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Acute Variceal Bleeding Is It Only the Success of Hemostasis That Guarantees the Positive Outcome?

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Abstract

Acute variceal bleeding remains with a high mortality rate (around 15%). Treatment is based on the combined use of vasoactive drugs, endoscopic band ligation, and antibiotic therapy. Effective resuscitation (blood transfusions, volume replacement) is essential to prevent complications. In case of failure - transjugular intrahepatic portosystemic shunt (TIPS) with appropriate indications and limitations related to the prognosis of the individual patient. Balloon tamponade or specially designed coated esophageal stents can be used as a bridge to definitive therapy in unstable patients. Early TIPS should be the first choice in patients at high risk of treatment failure (Child-Pugh B with active bleeding or Child-Pugh C < 14). This article discusses the latest advances in variceal bleeding management in line with current recommendations of the Baveno VI Consensus Conference.

Introduction

Acute variceal bleeding (AVB) represents 70% of all episodes of upper gastrointestinal bleeding in cirrhotic patients [1], [2]. The introduction of endoscopic therapies (initially sclerotherapy and subsequently endoscopic band ligation), pharmacological therapy (vasopressin, somatostatin, and their analogs), and transjugular intrahepatic portosystemic shunt (TIPS) altered treatment success and prognosis in these patients.

Improving treatment to achieve hemostasis and general management led to a significant reduction in mortality from about 40% in the 1980s [3] to 15–20% in the early 2000s [4]. However, even in the last published series, it remains above 15% [5], which makes this complication one of the most serious medical emergencies.

AVB is no longer the main cause of mortality in these patients. Nowadays, most deaths are related to deterioration of liver and kidney function or due to infections [4], [5]. Therapy should focus not only on bleeding control but also on hepatoprotection, measures to preserve renal function and prevent infections [6].

The main determinants of mortality are the basic functions of the liver and kidneys. The current predictor model for mortality is the result of MELD score (which includes INR, bilirubin, and creatinine) [5]. A MELD score >19 points is associated with >20% mortality, while a MELD score <11 points is associated with a mortality risk <5% [5]. This can be used for stratification of risk patients and determination of therapeutic behavior [7] The initial therapy should be aimed at hemodynamic resuscitation, initiation of vasoconstrictor therapy, antibiotics, and endoscopic therapy.

General Management

General management of the bleeding patient is aimed at correcting hypovolemic shock (volume replacement and blood transfusion) and preventing complications related to gastrointestinal bleeding (bacterial infections, liver decompensation, and renal impairment) [8]. Volume replacement therapy should be started as soon as possible with plasma volume replacements to maintain the systolic blood pressure of about 100 mm Hg.

Rapid correction of hypovolemia is essential in reducing the risk of renal failure and impaired hepatic perfusion. The past contrast thesis of maintaining relative hypovolemia (hypovolemia-induced reflex splanchnic vasoconstriction reduces portal pressure leading to better bleeding control) has uncertain evidence and is likely to increase the risk of complications.

Modern hemostasis techniques are highly effective and most deaths are not associated with persistent bleeding but with complications that could be associated with hypovolemia.

The blood transfusion strategy (differentiated by volume replacement) deserves special attention. A recent randomized study in patients with acute upper GI bleeding showed that a restrictive transfusion policy using a hemoglobin transfusion threshold of 70 g/L and a target of 80–90 g/l improved survival compared to the liberal strategy (Hb threshold of 90 g/L) and a target of 100–110 g/L [9].

The results were also checked in the subgroup of patients with cirrhosis and AVB, patients with rapid persistent bleeding or ischemic heart disease were excluded from the study.

Correction of hemostasis is still a controversial issue in patients with cirrhosis and bleeding complications. It is widely accepted that prothrombin time or INR are not reliable indicators of coagulopathy and/or risk of further bleeding. There are currently insufficient data to make recommendations for the role of platelet transfusions or fresh frozen plasma, as this has not been evaluated in randomized trials. Stable information is now available on the potential role of recombinant activated factor VII (rFVIIa). This was evaluated in two randomized controlled trials given in addition to standard therapy. The first was performed in a general population of patients with AVB [10]. The second is aimed at high-risk patients, defined as patients with active bleeding on endoscopy and Child-Pugh score ≥8 points [11]. Both studies do not show relevant benefits of rVIIa. Both studies reported a lower incidence of rVIIa treatment failure in the first 5 days after bleeding, and this effect was more noticeable in patients with a Child-Pugh score >8. No effect on mortality was reported, and studies showed a potential risk for arterial thrombotic events, rFVII is currently not recommended in the treatment of AVB. In the conditions of AVB (in the absence of antibiotic prophylaxis), approximately, 20% of patients are infected on the day of admission, and up to 50% develop an infection during their hospital stay [12]. Most infections develop in the first 5–7 days after the bleeding episode. The most commonly reported infections were bacteremia (19–56%), spontaneous bacterial peritonitis (19–37%), urinary tract infections (12–34%), and pneumonia (12–19%) [12], [13], [14], [15]. Bacterial infections increase mortality associated with AVB [12], [13], [14], [15], [16], [17] and in smaller studies have been associated with failure to control bleeding and increased re-bleeding [17], [18], [19].

Systematic examinations and meta-analyzes show a clear reduction in the rate of bacterial infections, re-bleeding, and mortality with antibiotic prophylaxis [12], [13], [14], [15], [19], [20]. Accordingly, antibiotic prophylaxis is applied as early as possible in the manifestation of AVB and lasts 5–7 days in all patients [8], [20]. The connection between worsening of hepatic function and increasing risk of bacterial infection is well known [15], [20], [21].

The data from a recent observational study in 381 AVB patients who either received or did not receive antibiotic prophylaxis support the stratified increase in bacterial infection according to Child Pugh [22]. The risk of infections in Child-Pugh A patients who have not been treated with antibiotics is negligible, suggesting that antibiotic prophylaxis can be avoided in these patients. However, prospective multicenter trials were proposed at the Baveno VI Consensus Conference before a formal recommendation could be made to avoid antibiotic prophylaxis in patients with AVB with Child-Pugh A [23].

Antibiotic choice should receive special attention here. Use of an antibiotic in variceal bleeding, in patients with cirrhosis, in a meta-analysis of 12 placebo-controlled studies resulted in reduced mortality (RR 0.79, 95% CI 0.63–0.98), bacterial infections (RR 0.43 95% CI 0.19–0.97), and the occurrence of recurrent bleeding (RR0.5395% CI 0.19–0.97). A broad-spectrum antibiotic cephalosporin is recommended, for example ceftriaxone 2 g/24 h or quinolone, ciprofloxacin 2 × 500 mg/24 h.

Every patient receives individual antibiotic treatment, but due to the high percentage of quinolone-resistant intestinal bacteria, recommendations are in using of a 3rd generation cephalosporin/60/, for 5–7 days, and the treatment is adjusted after a microbiological test result (Tarragona strategy) [52].

Hepatic encephalopathy management (HE) in AVB must be established on the latest AASLD/EASL recommendations [24].

In the study of Sharma *et al*., 70 patients with AVB were randomized to be treated with lactulose versus non-lactulose recipients with the primary goal of developing HE within 5 days [25] HE developed in 40% of the placebo group and 14% of the lactulose group.

In the second Maharshi study *et al*. [26], 120 patients with AVB were randomized to lactulose versus rifaximin with a primary outcome - the onset of HE within 5 days. There is no significant difference in the percentage of patients who developed HE (17% of the lactulose group and 15% of the rifaximin group), the duration of hospitalization, or mortality.

Although both groups of researchers suggest therapy in the prevention of HE, to be included as part of the standard, the Baveno VI consensus concludes that there is insufficient data to recommend prevention of hepatic encephalopathy in patients with AVB. Studies in high-risk patients are needed.

Acute renal impairment (in AVB) is the result of a critical decrease in intravascular volume, bacterial infections, and nephrotoxic drugs. In a study by Cardenas *et al*. involving 161 patients [27], [29], renal failure was diagnosed in 11% of patients (rise of creatinine levels with ≥50% to >132 micromol/l in the first 7 days after AVB) and is transient in 40% of cases. Mortality was 55% in patients with renal failure compared with 3% in those without renal failure. Transient renal failure was associated with the highest mortality at 83%. Acute renal impairment in cirrhotic patients with AVB appears to be a stable predictor of mortality.

The recommendations of the International Ascites Club for the prevention and treatment of ARI in cirrhotic patients [28], [30] can be applied in the management of AVB and include removal of all potentially nephrotoxic drugs, adequate replacement of plasma volume, rapid detection and early treatment of bacterial infections and selected patients, early initiation of vasoconstrictor therapy.

Bleeding Control

The first-line hemostatic treatment of AVB is based on a combination of vasoactive drugs (somatostatin, octreotide, or terlipressin) and endoscopic therapy (endoscopic band ligation). This is based on a meta-analysis comparing only endoscopic treatment with combined endoscopic and medication treatment, which showed that the addition of vasoactive drugs to endoscopic therapy significantly improved initial bleeding control and the rate of 5-day recurrent bleeding.

Despite the fact that 6-week mortality rate is associated with unsuccessful treatment, the meta-analysis does not show increased survivability in combined therapy [29], [30], [31], [32]. There is one trial which compares EBL with medical therapy (low doses of terlipressin) and medical therapy alone. This trial includes patients with non-active variceal bleeding at the time of endoscopy and again shows that combined therapy is better than medical therapy alone in reducing the likelihood of early rebleeding and treatment failure. Therefore, the recent recommendation is that all patients with variceal bleeding be treated with combined medical and endoscopic therapy, even if there is no active bleeding at the time of endoscopy.

Treatment with vasoactive medications should be initiated as soon as possible before endoscopy [23], [24]. Two groups of vasoactive medications are used In patients with variceal bleeding – vasopressin and its analogs and somatostatin and its analogs. Terlipressin is a vasopressin analog and induces a systemic and splanchnic vasoconstriction thereby reducing portal vein pressure. Somatostatin and its analog octreotide cause vasoconstriction of the splanchnic circulation by suppressing glucagon-mediated vasodilatation. The latter leads to reduction of the portal circulation, collateral pressure, and better renal circulation.

A recent meta-analysis shows that vasoactive agents are associated with reduced 7-day mortality rate (RR 0.74; 95% CI 0.57–0.95), lower hemotransfusion rates, and reduced hospital stay [31], [34]. Which vasoactive drug to use depends on local resources. Terlipressin, somatostatin, and octreotide could be used with comparing results [31], [34]. A recent randomized control trial (n = 780) compares the efficacy of terlipressin, somatostatin, and octreotide in combination with endoscopic therapy in the management of variceal bleeding. 5-day treatment with all vasoactive medications shows comparable results [32], [35]. A big randomized studio with 720 patients [35], compares the efficacy of all three vasoactive drugs in the management of variceal bleeding, rebleeding, and mortality with no significant difference between the three (Table 1).

Table 1: Randomized trial comparing results from the three regimens [35]

	Terlipressin	Somatostatin	Octreotide
	n = 261	n = 259	n = 260
Bolus before endoscopy	2 mg i.v. bolus	250 µg i.v. bolus	50 µg i.v. bolus
Five day dosage	1 mg every 6 h for 5 days	250 µg/h i.v. for 5 days	25 µg/h i.v. for 5 days
Active bleeding at initial endoscopy	43.7%	44.4%	43.5%
Therapeutic success on the 5th day	86.2%	83.4%	83.8%
Rebleeding	3.4%	4.8%	4.4%
Mortality	8%	8.9%	8.8%

All three vasoactive medications show a better safety profile according to this trial, except hyponatremia (defined as a drop in serum Na > 5mmEq from baseline to <130 mmEq/l). 11.5% (30 of 261) of patients of the terlipressin group develop hyponatremia as compared to 1.5% of those receiving somatostatin and 1.2% of those receiving octreotide ($p < 0.001$) [32], [35]. This side effect has been reported earlier [36]. Baveno VI recommends following sodium levels when [33] using terlipressin [23], [24]. Furthermore, terlipressin is associated with cardiovascular complications such as limb ischemia, cardiac arrhythmia, arterial hypertension, left ventricular insufficiency, myocardial ischemia and sudden death, which was not observed when using somatostatin and octreotide. Because of this, terlipressin is contraindicated in patients with a history of cardiovascular conditions.

It is not well established for how long the vasoactive drug should be administered (from 8 h to 6 days according to different schemes) [34], [37]. Only one RCT compares two treatment regimes for terlipressin: 24 h and 72 h both showing comparable results in variceal bleeding after successful EBL. Most recent recommendations are that the drug should be administered for 5 days in combination with endoscopic therapy. Endoscopic therapy should be done not longer than 12 h from admission

after hemodynamic resuscitation [23], [24]. Erythromycin (motilin receptor agonist) should be administered before endoscopy if no contraindications are present. Recent meta-analysis shows that erythromycin (250 mg IV 30–120 min before endoscopy) reduced the need for second-look endoscopy, hemotransfusion requirements, and reduced hospital stay [35], [39].

Current evidence supports EBL as an endoscopic therapy of choice in variceal bleeding management with lower complication rates and mortality than sclerotherapy [36], [40], with the latter associated with increased portal pressure [37], [41].

Pharmacologic and endoscopic treatment of variceal bleeding fails to control bleeding in 10–20% of patients [38], [42]. If the bleeding is mild and liver function is normal, second endoscopic therapy is indicated [8], which, if unsuccessful, salvage therapy should be initiated before the patient's condition deteriorates. Balloon tamponade should be used as a temporary (not more than 24 h) solution until more definitive treatment [23], [24]. [39] [43]. Rebleeding after balloon deflation is observed in half of the patients. Serious adverse events are frequent including esophageal rupture, proximal migration and asphyxiation, aspiration, which are fatal in 6–24% of cases [38], [42]. Self-expandable fully covered metal stents could be used to achieve definite hemostasis in most of the patients with refractory bleeding with better success rates and less complications compared to balloon tamponade despide longer periods of treatment [23], [24], [40], [41], [42] [44], [45], [46].

A multicenter RCT from Spain [43], [47] compared fully covered metal stents with balloon tamponade with the main endpoint of variceal bleeding control with less complications and better survivability on day 15. The trial was abandoned with interim analysis data (n = 28) because of insufficient number of patients. The primary endpoint was achieved in 66% of cases in the stent group as compared to 20% in balloon tamponade.

TIPS and surgical shunts are effective in controlling variceal bleeding (the rate of control is close to 95%), but because of liver function deterioration and encephalopathy, mortality rates are still high [44], [48]. TIPS is a method of choice as most of the patients who need salvage therapy have advanced liver disease with high surgical risk. In patients with liver cirrhosis Child-Pugh over 13 points TIPS mortality rates are close to 100%.

Two RCTs have established the benefits of early TIPS (no more than 72 h of admission) in the prevention of rebleeding and mortality [45], [46] [49], [50]. Patients were chosen based on hepatic-venous pressure gradient (HPVG) greater than 20 mmHg [45] , [49] and based on Child-Pugh C 10–13 p or Child B with active variceal bleeding. Both trials show lower mortality rates in early TIPS compared to standard therapy.

Recent data show the efficacy of early TIPS bleeding control, but the effect on mortality is not well established [47], [48], [51], [52].

These results show that the management of variceal bleeding should be stratified according to patient risk profile and high risk patients should benefit from more aggressive therapy such as prophylactic TIPS. Baveno VI consensus recommends TIPS in patients with Child-Pugh B cirrhosis and active bleeding and Child-Pugh C (<14 points). Criteria for high risk patients are not established [23], [24].

Conclusion

AVB is an area of increased interest [49], [53]. Choosing the study endpoint, however, has been an area of debate for years. Most of the trials used several definitions for "unsuccessful treatment," which focused on achieving hemostasis [50]. This concept was famous for many years when the efficacy of therapy was lower (~60%) than today (~85%). Treatment failure is associated with increased mortality. Recently, FDA [51] questioned the clinical significance of treatment failure as a primary endpoint of variceal bleeding medication efficacy based on the fact that better treatment is not associated with increased survival. With mortality rates of 15–20% with standard therapy which has not decreased in the past decade, there is certainly a place for new methods and strategies in the management of these patients. Baveno VI recommends that new trials focus on mortality as a primary endpoint. New methods and treatments should include strategies for hepatic function improvement and protection, since it is the main factor of mortality in AVB.

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