Mini-Symposium

Treatment of acute variceal bleeding

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Abstract

The management of variceal bleeding remains a clinical challenge with a high mortality. Standardisation in supportive and new therapeutic treatments seems to have improved survival within the last 25 years.

Although overall survival has improved in recent years, mortality is still closely related to failure to control initial bleeding or early re-bleeding occurring in up to 30–40% of patients. Initial procedures are to secure and protect the airway, and administer volume replacement to stabilize the patient.

Treatment with vasoactive drugs should be started as soon as possible, since a reduction in portal pressure is associated with a better control of bleeding and may facilitate later endoscopic procedures. Vasopressin and its analogues Terlipressin and somatostatin and analogues are the two types of medicine, which has been evaluated. In meta-analysis, only Terlipressin have demonstrated effects on control of bleeding and on mortality. Somatostatin and its analogues improve control of bleeding, but show in meta-analysis no effects on mortality.

Approximately 20% of patients with variceal bleeding will suffer from an infection, when they are hospitalized. Invasive procedures will further increase the risk of bacterial infections. Meta-analysis of clinical trials comparing antibiotics with placebo demonstrates that antibiotic prophylaxis improves survival with 9% ($p < 0.004$). Quinolones or intravenous cephalosporins should be preferred.

Early endoscopy should be performed in patients with major bleeding. Endoscopic therapy increases control of bleeding and decreases the risks of rebleeding and mortality. Ligation is probably more effective than sclerotherapy with fewer complications and should therefore be preferred, if possible. In case of gastric varicel bleeding, tissue adhesives should be used.

In conclusion: Improvements in resuscitation and prevention of complications have together with introduction of vasoactive drugs and refinement of endoscopic therapy majorly changed the prognosis of the patient presenting with variceal bleeding.

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1. Introduction

Bleeding in portal hypertension is most frequently caused by gastro-oesophageal varices (65–70%) and by isolated gastric varices (10–15%). Other frequent causes of acute bleeding in portal hypertension are portal hypertensive gastropathy, Mallory Weiss lesions and peptic ulcer bleeding [1,2].

The management of variceal bleeding remains a clinical challenge with a high mortality. Standardisation in supportive and new therapeutic treatments seems to have improved survival within the last 25 years [3,4]. The beneficial effect on survival has been observed in parallel with introduction of drugs, which are capable to decrease portal pressure, optimised endoscopic therapy, antibiotics and interventional radiologic procedures.

Six weeks mortality has in this period decreased from approximately 40% to approximately 15%. Although overall survival has improved in recent years, mortality is still closely related to failure to control the initial bleeding or early re-bleeding, which occurs in up to 30–40% of patients within the first 5 days after the initial bleeding episode [5,6].

Since variceal bleeding is a medical emergency, all variceal bleeding episodes should be managed in an intensive care setting by a team of experienced medical staff, includ-
ing well-trained nurses, clinical hepatologists, endoscopists, anesthesiologists, availability of surgery and interventional radiology procedures.

The main pharmacologic treatments are somatostatin and its analogues or Vasopressin and its analogues [7].

The rational for the pharmacologic treatment is to reduce portal pressure by vasoconstrictor drugs that act by decreasing portal inflow and mediate splanchnic vasoconstriction [8]. Pharmacological treatment is easily administered and can be started during transferal to hospital by medical or paramedical teams.

On the contrary, emergency endoscopic therapy requires skilled endoscopists and especially sclerotherapy and less frequent ligation are associated with adverse events in 10–20% of patients [4,9–11].

Initial procedures and treatment are identical for patients with oesophageal variceal bleeding and patients with gastric variceal bleeding.

The management of gastric varices that do not respond to pharmacologic treatment will often differ from the treatment of oesophageal varices and the two types of bleeding will therefore partly be covered separately.

2. Diagnosis

Variceal haemorrhage is defined as bleeding from an oesophageal or gastric varix at the time of endoscopy. Varices are accepted as the bleeding source, when a venous (non-pulsatile) spurt is seen or when there is fresh bleeding from the esophageal-gastric junction in the presence of varices or when there is fresh blood in the fundus, when gastric varices are present. In the absence of active bleeding (up to 50% of cases) either a “white nipple sign” [12] or the presence of medium or large varices with no other potential bleeding lesions suggest varices as the source of haemorrhage.

3. Factors modifying key events in acute variceal bleeding

Homogeneous definitions of entry criteria and key events within and across clinical trials are crucial for the evaluation and understanding of clinical trials, whether they are multicenter and randomised or not.

The prognosis in patients presenting with upper gastrointestinal bleeding is determined by portal pressure [13] and clinical factors, such as severity of liver disease and the magnitude of bleeding, and biochemical status. In well-compensated patients characterized by absence of jaundice and without ascites and encephalopathy, mortality is low [1], while bleeding is associated with a high mortality in decompensated patients, especially in case of renal impairment. The best-validated prognostic scores in cirrhosis are Child-Pugh score [14] and the Model for End-stage Liver Disease [15]. Child-Pugh score has been validated in several trials and the predictive accuracy has overall shown to be satisfactory. Child-Pugh score includes parameters, such as ascites and encephalopathy, which in the acute setting often rely on a subjective judge, while MELD score purely rely on biochemical values. Inclusion of subjective parameters as entry criteria may lead to undesired selection bias, if participating centres do not strictly include patients aimed for the actual trial. In a recent trial of Factor VIIa entry criteria were patients with signs of active oozing or spurring variceal bleeding and Child-Pugh score ≥9. Although, signs of active bleeding were clearly stated in the protocol, some centres misinterpreted this information and included patients with less severe bleeding due to endoscopic therapy. Because of the complexity of the trial, it was decided to have a Clinical Evaluation Committee (CEC). CEC received continuously case record forms from the centers. In case of minor protocol violations a mail was submitted to the center with information of the mistake, while in case of a severe violation a yellow card was issued to the center (Fig. 1a), and in case of another yellow card the center was excluded from the trial. These efforts led to more focus on targeting the high-risk patients, providing clarification on the definition of active bleeding and correct application of Child-Pugh score, which might explain the increase in the failure rate in the placebo group throughout the trial (Fig. 1b).

Experience from this trial suggests caution with regard to the use of inclusion criteria with subjective components, such as Child-Pugh classification recommended by the Baveno conferences [16]. Furthermore, presence of an independent CEC with expertise within the field seems to improve the quality of the trial.

4. Resuscitation and correction of hypovolaemia

Initial procedures are to secure and protect the airway, especially in order to prevent pulmonary aspiration, an increased risk phenomena, which is further exacerbated by endoscopic procedures. Therefore intubation should be considered at an early stage, especially in encephalopathic patients or in case of uncontrolled severe bleeding. Patients should be monitored with pulse oximetry with a possibility to supply oxygen and presence of facilities for suction of airway.

Since variceal bleeding is often massive, it is essential to introduce at least one large (14–18 gauge) intravenous line in order to correct hypovolaemia and administer blood products, if necessary.

Volume replacement should be initialised as soon as possible to prevent complications such as hypovolemic shock or decreased perfusion of vital organs. Plasma substitutes such as gelatine-based colloids, albumin or fresh frozen plasma are widely used. There is no specific evidence to support the selection of the type of plasma expander. If hypovolaemia is not corrected renal failure may develop with an increased risk of mortality [17]. However, special care should be taken not to overtransfuse the patients since this may lead to an increase in portal pressure and thereby a higher risk of early
Fig. 1. (a) Number of correction mails sent to trial centers at each of eight meetings in the Clinical Evaluation Committee. Corrections decrease over time. (b) Number of end points for patients randomized to either two different doses of factor VIIa or placebo showing an increase in the rate of end points in the placebo group. Constructed from data of Bosch et al. [50].

Re-bleeding as well as pulmonary congestion [18]. Transfusion with red packed blood cells should be preferred with the aim of achieving a haematocrit between 25 and 30% (haemoglobin at approximately 8 g/dL or 5 mmol/L), depending on co-morbidities, etc.

Transfusion should be individualized according to bleeding severity, presence of other coagulopathies and may in seldom cases include platelet transfusion.

Nasogastric intubation and aspiration is often practiced, but has never been documented to improve survival or decrease complication rate and is therefore still controversial. In cases of massive uncontrolled bleeding, insertion of a Sengstaken tube should be considered. The use of balloon tamponade should be kept on a minimum due to the high rate of complications such as aspiration with pneumonia, necrosis of oesophageal mucosa and obstruction of airways [19,20].

When therapy aiming at maintaining haemodynamic stability is initiated vasoactive compounds and antibiotics should be administered. Diagnostic endoscopy should be performed as soon as possible after admission (within 12 h), especially in patients with clinical significant bleeding. A longer delay (within 24 h) can be accepted in case of minor bleeding which response completely to vasoconstrictors.

5. Treatment and prevention of complications to bleeding

5.1. Prevention and treatment of infection

Bacterial infections are frequent in cirrhosis, and up to 20% of patients with cirrhosis and gastrointestinal bleeding...
have a bacterial infection at initial hospitalisation [21–25] and further 50% may later during the hospitalisation develop infection. Most frequent causes of bacterial infections are urinary tract infections (12–29%) caused by gram-negative bacilli (E. coli or Klebsiella), spontaneous bacterial peritonitis (7–23%) caused by gram-negative bacilli and aerobic gram-positive cocci and Staphylococcus species [23,24]. Presence of bacterial infections seem to be closely related to prognosis in bleeding cirrhotic patients, moreover bacterial infections are also associated with a higher risk of variceal rebleeding. Two meta-analysis [21,22] have uniformly shown that short-term antibiotic prophylaxis has a significant beneficial effect on mortality with a decrease of approximately 9% as well as a decrease in the incidence of bacterial infections. The choice of antibiotic and route of administration does vary within the eight controlled trials, which compared antibiotics with placebo or no intervention. Five of the eight trials tested Quinolones either alone or associated with Amoxicillin/Clavulunic acid. The doses used ranged from 400 to 1000 mg daily, and the treatment duration varied from one single dose up to 10 days. A relative risk reduction of 29% (95% CI, 6–46%) in number of death and of 58% (95% CI, 48–66%) in the incidence of bacterial infections was observed in patients receiving antibiotic prophylactics compared to placebo or no intervention.

Quinolones are easily absorbed, and the results of the trials show that oral administration seems equal to intravenous administration. Quinolones (i.e. Norfloxacin) 400–500 mg twice a day for 5–7 days is reasonable to suggest, and oral administration should be preferred, if possible. However, a recent randomised controlled study comparing oral Norfloxacin (400 mg twice daily) and intravenous Ceftriaxone (1 g per day) intravenously in patients with severe cirrhosis and bleeding, showed a significantly higher proportion of bacterial infections in patients receiving Norfloxacin (33% vs. 11%, p = 0.03) [25]. In conclusion, all cirrhots with upper gastrointestinal bleeding should receive prophylactic treatment with antibiotics either Quinolones or intravenous cephalosporin’s for 5–7 days. Amino-glycosides should be avoided due to risk of renal toxicity [26].

### 5.2. Renal function

Adequate amounts of fluid should be administered in order to keep the urine output maintained over 40 ml/per hour. The intravascular volume should be maintained and nephrotoxic drugs should be avoided, especially amino-glycosids and NSAID. Renal failure may develop due to variceal bleeding and hypovolaemic shock in which case dialysis should be considered. Tense ascites can be treated with paracentesis and in case of high volume paracentesis in combination with albumin replacement [27].

### 6. Specific treatment of variceal bleeding in cirrhosis

#### 6.1. Vasoactive drugs

The aim of pharmacologic treatment is to reduce portal pressure, which relate closely to variceal pressure. The rational behind this treatment is that a higher portal pressure (>20 mmHg) is associated with a less favourable prognosis as shown by Moitinho et al. and Vinel et al. [13,28] and more recently confirmed in a study by Villanueva et al. [29], who observed that patients with variceal bleeding and a reduction in portal pressure during somatostatin infusion had a better outcome than patients without a pharmacological effect.

Vasoactive drugs can be administered easily, they are rather safe and do not require skilful personal. The treatment can be initialised in the hospital, at home or during transfer to the hospital, which may improve survival in patients with massive bleeding. Furthermore, vasoactive treatment may facilitate the endoscopic procedure [30].

Two different types of medication are actually used in variceal bleeding with different kind of action. Vasopressin and its analogue Terlipressin and natural somatostatin or its analogues.

It is difficult to compare the efficacy of the various drugs because the protocols vary with respect to the duration of administration of the drugs, the time points the drugs are administered with respect to endoscopy, whether they are compared to placebo another vasoactive drug or with endoscopy or combination thereof.

#### 7. Terlipressin

Terlipressin is a long-acting synthetic vasopressin analogue with fewer cardiovascular side effects compared to vasopressin. Patients with cirrhosis and portal hypertension exhibit a hyperdynamic circulation with vasodilatation. Terlipressin modifies systemic haemodynamics with a decrease in cardiac output and an increase in the arterial blood pressure and the systemic vascular resistance.

This leads to a decrease in splanchnic inflow. This decline together with vasoconstriction of the splanchnic vascular bed decreases portal pressure with approximately 20% after a single dose [31]. The effect is achieved within 30 min and is still significant 4 h after administration. A meta-analysis of the seven published randomised controlled trials comparing placebo and Terlipressin shows that Terlipressin is more effective than placebo for control of variceal bleeding [32]. The overall efficacy of Terlipressin in controlling acute variceal bleeding is 75–80%. The meta-analysis indicates that Terlipressin was associated with a statistically significant reduction in all cause mortality compared to placebo (relative risk (RR) 0.66, 95% confidence interval, 0.49–0.88). The beneficial effect on mortality was mainly due to a significant decrease in failure to control acute bleeding for patients receiving terlipressin (RR 0.63 (0.45–0.89)). Terlipressin has
been compared to somatostatin in three trials [33–35] and to endoscopic sclerotheraphy in one study [36]. No statistically significant difference was observed between terlipressin and either somatostatin or endoscopic treatment in any of the measured outcomes. Terlipressin is the only vasoactive treatment that has been shown to document effect in meta-analysis on mortality after variceal bleeding.

Furthermore, Terlipressin has also a beneficial effect on renal function in patients with decompensated cirrhosis and in hepato-renal failure [37, 38] and may thereby prevent renal failure, which is frequently observed in patients with variceal bleeding. Most likely, it should be initiated when variceal bleeding is suspected at a dose of 2 mg/4 h for the first 48 h, and it may be continued for up to 5 days at a lower dose of 1 mg/4 h or 12–24 h after cessation of bleeding.

Side effects of Terlipressin are related to vasoconstriction, such as myocardial ischaemia, intestinal infarction and limb ischaemia [39].

8. Somatostatin and analogues

Somatostatin has been widely used in the treatment of acute variceal bleeding. The best effect is most likely achieved by bolus injections. Somatostatin reduces portal pressure (HVPG) of approximately 17% without affecting systemic haemodynamics [40]. The effect on HVPG has also been proven during active bleeding [40]. The effect of Octreotide on portal pressure is far more controversial [41]. Continuous infusion seem to have no effect on HVPG [42, 43], and the effect seems to vanish during repeated bolus injections [44]. However, infusion of Octreotide is able to prevent the increase in portal pressure after a meal, which may have some similarities with blood in the intestine during bleeding. The optimal dose of Octreotide is poorly defined. It is usual given as an initial bolus of 50 μg followed by an infusion of 25–50 μg/h.

Somatostatin has in a single randomised clinical trial significantly improved the rate of control of bleeding [45]. A meta-analysis of all randomised controlled trials comparing somatostatin and its analogues observed a reduction of patients failing to control acute bleeding with a relative risk reduction of 0.67 (0.53–0.86) and a borderline significant decrease in risk of rebleeding [46]. However, despite beneficial effect on control of bleeding, somatostatin and its analogues remain yet to demonstrate effect on mortality rate. Somatostatin and octreotide have been compared to sclerotherapy showing no difference in efficacy and a lower number of major complications [9, 29]. Although, the efficacy of Octreotide is controversial, the rate of rebleeding is reduced, when administered on top of sclerotherapy [47]. Side effects of octreotide and somatostatin are seldom and less frequent than with terlipressin.

Usual scheme for somatostatin administration is an initial bolus of 250 μg followed by a 250 μg/h infusion, which can be maintained until 24 h bleeding free period.

9. Recombinant factor VIIa

Patients with cirrhosis may often suffer from coagulopathy, which may progress during bleeding. Factor VIIa is capable almost to [48] normalise the coagulation system, even during bleeding. The drug has been evaluated in two randomised clinical trials as an additive to endoscopic and vasoactive therapy [49, 50]. Overall no effect was observed on composite end-point (control of acute bleeding, rebleeding rate and mortality). In the second trial, which only involved patients with Child-Pugh score of ≥ 9, a significant decrease in 42-day mortality was observed.

This may seem surprising since factor VIIa was administered for less than 48 h, and no effect occurred on control of acute bleeding or rebleeding within the first 5 days. It can be speculated that factor VIIa has a selective effect on the clot formation on the varix and thereby decrease the risk of rebleeding after day 5, since the decrease in 42-day mortality was accompanied by a reduction in rebleeding rate in the period day 5–42. Prevailing data and the cost of factor VIIa cannot justify to recommend factor VII a as a first line therapy for variceal bleeding. It can only be considered in cases as rescue therapy, when all other treatments have failed.

10. Conclusion, vasoactive therapy

Treatment with a vasoactive drug should be initiated on admission of a patient with portal hypertension and suspicion of variceal bleeding. Since trials with Terlipressin show no heterogeneity, while trials dealing with somatostatin and its analogues show heterogeneity, and are without significant effect on mortality, which is decreased by terlipressin, this drug should be first line treatment, if it is available. Somatostatin and its analogues may have equal effect, and should be used if terlipressin is not administered. Terlipressin and somatostatin or analogues given in combination have never been evaluated.

11. Endoscopic therapy

11.1. Gastro-oesophageal varices

Endoscopic therapy is widely used for treatment of variceal bleeding. Sclerotherapy has been proven effective in control of acute bleeding and decreases the 42-day mortality, and is also effective in preventing variceal rebleeding compared to sham therapy or medical therapy with vasopressin or balloon tamponade [51]. A meta-analysis of five studies (n = 251) comparing sclerotherapy with sham treatment, balloon tamponade and/or vasopressin in patients with active variceal bleeding showed a significant beneficial effect of sclerotherapy on control of acute bleeding (OR 8.5 (3.6–20.0)), rebleeding during first 2 weeks hospitalisation (OR 0.36 (0.21–0.62)) and mortality (OR 0.57 (0.33–0.98)).
However, endoscopic therapy requires a skilled endoscopist and especially sclerotherapy is quite frequent associated with adverse events [9,52] such as aspiration, pneumonia, infections, ulcers with bleeding and after long term treatment oesophageal stenosis. Banding ligation has been compared with sclerotherapy in several RCT’s for the long-term prevention of variceal bleeding and found superior to sclerotherapy [52]. Banding ligation has fewer complications and fewer procedures are needed to eradicate oesophageal varices compared to sclerotherapy, and should therefore most likely be preferred, although few RCT’s have compared emergency sclerotherapy with emergency banding [53–55]. Ligation can in case of severe and profuse bleeding be difficult to perform, because the blood in oesophagus may fill the plastic cap on which the elastic bands are placed and thereby decrease the field of the view. Initial endoscopic therapy may in such cases be sclerotherapy.

Endoscopic therapy and vasoactive treatment show equal efficacy with a control of bleeding in 80–85% patients. Vasoactive treatment has not been compared with endoscopic ligation while a meta-analysis reported more frequent adverse events with sclerotherapy compared to vasoactive drugs. A reasonable recommendation is initially to treat all patients with vasoactive drugs, and only in failures of vasoactive treatment to perform endoscopic therapy in the very acute setting, especially in cases when a skilled endoscopist is not available. Ligation should be preferred (Fig. 2).

No other endoscopic treatments have shown efficacy in large controlled trials in patients with gastro-oesophageal bleeding varices.

12. Combined treatment

Since endoscopic therapy and medical therapy with vasoactive drugs each have been reported to control bleeding in up to 80–85% of patients and their mode of action are completely different, a synergistic effects of the two treatments can be anticipated. A meta-analysis of Banares and co-workers [36], who compared endoscopic therapy with combined endoscopic and pharmacologic treatment, showed that control of acute bleeding was more often achieved with combined treatment than after endoscopic treatment alone. Eight studies involving 939 patients were included in the meta-analysis finding a beneficial effect on control of bleeding of OR 1.12 (1.02–1.23) and control of 5-day bleeding risk of OR 1.28 (1.18–1.39). In total eight and five patients were needed to safe one control of acute bleeding and five for control of 5-day bleeding, respectively. However, no significant effect could be demonstrated on mortality (OR 0.73 (0.45–1.18)).

![Algorithm for bleeding esophageal varices](image)

**Fig. 2. Algorithm for treatment of patients with acute variceal bleeding.**
13. TIPS

TIPS can be used as a rescue intervention when other therapies have failed. This subject is in the actual journal covered in another review.

14. Isolated gastric varies

Although gastric varies seem to bleed less frequent than oesophageal varices, the intensity of the bleeding and transfusion requirements are often greater, which lead to a higher mortality once bleeding has occurred [56,57]. There is a lack of randomised controlled trials, which evaluate various kinds of treatments in gastric variceal bleeding. Endoscope sclerotherapy or ligation are often difficult to accomplish in isolated fundic varies [58].

Treatment with tissue adhesives has within the last decade become more widespread. Lo et al. [59] observed in a study of 60 patients randomised to N-buty1-2-cyanoacrylate or ligation a significantly higher rate of haemostasis in patients randomised to glue. An observation supported by another trial comparing sclerotherapy with glue, which in the subset of 17 patients with active bleeding from gastric varices, more frequent observed obliteration of varices in patients treated with glue (100% vs. 44%) [60]. Complications are primarily thrombo-embolic such as pulmonary embolism, stroke and coronary embolism [61].

Transjugular intrahepatic portosystemic shunt (TIPS) has been used extensively in oesophageal variceal bleeding There is only limited data on TIPS treatment for gastric varices due to this type of bleeding being less common. TIPS could in this setting be an alternative treatment as first line therapy, because endoscopic treatment is more complicated with less favourable results in gastric variceal bleeding. In a study of 28 patients with actively bleeding fundal varices there was a 96% initial haemostasis and 28% rebleeding rate [62]. Balloon tamponade is often efficient as a bridge to a more definite treatment [63].

In conclusion: Gastric varices should be treated pharmacologically as gastro-oesophageal varices. Endoscopic therapy should include tissue adhesives (N-buty1-2-cyanoacrylate) [64].

15. Conclusion

In recent years clinical trails have documented several treatment modalities, which improve morbidity and mortality in acute variceal bleeding. To transpose these results to daily clinical practice in non-selected patients, departments should have specific routines and algorithms for acute variceal bleeding. These routines shall ensure immediate treatment based on best evidence.

Conflict of interest statement
None declared.


