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## Review

# Current approaches to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding

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## Abstract

**Objective:**

Esophageal variceal bleeding is the most dangerous complication in patients with liver cirrhosis, and it is accompanied by high mortality. Their treatment can be complex, and requires a multidisciplinary approach. This review examines current approaches to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding.

**Methods:**

PubMed, Google Scholar, and Cochrane Systematic Reviews were searched for articles published between 1987 and 2015. Relevant articles were identified using the following terms: 'esophageal variceal bleeding', 'portal hypertension' and 'complications of liver cirrhosis'. The reference lists of articles identified were also searched for other relevant publications. Inclusion criteria were restricted to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding.

**Results:**

It is currently recommended to combine vasoactive drugs (preferable somatostatin or terlipressin) and endoscopic therapies (endoscopic band ligation as first choice, sclerotherapy if endoscopic band ligation not feasible) for the initial treatment of acute variceal bleeding. Antibiotic prophylaxis must be regarded as an integral part of the treatment. The use of a Sengstaken–Blakemore tube is appropriate only in cases of refractory bleeding if the above methods cannot be used. An alternative to balloon tamponade may be the installation of self-expandable metal stents. The transjugular intrahepatic portosystemic shunt is an extremely useful technique for the treatment of acute bleeding from esophageal varices. Although most current clinical guidelines classify it as second-line therapy, the Baveno VI workshop recommends early transjugular intrahepatic portosystemic shunt with expanded polytetrafluoroethylene-covered stents within 72 h (ideally <24 h) in patients with esophageal variceal bleeding at high risk of treatment failure (e.g. Child–Turcotte–Pugh class C < 14 points or Child–Turcotte–Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy. Urgent surgical intervention is rarely performed and can be considered only in case of failure of conservative and/or endoscopic therapy and being unable to use a transjugular intrahepatic portosystemic shunt. Among surgical operations described in the literature are a variety of portocaval anastomosis and azygoportal disconnection procedures.

**Conclusions:**

To improve the results of treatment for patients with liver cirrhosis who develop acute esophageal variceal bleeding, it is important to stratify patients into risk groups, which will allow one to tailor therapeutic approaches to the expected results.

## Introduction

Esophageal variceal bleeding is the most dangerous complication in patients with liver cirrhosis. Even when using state-of-the-art treatment, mortality typically reaches 20%, and, while in the first 5 days it is mainly due to blood loss, in the next 6 weeks death is the result of the development of multiple organ dysfunction<sup>1</sup>. It has been found that important predictors of adverse outcome are the values of the hepatic venous pressure gradient (HVPG), measured within 24 hours after stabilization of hemodynamics, exceeding 20 mmHg, as well as severe liver failure. In addition, these predictors include impaired renal function, bacterial infection, hypovolemic shock, active esophageal variceal bleeding during endoscopy and early relapse with the need for transfusion of more than four doses of packed red blood cells, the presence of hepatocellular carcinoma and portal vein thrombosis<sup>2</sup>.

The Baveno VI workshop defined key events regarding variceal bleeding episodes<sup>3</sup>:

- Six-week mortality should be the primary endpoint for studies on treatment of acute variceal bleeding.
- Five-day treatment failure is defined using Baveno IV/V criteria without adjusted the blood requirement index and with a clear definition of hypovolemic shock.
- Baveno IV/V criteria correlate with 6 week mortality and should be included in future studies as a secondary endpoint to allow further validation.
- Additional endpoints should be reported including: need for salvage therapy (tamponade, additional endoscopic therapy, transjugular intrahepatic portosystemic shunt [TIPS], surgery, etc.), blood transfusion requirements and days of ICU/hospital stay.

The management of patients with liver cirrhosis who have acute esophageal variceal bleeding is complex, and requires a multidisciplinary approach. This strategy provides for early diagnosis of complications, maintaining vital body functions and specific therapy aimed at the provision of local hemostasis and reduction of portal pressure. This review examines current approaches to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding.

## Methods

PubMed, Google Scholar, and Cochrane Systematic Reviews were searched for articles published between 1987 and 2015. Relevant articles were identified using the following terms: 'esophageal variceal bleeding', 'portal hypertension' and 'complications of liver cirrhosis'. The reference lists of articles identified were also searched for other relevant publications. Inclusion criteria were

restricted to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding.

## General treatment principles for patients with liver cirrhosis who have acute esophageal variceal bleeding

### Endoscopy

Esophagogastroduodenoscopy with therapeutic manipulations aimed at stopping esophageal variceal bleeding should be performed as early as possible as there is a direct correlation between a delay of more than 15 hours and in-hospital mortality<sup>4</sup>. For better visualization, in the absence of contraindications (QT prolongation), 30–120 minutes prior to the procedure an intravenous infusion of 250 mg of erythromycin should be considered<sup>3</sup>. Erythromycin, affecting motilin receptors, increases gastric motility.

The diagnosis of esophageal variceal bleeding is made based on the presence of bleeding. In the absence of bleeding, indirect symptoms of the complication are the 'white nipple sign' and blood clots on varices, as well as blood in the lumen of the esophagus and/or stomach if other possible causes have been ruled out<sup>5</sup>.

### Assessment of severity of liver disease

For almost half a century the standard for assessing disease severity, risk of death after surgical interventions for portal hypertension and prognosis in patients with liver cirrhosis has been the Child–Turcotte–Pugh (CTP) score (Table 1). Its main disadvantages are empirical selection of the main components, using arbitrary threshold values for quantitative indicators, ambiguity of qualitative variables, as well as ignoring other critical factors such as the severity of kidney dysfunction<sup>6</sup>. However, the score is widely used

Table 1. The Child–Turcotte–Pugh score.

| Indicators         | Degree of deviation from the norm (points) |            |           |
|--------------------|--------------------------------------------|------------|-----------|
|                    | 1                                          | 2          | 3         |
| Ascites            | None                                       | Controlled | Resistant |
| Encephalopathy     | None                                       | Minimal    | Coma      |
| Bilirubin (μmol/L) | <34                                        | 34–51      | >51       |
| Albumin (g/L)      | >35                                        | 28–35      | <28       |
| Prothrombin(s)     | <4                                         | 4–6        | >6        |

The Child–Turcotte–Pugh score is obtained by adding the score for each parameter.

A: 5–8 points (low surgical risk); B: 9–11 points (medium surgical risk); C: 12–15 points (high surgical risk).

to predict treatment outcomes, as well as in retrospective and randomized clinical trials. For example, a multivariate analysis of 468 patients with liver cirrhosis admitted with acute esophageal variceal bleeding, conducted by Carbonell *et al.*<sup>7</sup>, showed that the independent prognostic factors of survival were low scores on the CTP score, young age, antibiotic prophylaxis, endoscopic therapy and the absence of hypovolemic shock. On the contrary, unfavorable variables that increase the risk of early mortality, are CTP C liver cirrhosis, leukocytosis of more than  $10 \times 10^9/L$  and portal vein thrombosis<sup>8</sup>.

The complex issues of optimization and selection of priorities of liver transplantation were the main stimulus to the development and wide use of the MELD (Model for End Stage Liver Disease) score. Like the CTP score, the MELD has a number of disadvantages. Despite the fact that the variables were selected based on multivariate statistical analysis, the final list was determined empirically. In this context, it is possible that some important factors were not taken into account. Another limitation of the MELD score is the absence of clear discriminant values. In practical terms, when no computing equipment is available, obvious difficulties may arise during the calculation of the data obtained<sup>9</sup>.

Reverter *et al.*<sup>10</sup>, in a large series of patients with acute variceal bleeding, tested the performance (discrimination and calibration) of previously described models, including the MELD score, CTP score, predictive models proposed by D'Amico *et al.*<sup>11</sup> and Augustin *et al.*<sup>12</sup>, and developed a new MELD calibration in predicting 6 week mortality after acute esophageal variceal bleeding. The authors showed that with values of MELD score greater than 19 it exceeded 20%, while with values of MELD score under 11 it was approximately 5%.

## Resuscitation

Initial resuscitation of patients with liver cirrhosis who have esophageal variceal bleeding corresponds to the general pattern of ABC (Airway open + Breath + Circulation) and is aimed at maintaining optimal delivery of oxygen to the tissues. Due to the high risk of aspiration of gastric contents and blood, especially in patients with encephalopathy and during endoscopic manipulation, it is important to pay special attention to airway patency, and in some cases to consider the need for intubation of trachea<sup>13</sup>. It is essential to maintain adequate saturation of blood with oxygen and carry out pulse oximetry. Given the massive nature of esophageal variceal bleeding, it is always necessary to ensure adequate peripheral venous access for full infusion therapy and often for transfusion of blood components.

## Restoration of circulating blood volume and blood transfusion

The issue of optimal restoration of circulating blood volume is still being debated. It is known that hypovolemia and prolonged hypotension may lead to the development of renal failure and infectious complications. However, blood transfusion must be given with caution, maintaining systolic blood pressure at 100 mmHg. This will avoid increased portal pressure and recurrence of esophageal variceal bleeding. In addition, the guidelines of the American Association for the Study of Liver Diseases recommend maintaining hemoglobin within 8 g/dL, except in patients with ongoing bleeding, coronary heart disease or brain ischemia<sup>14</sup>. In a large multicenter randomized controlled trial on 849 patients with upper gastrointestinal bleeding, limited transfusion therapy maintaining hemoglobin level of 7–9 g/dL resulted in a significantly higher 45 day survival rate than a liberal transfusion strategy and maintaining hemoglobin at 9–11 g/dL. In a separate analysis of patients with CTP A and B liver cirrhosis (31% of total) similar results were obtained, with a significant reduction in the frequency of recurrent bleeding<sup>15</sup>.

## Correction of coagulopathy

The traditional idea that disorders of hemostasis in patients who have liver cirrhosis, *a priori*, play an important role in the development of esophageal variceal bleeding, was not confirmed by recent research. Granted, their thrombocytopenia, reduced levels of coagulation factors II, V, VII, IX, X and XI, and hyperfibrinolysis contribute to anticoagulation, but it is usually compensated by adaptive changes in the hemostatic system. First, the decline in the number and functional activity of platelets is accompanied by a significant increase in the level of the plasma thromboplastic factor – von Willebrand factor, which is synthesized by activated endothelial cells as a result of hemodynamic changes and the effects of various humoral substances accompanying portal hypertension. Secondly, reduction in the level of coagulation factors is offset by the lack of natural anticoagulant proteins C, S and antithrombin, as well as significant resistance to the inhibitory action of thrombomodulin. Finally, hyperfibrinolysis may be balanced by the concomitant reduction of profibrinolytics. However, under uncontrolled esophageal variceal bleeding this balanced state of hemostasis is easily disrupted, leading to a shift of the equilibrium towards either hypo- or hypercoagulation<sup>16</sup>.

The hemostatic effect of fresh frozen plasma and platelet concentrate in this situation has not been properly proven<sup>17</sup>. No significant advantages of desmopressin treatment have been revealed, despite its ability, along with increasing factor VIII clotting and von Willebrand factor, to significantly reduce the bleeding time and

Table 2. Classification of acute kidney injury according to AKIN.

| AKI stage             | Serum creatinine criteria                                                                                                                                                                                | Urinary output criteria                                    |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| AKI stage 1 (risk)    | Increase in serum creatinine of $\geq 0.3$ mg/dL within 48 h or an increase of $\geq 150$ –200% (1.5–2-fold) from baseline                                                                               | Urinary output $< 0.5$ mL/kg/h for $> 6$ h                 |
| AKI stage 2 (injury)  | Increase in serum creatinine to 200–299% (2–3-fold) from baseline                                                                                                                                        | Urinary output $< 0.5$ mL/kg/h for $> 12$ h                |
| AKI stage 3 (failure) | Increase in serum creatinine to $\geq 300$ % ( $> 3$ -fold) or from baseline or serum creatinine of $\geq 4$ mg/dL with an acute increase of $\geq 0.5$ mg/dL or initiation of renal replacement therapy | Urinary output $< 0.3$ mL/kg/h for 24 h or anuria for 12 h |

AKIN: acute kidney injury network. AKI: acute kidney injury.

activated partial thromboplastin time<sup>18</sup>. In contrast, recombinant activated coagulation factor VII not only contributed to successful hemostasis in acute esophageal variceal bleeding, but also reduced the frequency of early relapses and positively affected 5 day mortality in patients with decompensated liver cirrhosis (over 8 points on the CTP score). However, significant barriers to its routine use are increased risk of arterial thromboembolic complications and the high cost of the drug<sup>19</sup>.

### Antibiotic therapy

Endotoxemia due to the translocation of gram-negative bacteria from the intestine plays an important role in the pathogenesis of complications of portal hypertension in liver cirrhosis and, in particular, esophageal variceal bleeding<sup>20</sup>. To prevent its early recurrence, all modern guidelines and consensus decisions point to the need for including antibiotic therapy. Guidelines recommend oral administration of 400 mg of norfloxacin every 12 hours for 7 days or, in patients with decompensated liver cirrhosis, intravenous administration of ceftriaxone, 1–2 g/day for 7 days<sup>21</sup>. In a systematic review and meta-analysis, Chavez-Tapia *et al.*<sup>22</sup> noted that the use of antibiotics significantly reduces total mortality, the frequency of recurrence of esophageal variceal bleeding and the length of hospitalization. However, the issue of mandatory use of antibiotics in patients with CTP A liver cirrhosis requires further evaluation<sup>23</sup>.

### Treatment of renal dysfunction

A threatening complication of esophageal variceal bleeding in patients with decompensated liver cirrhosis, associated with poor short-term survival, is acute kidney injury, the term that has replaced the previously used 'acute renal failure'. This condition may be accompanied by acute tubular necrosis and is due to a decrease in renal blood flow under hypovolemia, as well as bacterial infection that accompanies blood loss even in the absence of septic shock<sup>24</sup>. For a long time the traditional diagnostic

criteria of renal failure was an increase in serum creatinine level by more than 50% from baseline to threshold values greater than 1.5 mg/dL (133  $\mu$ mol/L). In recent years, the criteria have changed, essentially turning into a system for the stage-by-stage assessment of acute kidney injury, based on the determination of long-term serum creatinine level. In patients with liver cirrhosis, AKIN (acute kidney injury network) criteria have been introduced for early detection of complications and timely therapy based on process stages; these criteria have also proved to be good predictors of adverse outcomes (Table 2).

Treatment of patients who have liver cirrhosis with acute kidney injury at an early stage is to reduce the doses of diuretics, withdraw potentially nephrotoxic drugs, vasodilators and nonsteroidal anti-inflammatory drugs. Hypovolemia should be corrected with crystalloids or albumin. It is also important to detect and treat bacterial infections at an early stage. As the disease progresses, diuretics should be completely avoided, and the dose of albumin should be 1 g per kg of body weight per day, but not more than 100 g. Some experts also suggest early use of vasoconstrictors, such as terlipressin, noradrenaline or midodrine<sup>25</sup>. In particular, terlipressin is administered in bolus injections starting from 0.5–1 mg every 4–6 hours, or as a continuous intravenous infusion at 2 mg/day. If the creatinine level is not reduced by more than 25% by the third day, the amount administered by intravenous injection is increased to 2 mg every 4 hours or up to 12 mg/day in continuous infusion<sup>26</sup>.

### Nutrition

As ill-timed feeding of patients with liver cirrhosis admitted to hospital with esophageal variceal bleeding contributes to increased susceptibility to infections and impaired renal function, their feeding should be resumed 24 hours after achieving hemostasis. Because of the lower cost and the lack of complications, enteral nutrition is always preferable to parenteral. It should also be noted that there is currently no evidence in favor of low-protein diets<sup>27</sup>.



## Prevention of hepatic encephalopathy

According to the recommendations of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, in order to prevent hepatic encephalopathy in patients who have liver cirrhosis with esophageal variceal bleeding, lactulose is administered 25 ml every 12 hours to achieve 2–3 soft stools, with subsequent dose selection for maintaining 2–3 soft stools per day<sup>28</sup>.

## Specific treatment of acute esophageal variceal bleeding

In accordance with current clinical guidelines, specific activities of the first line for esophageal variceal bleeding should combine vasoactive drug therapy with endoscopic methods of hemostasis<sup>3</sup>.

### Vasoactive drug therapy

The effect of drugs used for the treatment of portal hypertension, is, mainly, the reduction of splanchnic hyperemia and decrease in severity of hyperdynamic circulatory status, which helps reduce the pressure in both the portal vein and varices<sup>29</sup>. Once bleeding has occurred there is a real threat to the patient's life; the drugs should be administered as early as possible, ideally before hospital, and for at least 5 days<sup>30</sup>. A meta-analysis by Wells *et al.*<sup>31</sup> showed that timely application of vasoactive drugs ensures effective hemostasis, reduces the need for blood transfusions, the duration of hospitalization and 7 day mortality.

Terlipressin (N-triglycer-8-lysine-vasopressin), a synthetic analogue of vasopressin, the hormone of the posterior pituitary, with a longer biological activity and a better safety profile, acts on specific V<sub>1</sub> receptors of the smooth muscles of the arteries, in particular the arterioles of the abdominal cavity, and causes their contraction. Møller *et al.*<sup>32</sup>, having studied the influence of terlipressin on hemodynamics in patients with liver cirrhosis with portal hypertension, found that an intravenous bolus of 2 mg of the drug leads to a rapid reduction of portal pressure and hepatic blood flow (by 17% and 29% respectively), increased blood pressure and systemic vascular resistance (by 26% and 61% respectively), as well as a decrease in cardiac output, heart rate and artery distensibility (by 18%, 11% and 32% respectively).

The effect of terlipressin remains up to 4 hours, which allows one to administer it in periodic intravenous injections, but if necessary a continuous infusion is also possible<sup>33</sup>. For adults with body weight over 40 kg with esophageal variceal bleeding, terlipressin is injected every 4 hours by 2 mg in the first 1–2 days and by 1 mg

for the 2–5 following days<sup>34</sup>. In these periods, its efficiency is 75–80% and 67%, respectively<sup>35</sup>.

The most frequent side effects associated with the use of terlipressin are moderate abdominal pain, arterial hypertension, and hyponatremia; these are usually reverted after canceling the drug. Severe cardiovascular and ischemic disorders occur in approximately 15% of patients. In this regard, terlipressin is not recommended for patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease, cardiomyopathy, bronchial asthma, chronic obstructive pulmonary disease, or having cardiac rhythm disturbance; caution should be used for elderly and/or hypertensive subjects<sup>36</sup>.

Somatostatin is a cyclic 14-amino acid peptide, which is secreted by the nerve, endocrine and enteroendocrine cells in the hypothalamus and the digestive system (stomach, intestines, and delta cells of the pancreas). Synthetic analogues of the drug (octreotide, octride, vapreotide, etc.) are also used to treat esophageal variceal bleeding in patients with liver cirrhosis.

Somatostatin, by blocking G-protein coupled ET<sub>A</sub> receptors, prevents stellate cells of the liver from contraction induced by endothelin-1, and contributes to the expansion of sinusoids and the reduction of hepatic vascular resistance. A similar effect of octreotide is associated with a decrease in intracellular Ca<sup>2+</sup><sup>37</sup>.

The reduction of portal inflow caused by somatostatin is explained by the weakening of splanchnic hyperemia due to somatostatin's antisecretory effect on the secretion of glucagon and other gastrointestinal vasodilating peptides. The positive effect of octreotide on splanchnic blood flow is due to the potentiation of protein kinase of C-dependent vasoconstrictors through subtype 2 somatostatin receptors<sup>38</sup>.

In patients who have liver cirrhosis with portal hypertension an intravenous bolus of 250 µg of somatostatin contributes to a 28.4% reduction of wedged hepatic venous pressure and a 15–71% reduction of the pressure in the esophageal varices. Continuous infusion of the drug reduces wedged hepatic venous pressure by 17% and hepatic blood flow by 17.4%. High doses of somatostatin (500 µg/h) have a more pronounced effect on these indicators, also reducing azygos blood flow by 45% in the case of bolus injection and by 23% with continuous infusion. Unfortunately, the positive effect of the drugs in this group on hemodynamics is short, despite the much larger half-life of synthetic analogues of somatostatin compared with the natural hormone; this is probably due to desensitization or tachyphylaxis<sup>39</sup>.

With bleeding from esophageal varices, 250 µg of somatostatin is initially injected as a bolus, and then in the form of continuous infusions, 250–500 µg/h for 2–5 days. The first dose of octreotide and vapreotide is 50 µg followed by an infusion of 50 µg/h. Severe complications in the course of this therapy are rare. Approximately 21% of

patients may have vomiting and hyperglycemia, which, as a rule, can be easily remedied<sup>40</sup>.

In general, somatostatin showed sufficient efficacy in the treatment of esophageal variceal bleeding, and in its effects on hemostasis and mortality it was similar to terlipressin, with a better safety profile<sup>41</sup>. At the same time, the efficacy of octreotide as monotherapy for portal hypertension is not currently established<sup>42</sup>.

## Endoscopic methods of hemostasis

Endoscopic sclerotherapy of esophageal varices has been developing since the mid-1970s. In this method, a sclerosant is injected directly into the varicose veins of the gastroesophageal junction region (5% solution of ethanolamine oleate), and paravasally (1% solution of aethoxysklerol (polidocanol))<sup>43</sup>. According to Laine *et al.*<sup>44</sup>, endoscopic sclerotherapy can control esophageal variceal bleeding in at least 62% of patients, it significantly reduces the frequency of early recurrence and has a positive impact on early mortality. It had no advantages over vasoactive drugs<sup>45</sup>, but with simultaneous use of both methods, the hemostatic effect was higher than with each of them individually<sup>46</sup>.

There are early (within the first 24 hours after injection) and late (a few days or weeks) complications of endoscopic sclerotherapy, which can be local and systemic. Moderate transient impairment of esophageal motility in the presence of varices is often observed. However, persistent dysphagia is usually associated with the formation of cicatricial strictures, the risk of which depends on the number of procedures and the amount of sclerosant injected. A serious late complication is ulcers of the esophageal mucosa, and extensive lesions can cause bleeding and lead to necrosis of the wall, perforation and mediastinitis. Although bacteremia after endoscopic sclerotherapy is observed in every second patient, it is normally latent, and the majority of infectious complications such as meningitis, paranephritis, brain abscess, endocarditis, and pneumonia, are rare<sup>47</sup>. One disadvantage of the procedure, noted in a number of cases, is the increase of HVP, which may be the cause of early recurrent bleeding<sup>48</sup>.

Endoscopic band ligation (EBL) of esophageal varices, proposed by G. V. Stiegmann in the late 1980s<sup>49</sup>, is currently the endoscopic method of choice for the treatment of variceal bleeding. Unlike the induction of chemical inflammation and thrombosis after the introduction of sclerosing agents, the elastic ring ligature, covering the areas of the mucosal and submucosal layers of the esophagus in the area of varix, causes strangulation and subsequent fibrosis. Since the involved tissue volume is small, ulceration that occurs is always superficial, and pathological changes are insignificant. Compared with

endoscopic sclerotherapy, EBL of esophageal varices obliterates them more rapidly and is accompanied by less early recurrence of bleeding<sup>50</sup>. In addition, the combined use of endoscopic EBL with terlipressin or octride was more effective than therapy with vasoactive drugs alone<sup>51,52</sup>.

## Sengstaken–Blakemore tube and self-expandable metal stents

The use of a Sengstaken–Blakemore triple-lumen tube allows the achievement of primary hemostasis in 40–90% of patients with acute esophageal variceal bleeding. However, the high frequency of early relapses after deflation and the risk of developing life-threatening complications make its use appropriate only in cases of refractory bleeding if the above methods cannot be performed<sup>53</sup>.

An alternative to balloon tamponade may be the installation of self-expandable metal stents specifically designed for the treatment of acute esophageal variceal bleeding. This method has fewer side effects, allows enteral nutrition, and the possibility of long-term stent placement makes it possible to stabilize the patient's condition and plan for bridge therapy, e.g. TIPS or repeated endoscopic treatment. If the procedure is performed successfully, the efficiency of primary hemostasis reaches 70–100%. The main drawback is stent migration, which occurs in 20% of patients<sup>54</sup>.

## Transjugular intrahepatic portosystemic shunt

Numerous studies have shown that TIPS is an extremely useful technique for the treatment of acute esophageal variceal bleeding, and can achieve final hemostasis in up to 90–95% of cases. However, most current clinical guidelines classify it as second line therapy and recommend using it only if pharmacological and/or endoscopic therapy is ineffective. This approach is explained by TIPS-related high mortality, especially in patients with decompensated liver cirrhosis. It was noticed that in some of them that initially stable liver function by the time of using TIPS was compromised by refractory bleeding, which caused the unfavorable outcome<sup>55</sup>.

Experience gained in the use of TIPS, as well as the development of new technologies, in particular the introduction of expanded polytetrafluoroethylene-covered stents with significantly prolonged patency and reduced incidence of encephalopathy, was the impetus for a reconsideration of the role of this method in the treatment of esophageal variceal bleeding.

In the randomized, clinical trial by García-Pagán *et al.*<sup>56</sup>, 31 patients with liver cirrhosis with acute esophageal variceal bleeding received standard first-line therapy (pharmacotherapy–EBL group), and 32 had been treated

with vasoactive drugs plus endoscopic therapy to treatment with a polytetrafluoroethylene-covered stent within 72 hours after randomization (early TIPS group). During a median follow-up of 16 months, rebleeding or failure to control bleeding occurred in 14 patients in the pharmacotherapy–EBL group compared with 1 patient in the early TIPS group. The 1 year actuarial probability of remaining free of this composite endpoint was 50% in the pharmacotherapy–EBL group versus 97% in the early TIPS group. Sixteen patients died (12 in the pharmacotherapy–EBL group and 4 in the early TIPS group). The 1 year actuarial survival was 61% in the pharmacotherapy–EBL group versus 86% in the early TIPS group. Seven patients in the pharmacotherapy–EBL group received TIPS as rescue therapy, but four died. The number of days in the intensive care unit and the percentage of time in the hospital during follow-up were significantly higher in the pharmacotherapy–EBL group than in the early TIPS group. No significant differences were observed between the two treatment groups with respect to serious adverse events. Thus, in these patients with liver cirrhosis who were hospitalized for acute variceal bleeding and at high risk for treatment failure, the early use of TIPS was associated with significant reductions in treatment failure and in mortality.

In a prospective study, Rudler *et al.*<sup>57</sup> showed that early TIPS placement effectively prevents rebleeding in high risk patients with liver cirrhosis and variceal bleeding but does not significantly improve survival. The authors emphasize the importance of investigating cardiac failure before the procedure.

The Baveno VI workshop recommends early TIPS with expanded polytetrafluoroethylene-covered stents within 72 h (ideally <24 h) in patients with esophageal variceal bleeding at high risk of treatment failure (e.g. CTP C liver cirrhosis with less than 14 points or CTP B liver cirrhosis with active bleeding) after initial pharmacological and endoscopic therapy<sup>3</sup>.

## Surgical treatment

Surgical intervention for acute esophageal variceal bleeding is rare, and can only be considered if conservative and/or endoscopic therapy fails, and TIPS cannot be used for technical or organizational reasons or due to anatomic problems. Among surgical treatments are portacaval anastomosis and azygoportal disconnection operations.

It has been shown that distal splenorenal shunt or small-diameter portacaval H-graft shunt (partial portosystemic shunt) can be an effective and safe emergency procedure. High mortality has been observed in patients with CTP C liver cirrhosis undergoing portal decompression<sup>58,59</sup>.

A unique experience of applying emergency direct portacaval anastomosis for over 50 years was recently presented by the surgical clinic of the University of California in San Diego. In two prospective randomized clinical trials involving a total of 365 patients with liver cirrhosis, they compared the efficiency of this operation with endoscopic sclerotherapy and TIPS. Patients were almost identical in terms of the degree of liver dysfunction, a third of them had CTP C liver cirrhosis. In all groups, the time of the start of therapy did not exceed 8–12 hours. In the end, primary hemostasis was achieved in the endoscopic sclerotherapy group in 20% of cases, TIPS in 22%, portacaval shunting in 97–100%; recurrent encephalopathy occurred in 35%, 61%, and 15% of cases, respectively. Survival was five times higher in patients having undergone surgery<sup>60</sup>. It should be noted that other authors have not obtained similar results.

Voros *et al.*<sup>61</sup> reported that a modified Sugiura operation performed urgently on 46 patients with liver cirrhosis (4 with CTP A, 16 with CTP B, and 26 with CTP C), helped to stop esophageal variceal bleeding in all of them. Postoperative mortality amounted to 23.9%, with nine patients with CTP C and two with CTP B. In the long-term observation period of 14 months to 22 years, the recurrence of bleeding occurred in 58.4% of cases, and the 5 year survival rate was 62.5%.

## Conclusion

Progress in understanding the pathogenesis of portal hypertension under liver cirrhosis and the development of new technologies has led to notable advances in controlling esophageal variceal bleeding. Yet, even using current standards of treatment, mortality associated with esophageal variceal bleeding remains high. We can assume that stratification of patients into risk groups will enable tailoring therapeutic approaches to the expected results for each of the groups, namely, initiating early use of more aggressive methods in patients with predictors of poor outcomes, and to protect individuals with a good prognosis from unnecessary invasive procedures. Further study of this issue will contribute to improved treatment of this severe complication.

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