repercussions were similar. In addition, there are more and more data showing that the use of PPI in cirrhotic patients favors bacterial infections including spontaneous peritonitis [18,19]. Initiation of PPI before endoscopy is debated but commonly practiced in cirrhotic patients. It has been proven to facilitate endoscopy in ulcer bleedings in a large prospective cohort study [20]. Whether this strategy is effective in cirrhotic patients is uncertain, as only 5% of the patients included in this study were cirrhotic. In any case, high-dose PPI should be discontinued when ulcer is ruled out.

Specific measures

The management of variceal bleeding associates vasoactive drugs, antibiotic prophylaxis and EBL [6]. An algorithm for the use of specific measures is detailed in Figure 1.

Vasoactive drugs

Three types of drugs are available: somatostatin, somatostatin analogs such as octreotide, and terlipressin. All these drugs

induce splanchnic vasoconstriction and reduce portal pressure. The choice depends on availability, cost and contraindications. Somatostatin has an effect on splanchnic hemodynamic through splanchnic arterial vasoconstriction, leading to a decrease in portal pressure (reflected by wedged hepatic pressure) [21,22]. This effect has been shown during variceal bleeding [23,24]. Somatostatin, administered early before endoscopy, tested against placebo, has led to fewer cases of active bleeding during endoscopy and fewer hemorrhagic recurrences [25]. In practice, somatostatin or octreotide should be administered as early as possible with bolus infusion of 250 µg and 50 µg followed by continuous infusion of 250 µg/h and 50 µg/h, respectively [26,27]. Terlipressin is a vasopressin analog. It is an arterial vasoconstrictor with splanchnic and general effect. It should not be used in high-cardiovascular-risk patients. Early administration of terlipressin against placebo during variceal bleeding has led to an improved survival [28,29]. Recently, a randomized trial including more than 1000 patients has compared the administration of somatostatin, terlipressin or octreotide after EBL and antibiotic prophylaxis [30]. Efficacy (hemorrhage control at Day 5) was similar in the three groups. More adverse effects were observed in the terlipressin group, especially hyponatremia, which should be monitored in case of terlipressin use. In practice, there is no recommendation on which drug to use and the first available should be preferred.

Antibiotic prophylaxis

Without antibiotic prophylaxis, 30–40% of cirrhotic patients presenting with upper GI bleeding will develop a bacterial infection within 1 week after admission [31]. These infections originate from bacterial translocation towards mesenteric lymph nodes, blood stream and potentially ascites. Translocation is facilitated by GI bacterial overgrowth, higher intestinal barrier permeability and altered immunity during cirrhosis. Most infections are due to gram-negative bacteria. Anaerobic bacteria are rarely isolated. Cirrhotic patients with all causes of upper GI bleeding (directly related to portal hypertension or not) are concerned. Infections are associated with a higher rate of early rebleeding and a higher mortality [31–34]. The risk of infection rises with the severity of cirrhosis [35]. A systematic antibiotic prophylaxis during upper GI bleeding leads to fewer infections and a lower short-term mortality, which seems to be the consequence of a lower rate of early rebleeding [32–36]. For these reasons, antibiotic prophylaxis is recommended for 7 days in all cirrhotic patients admitted for upper GI bleeding [6]. Oral norfloxacin, 400 mg twice daily, can be used because of its activity against gram-negative bacteria and its weak intestinal absorption. Other quinolones, such as ciprofloxacin or ofloxacin, can also be used when the oral route is impossible, as well as amoxicillin-clavulanic acid or third-generation cephalosporins.

Gram-negative bacteria resistance to quinolones is a rising concern and the use of quinolones has been challenged. A study has compared antibiotic prophylaxis with IV ceftriaxone or oral norfloxacin in severe patients (Child Pugh B or C). The use of

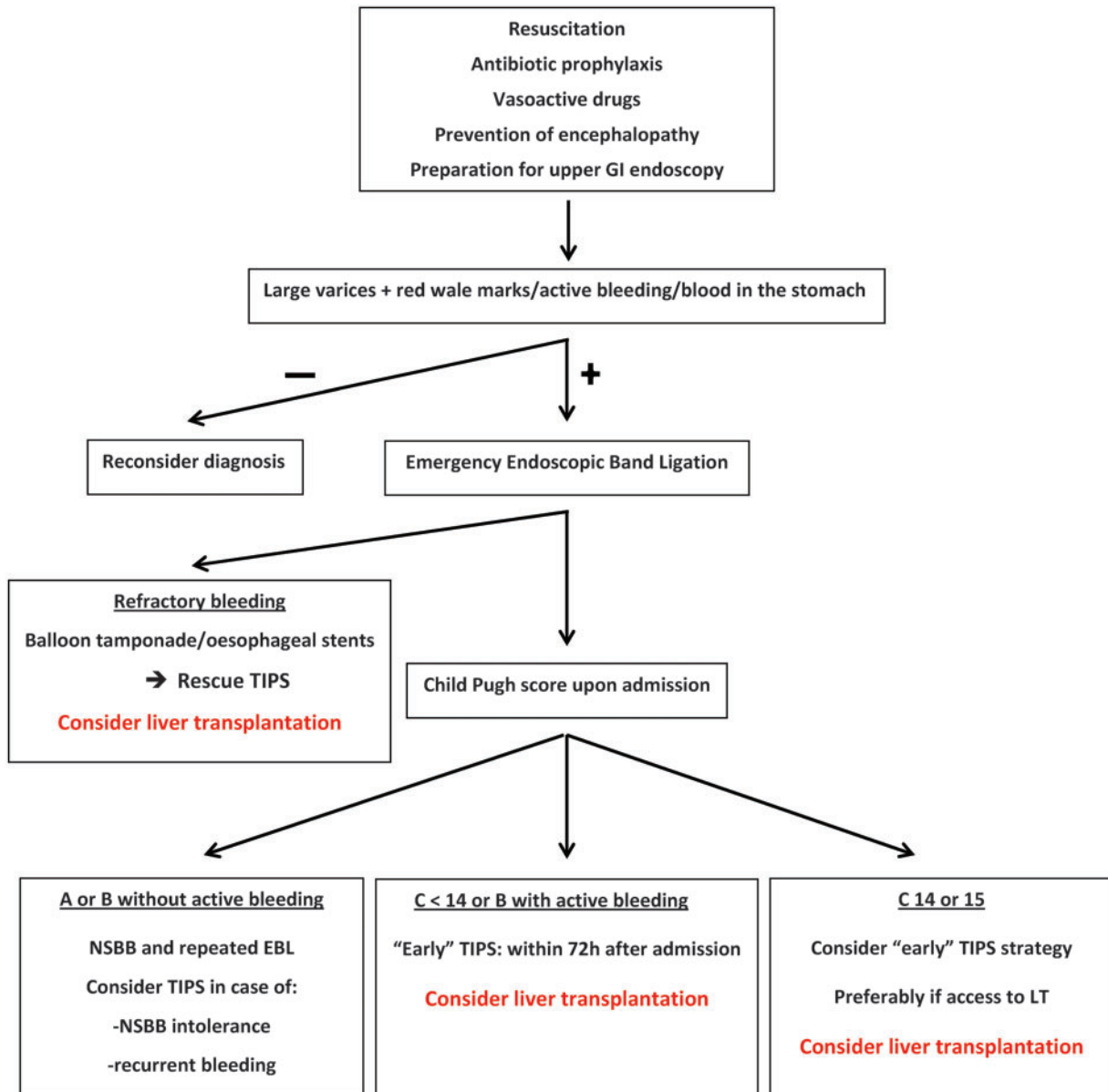


Figure 1. Algorithm for the management of acute variceal bleeding.

ceftriaxone was associated with a lower rate of suspected or proven infections [37]. The authors attributed the results to the high rate of quinolone-resistant bacteria. Nevertheless, this conclusion must be balanced, for two reasons. The rate of quinolone-resistant bacteria in the hospital where the study was performed was unknown. Infections were also more frequent in the quinolone group than in most studies previously published. Baveno VI's recommendations state that IV ceftriaxone should be considered in patients with advanced cirrhosis, in hospital settings with a high prevalence of quinolone-resistant bacteria or in patients with previous quinolone prophylaxis. Recently, in Child Pugh A patients only, a non-randomized study showed that infections occurred at a similar frequency (1% vs 2%) with or without antibiotic prophylaxis [35]. The advantage of antibiotic prophylaxis in these patients is thus a matter of debate, especially at a time when use of antibiotics should be cautious due to the spread of multi-resistant bacteria. Further randomized

studies will address this question and eventually lead to avoidance of antibiotic prophylaxis in Child Pugh A patients.

Endoscopic treatment

Endoscopic diagnosis of variceal bleeding relies on the presence of large varices and red wale marks or active bleeding. The presence of blood in the stomach without any other cause but large varices is also possible. It is recommended to perform upper GI endoscopy as soon as possible (within 12 hours) after initial resuscitation [6]. Endoscopy should be performed by an endoscopist and a support staff proficient in endoscopic hemostasis techniques [6]. Airways should be protected in patients with altered consciousness. Furthermore, Baveno VI's recommendations state that acute variceal bleeding patients should be managed in an intensive-care or well-monitored unit. Sclerotherapy is the oldest endoscopic treatment for variceal bleeding. Due to almost constant formation of an ulcer on the

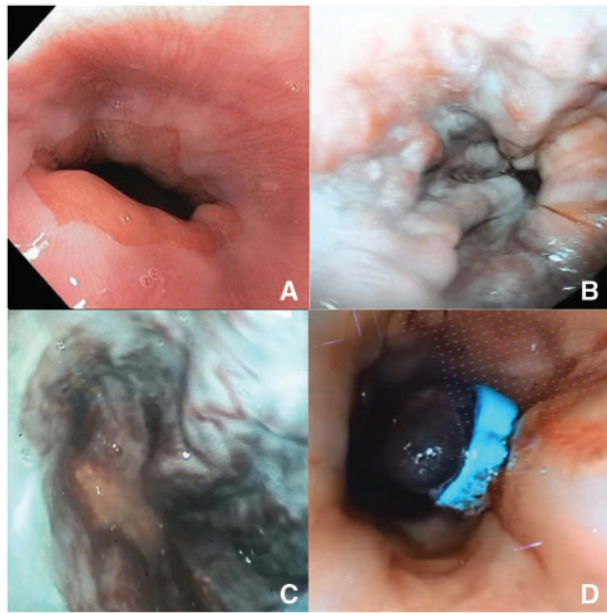


Figure 2. Endoscopic band ligation. (A) Normal esophagus. (B) and (C) Large esophageal varices with red wale marks. (D) Post-banding necrosis of varicose tissue.

site of injection, sometimes responsible for a hemorrhage, **sclerotherapy should be abandoned**. **EBL**, the actual **treatment of choice**, should be performed during initial endoscopy [38] (Figure 2). Minor complications can occur such as **dysphagia** or **chest pain**. **Post-banding ulcer** bleeding can occur around **Day 7** and be clinically significant. EBL has never been compared to the absence of endoscopic treatment. However, it has been compared to sclerotherapy in several studies, all in favor of less rebleeding and fewer side effects when performing EBL [39–41].

Balloon tamponade and self-expanding metal stent (SEMS)

Balloon tamponade through a nasogastric tube equipped with inflatable balloons (esophagus and stomach), usually named **Blakemore's tube**, is **effective** to control variceal bleeding [42,43]. It is associated with **severe complications** such as **necrosis** or **perforation** of the esophagus and **aspiration pneumonia**. **Endotracheal intubation** to protect airways is thus **necessary**. **Hemorrhage recurrence occurs in more than 50%** of cases after **deflation**. It is thus only a **temporary solution** when bleeding is not controlled. Recently, **esophageal SEMS** have been developed to **replace Blakemore's tube** [44]. They offer the advantages of allowing oral intakes after the acute phase and being **removable**. A recent randomized controlled trial comparing SEMS and balloon tamponade during refractory variceal bleeding showed a **better control of bleeding** and **fewer adverse events** when using esophageal stents [45]. Survival was better, but not significantly. **Baveno VI's recommendations state that esophageal stenting should be preferred to balloon tamponade.**

Emergency portosystemic shunts

Surgical portosystemic anastomoses, once the rescue treatment for refractory variceal bleeding, have been almost **abandoned**. Nowadays, intrahepatic shunting through transjugular insertion of a stent, commonly named a transjugular intrahepatic portosystemic shunt (**TIPS**), is the treatment of **choice** for **refractory variceal bleeding** as well as for **secondary prophylaxis** in severe patient, as we will further develop. **TIPS insertion during refractory variceal bleeding**, also called **salvage TIPS**, is **effective** to

control bleeding in almost all cases [46]. Nevertheless, **mortality after 1 year** remains high (around **50%**), even since the use of covered stents, with a low risk of thrombosis leading to recurrence of portal hypertension. Elevated mortality is due to other complications of severe cirrhosis such as infections, kidney failure and encephalopathy. **Salvage TIPS, eventually preceded by SEMS insertion** [47], can however be a very **attractive bridge** to liver **transplantation** (LT). In our experience, making the decision of inserting a rescue TIPS should take into account the possibility of a LT in a near future [48].

Early TIPS placement for severe patients

TIPS were **initially** dedicated to the **rescue** treatment of refractory bleeding. There are now data suggesting that the **most severe** patients **benefit** from a **systematic TIPS insertion after** an initial bleeding episode, commonly named '**early TIPS**' [49]. The pivotal study was published in the **NEJM** by García-Pagán et al. [50]. Child Pugh **C < 14** or **B** with **active bleeding** at initial endoscopy were eligible. After initial management (vasoactive drugs and emergency EBL), there were randomized to receive combined therapy (non-selective beta-blockers [NSBBs] and EBL) or a covered **TIPS within 3 days after initial bleed**, after control of bleeding. Patients in the **TIPS group** were more often **free from rebleeding** (97% vs 50%) and had a **higher 1-year survival** (86% vs 61%). External validation studies **confirmed the lower rebleeding rate** but the **benefit on survival** is still a matter of **debate** [51]. A possible explanation is that patients in a study were highly selected (63 patients recruited over 3 years in nine centers), thus not fully comparable to those in validation studies. However, a recent meta-analysis was in favor of a **benefit of survival** [52]. **Baveno VI's recommendations state that TIPS must be considered in Child Pugh C or B with active bleeding at initial endoscopy.** Availability of TIPS remains a practical issue. LT should rapidly be discussed in these patients, as the deterioration of liver function and occurrence of other complications of cirrhosis become at the forefront. Management of variceal bleeding in Child Pugh C 14 or 15 patients is still a matter of debate. These patients were excluded from the 'early TIPS' studies. In our experience, an '**early TIPS**' strategy is a solution **if** the patient can have **quick access to LT**, as liver **failure** and **encephalopathy** are likely to **keep deteriorating after TIPS** [48].

Prevention of hepatic encephalopathy (HE)

Baveno VI's recommendations do not include a specific strategy to prevent HE in the context of variceal bleeding. However, data from trials are now available. A prospective randomized controlled trial (RCT) included 70 patients admitted for variceal bleeding with no signs of HE. Patients were allocated to receive **lactulose** or placebo [53]. The proportion of patients **developing HE** was significantly **lower** in the **lactulose** group (14% vs 40%, $p = 0.03$). **Rifaximin** is a non-absorbable antibiotic used in the prevention of recurrence of HE. Its efficiency to prevent HE in the context of variceal bleeding has been found to be **similar** to that of **lactulose** in a prospective RCT [54]. There were **fewer digestive side effects** with **rifaximin**.

Secondary prophylaxis

NSBBs and EBL

Due to a high risk of **recurrent bleeding**, it is essential to initiate a **secondary prophylaxis after** the first episode. EBL associated with **NSBBs** is the first-line strategy recommended [6]. The **NSBB (propranolol and nadolol)** effect consists of **lowering portal pressure** through a **bradycardia** that leads to a **decrease**

in **cardiac output** (anti β 1 action) and a **splanchnic vasoconstriction** (anti β 2 action) [55]. **Carvedilol**, a potent **alpha- and beta-blocker**, has **never** been **tested** adequately in secondary prophylaxis. Its use is thus **not recommended**. **Repeated EBL**, usually every **2–4 weeks**, leads to a **disappearance** of **varices** and **reduces** the **risk** of **bleeding**. A recent trial compared EBL sessions at an interval of 1 or 2 weeks [56]. **Varices eradication** was obtained quicker in the **1-week group**, without additional complications. Nevertheless, the number of sessions needed, rebleeding rate and mortality were similar in both groups. Many studies have compared the use of NSBBs combined with EBL versus one of these treatments in a single therapy [57–59]. The results of a recent meta-analysis, combining the data of 23 trials, show a decrease in the risk of recurrent bleeding with a dual therapy, without any positive impact on survival [60]. However, survival was better in patients treated with NSBBs (single or combined therapy) compared to patients treated with EBL alone. Hence, **EBL therapy alone should never be recommended** and, if any contraindications to beta-blockers occur, TIPS should be discussed. Few severe patients (Child Pugh C) were included in these studies and it is uncertain whether the previous results are applicable to these patients.

NSBBs in patients with refractory ascites

Several studies have raised a **concern** about the **safety** of NSBBs in patients with **ascites**, as some papers claim a **higher mortality** in this subgroup when treated with NSBBs [61,62]. The **detrimental** effect of NSBBs appears to be more pronounced in patients who experienced an episode of **spontaneous bacterial peritonitis** (SBP) [62]. These results have been **challenged** by others studies that showed a **survival benefit** in patients with **ascites** treated with **propranolol** or **carvedilol**, even after adjustment for the severity of ascites or the occurrence of SBP [63,64]. Baveno VI's guidelines recommend to use NSBBs with **caution** in patients with refractory ascites and to discontinue the treatment if poorly tolerated: **systolic blood pressure** **<90 mmHg**, **hyponatremia** **<130 mmol/L**, episode of acute **kidney injury**. NSBBs can be restarted with titration if a precipitating factor for such an event has been identified and corrected. Baveno VI's guidelines recommend TIPS insertion in secondary prophylaxis if NSBBs cannot be used.

TIPS in secondary prophylaxis

Extending the 'early TIPS' criteria after a variceal bleeding episode is a much debated issue. Until **recently**, **studies** were performed using **bare stents**, **without** any **survival benefit** of TIPS as first-line therapy in this setting. Baveno VI's guidelines recommend TIPS if NSBBs cannot be used or if bleeding reoccurs in spite of a well-conducted combined therapy. Recently, two **RCTs** addressed this question, using **covered TIPS** [65,66]. They compared TIPS insertion versus a combined therapy in the first case [65] and used a tailored strategy starting initially with drugs alone in the second case [66]. Here, in the medical treatment group (no TIPS insertion), **hepatic venous pressure gradient** (HVPG) was systematically measured before and after starting a combination of **NSBBs** and **nitrates**. Patients **without** **hemodynamic response** were switched to EBL only. In both studies, there was significantly **less** recurrence of **bleeding** in **TIPS** groups, but survival rates were similar, as well life-quality assessments. As well as in studies evaluating the effects of NSBBs and EBL, few Child Pugh C patients were included. Hence, **TIPS** should **not** be **recommended** at **first-line** therapy for secondary prophylaxis.

Hemodynamic response-guided prescription of NSBBs

Monitoring hemodynamic response to NSBBs is **not recommended** in Baveno VI consensus and poorly feasible in routine practice in most centers. However, short- and long-term hemodynamic **responses** to NSBBs (decrease of **HVPG** **below 12 mmHg** or **more than 20% of baseline value**) are associated with a **lower risk** of **bleeding** in primary or secondary **prophylaxis** [67,68]. In the setting of primary prophylaxis, carvedilol has been effectively used as a second-line treatment in non-responders to propranolol [69]. Recently, a RCT has validated a step-by-step increase in pharmacological treatment of portal hypertension guided with repeated HVPG measurements [70]. In the setting of secondary prophylaxis, **nitrates** and eventually **prazosin** (an alpha-blocker) were **added** to **nadolol** in cases of acute and chronic non-responders, respectively. Patients in the control group were treated with nadolol and nitrates from the beginning and the treatment was not modified in non-responders (measurements still performed). Mortality and rebleeding rates were **lower** in **HVPG-guided therapy** patients alongside a deeper decrease in HVPG. It is worth noting that, in the Sauerbruch et al. study, the rebleeding rate was similar when comparing 8-mm TIPS and hemodynamic responders to NSBBs, highlighting the **potential benefits** of **monitoring hemodynamic response** to NSBBs [66].

Clinical benefit of statins in patients with variceal bleeding

Recently, Abrahams et al. demonstrated in a RCT that introducing simvastatin during an episode of variceal bleeding was associated with a **better** 1-year **mortality**, without improving the rate of rebleeding (in the setting of secondary prophylaxis with NSBBs and EBL) [71]. Child Pugh C patients did not take advantage of simvastatin prescription. The mechanisms underlying the **benefit** of statins in cirrhosis remain unclear, but their use is **promising**. Indeed, in a large Taiwanese retrospective cohort including hepatitis B (HBV), hepatitis C (HCV) and alcohol-related cirrhosis patients, it was shown that exposure to **statins** **reduced** the risk of **hepatocellular carcinoma** (HCC) and **decompensation** of **cirrhosis** [72].

Treatment of etiological factors

The treatment of the etiological factor(s) of cirrhosis is part of the management of complications of cirrhosis such as variceal bleeding. It has first been shown in cirrhosis related to **chronic HBV** that **viral suppression** with **nucleoside analogs** is efficient at **reducing** the risk of HCC and **portal hypertension**-associated complications including variceal bleeding [73–75]. Concerning **HCV**, **direct-acting antiviral** agents have recently led to high rates of **sustained viral response** (SVR). It has also been shown in HCV cirrhosis that achieving SVR was associated with a **lower** incidence of HCC and **complications** of portal hypertension [76]. Data are scarce in alcoholic cirrhosis but it is very likely that alcohol withdrawal has a positive effect on cirrhosis complications [77]. Patients with nonalcoholic steatohepatitis (NASH) cirrhosis are also at risk of developing complications of cirrhosis [78]. **Lifestyle intervention** has been shown to **improve** **histological** lesions of NASH [79]. In the near future, it is likely that lifestyle and pharmacological interventions will also prove efficient in limiting the occurrence of complications of NASH cirrhosis.

Conclusion

The specific management of variceal bleeding is well codified: vasoactive drugs, antibiotic prophylaxis and EBL. For severe patients (Child Pugh C < 14 or B with active bleeding), a TIPS should be discussed in order to be placed within 72 hours. TIPS should also be inserted when hemorrhage reoccurs in spite of a well-conducted secondary prophylaxis. LT should be discussed in the rare cases when TIPS does not control bleeding and when liver function is deteriorated. However, some questions are still under debate: Which patients really take advantage of an 'early TIPS' strategy? How to improve TIPS availability? Should we routinely measure hemodynamic response to NSBBs? Is antibiotic prophylaxis necessary in Child Pugh A patients? Which patients really take advantage of statins prescription? Answering those questions will allow decreasing mortality, which remains high in cirrhotic patients presenting with variceal bleeding.

Conflict of interest statement: none declared.

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