



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/mm<sup>6</sup>**. 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]. (hemorrhage control at Day 5) was \_\_\_\_\_ in the three groups. More adverse effects were observed in the \_\_\_\_\_ group, especially \_\_\_\_\_, which should be monitored in case of terlipressin use. In practice, there is \_\_\_\_\_ to use and the first available should be preferred.

Without antibiotic prophylaxis, \_\_\_\_\_ of cirrhotic patients presenting with upper GI bleeding \_\_\_\_\_ [31]. These infections originate from bacterial \_\_\_\_\_ 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 \_\_\_\_\_, bacteria are \_\_\_\_\_ isolated. Cirrhotic patients with all causes of upper GI bleeding (directly related to portal hypertension or not) are concerned. \_\_\_\_\_ are associated with a \_\_\_\_\_ and a higher \_\_\_\_\_ [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, \_\_\_\_\_ is recommended \_\_\_\_\_ in all cirrhotic patients admitted for upper GI bleeding [6]. \_\_\_\_\_, 400 mg twice daily, can be used because of its activity against gram-negative bacteria and its \_\_\_\_\_. Other quinolones, such as \_\_\_\_\_ or \_\_\_\_\_, can be used when the oral route is impossible, as well as \_\_\_\_\_ or \_\_\_\_\_. 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 \_\_\_\_\_ or oral norfloxacin in severe patients (Child Pugh B or C). The use of

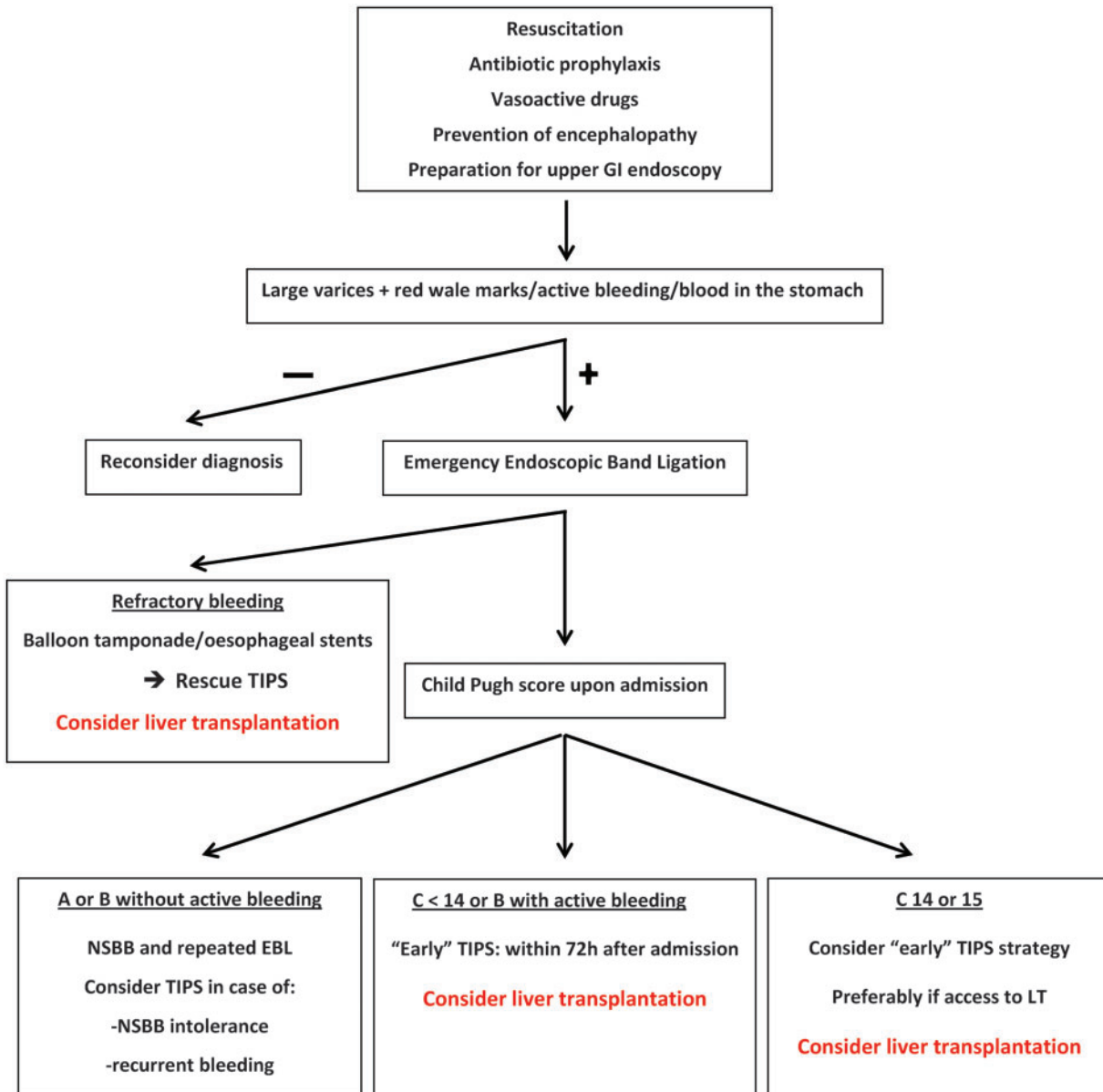


Figure 1. Algorithm for the management of acute variceal bleeding.

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





## 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.

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