GUIDELINES FOR CLINICAL PRACTICE

Acute esophageal variceal bleeding: Current strategies and new perspectives

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Abstract

Management of acute variceal bleeding has greatly improved over recent years. Available data indicates that general management of the bleeding cirrhotic patient by an experienced multidisciplinary team plays a major role in the final outcome of this complication. It is currently recommended to combine pharmacological and endoscopic therapies for the initial treatment of the acute bleeding. Vasoactive drugs (preferable somatostatin or terlipressin) should be started as soon as a variceal bleeding is suspected (ideally during transfer to hospital) and maintained afterwards for 2-5 d. After stabilizing the patient with cautious fluid and blood support, an emergency diagnostic endoscopy should be done and, as soon as a skilled endoscopist is available, an endoscopic variceal treatment (ligation as first choice, sclerotherapy if endoscopic variceal ligation not feasible) should be performed. Antibiotic prophylaxis must be regarded as an integral part of the treatment of acute variceal bleeding and should be started at admission and maintained for at least 7 d. In case of failure to control the acute bleeding, rescue therapies should be immediately started. Shunt therapies (especially transjugular intrahepatic portosystemic shunt) are very effective at controlling treatment failures after an acute variceal bleeding. Therapeutic developments and increasing knowledge in the prognosis of this complication may allow optimization of the management strategy by adapting the different treatments to the expected risk of complications for each patient in the near future. Theoretically, this approach would allow the initiation of early aggressive treatments in high-risk patients and spare low-risk individuals unnecessary procedures. Current research efforts will hopefully clarify this hypothesis and help to further improve the outcomes of the severe complication of cirrhosis.

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INTRODUCTION

Variceal bleeding is a major complication of portal hypertension and represents a leading cause of death in patients with cirrhosis[1,2]. Diagnostic and therapeutic developments have led to a significant improvement in the prognosis of this complication over the past two decades. However, early mortality after an episode of acute variceal

bleeding (AVB) remains high (15%-24%)[1-5]. This paper reviews the current knowledge, most recent advancements and research prospects in the management of patients with cirrhosis presenting with AVB of esophageal origin. The prognostic and therapeutic approach to patients bleeding from gastric varices is clearly different and is not considered in the present review.

NATURAL HISTORY OF ACUTE VARICEAL BLEEDING

Ruptured esophageal varices cause approximately 70% of all upper gastrointestinal (GI) hemorrhages in cirrhosis[6]. Therefore, a variceal origin should be suspected in any cirrhotic patient presenting with a GI bleeding until a diagnostic endoscopy is performed.

It is known from placebo-controlled trials that approximately 40%-50% of variceal hemorrhages stop spontaneously[7]. Current available therapies further increase control of bleeding in about 80% of patients. However, despite the application of the most effective treatments available, one out of four patients will still show either a failure to control the bleeding or an early recurrence of the hemorrhage in the first 6 wk after the initial bleeding[4-6]. This risk peaks during the first 5 d, the period in which 40% of all rebleedings occur. Afterwards, it decreases slowly, equaling at 6 wk the risk previous to the bleeding episode[1,4-6].

A similar improvement in the early mortality of AVB has been recognized in the past 30 years from the 42% of the seminal study by Graham and Smith[1] to 15%-24% with current therapies[1,4-6]. A recent population-based study from the USA showed a crude in-hospital mortality decrease from 18% to 11.5% between 1988 and 2004[8]. However, this early mortality rate is still very high and probably underestimates the true risk since pre-hospital mortality data are scarce, the only available estimation being 3%-4%[9]. The risk of death after an AVB episode shows a similar evolution to that of rebleeding, peaking during the first 5-10 d and slowly returning to the base line after 6 wk[1,5].

Due to the difficulties in recognizing a single cause of death after a variceal hemorrhage, the general consensus is that any death occurring within 6 wk of admission from the index bleeding should be considered as a bleeding-related death[10]. However, it is currently estimated that 20%-40% of deaths after AVB are secondary to uncontrolled bleeding and exsanguination while the majority of remaining cases are due to liver failure, infections and hepatorenal syndrome[6,10]. Therefore, management of these patients should require a global approach including hemostatic therapies but also prophylactic strategies to avoid the above mentioned complications.

PROGNOSTIC STUDIES IN ACUTE VARICEAL BLEEDING

The value of different clinical and hemodynamic variables in predicting the outcome after an AVB has been the subject of a number of studies in the past years[5,6,11-16] (Table 1).

Prognostic indicators of rebleeding have been assessed in most studies together with initial failure to control the acute bleeding and 5 d mortality as a composite endpoint referred to as "5 d failure". Severity of liver disease, quantified as Child-Pugh and Model for End-Stage Liver Disease (MELD) scores or its individual components, has been widely recognized as a robust independent predictor of 5 d failure. Active bleeding at initial endoscopy has also been identified as an important risk factor for 5 d failure in several studies[6,13,14]. The prognostic value of other reported factors (platelet count, etiology of cirrhosis, hematocrit, transfusion needs, shock, portal vein thrombosis) seem to be less reproducible between studies.

Regarding early mortality, severity of liver disease (mainly Child-Pugh class C) is also the main and most constant prognostic indicator. The presence of hepatocellular carcinoma or occurrence of early rebleeding when included in multivariate analysis have been also recognized as important independent risk factors for 6 wk mortality. Recognition of the prognostic relevance of potentially modifiable factors such as bacterial infection or renal failure is increasing since these complications could be regarded as targets of specific therapies aiming to improve global outcomes after AVB. Other prognostic clinical variables reported in different studies are shown in Table 1.

The hepatic venous pressure gradient (HVPG) has proven an excellent prognostic value for both treatment failure and survival after AVB[17]. A HVPG value ≥ 20 mmHg in the first 48 h after admission has been associated with higher treatment failure and mortality in several studies. However, the discriminating ability of HVPG after an AVB does not seem to be superior to the combined use of clinical variables[11].

In summary, available prognostic studies suggest that the combined use of clinical variables (mainly Child and/or MELD scores, active bleeding, hepatocellular carcinoma, bacterial infection and renal failure) along with HVPG measurements when available are likely to accurately predict prognosis after AVB. Although it is worth remarking that no available prognostic models based on these variables are suited for individual prognostication, it is nevertheless important to highlight the potential practical value of these predictive tools. A precise early classification of patients into different risk strata would make it possible to adapt the therapeutic approach to the expected outcomes of each stratum. The use of new statistical approaches based on techniques such as Classification and Regression Tree analysis (CART) may facilitate the recognition of prognostic subgroups as targets for specific interventions[5,18]. This method is especially adept at detecting relevant interactions between variables and provides intuitive decision trees allowing the identification of subgroups of patients that share a specific combination of clinical characteristics and a similar prognosis, as illustrated in Figure 1. The

Table 1 Most relevant prognostic studies in acute variceal bleeding published between 1999-2009

Authors (year)(Ref.)	n	Universal antibiotic prophylaxis	Hemostatic-treatment	Early rebleeding/ treatment failure	Prognostic factors for rebleeding/treatment failure	Early mortality	Prognostic factors for early mortality	Statistical technique	Validation of prognostic models
Ben Ari *et al* (1999)[13]	529	No	EST or VAD (+ EST if failure)	224 (42%)	Active bleeding at endoscopy, platelet count, time to admission, alcohol, heart rate, encephalopathy	92 (17%)	Encephalopathy, bilirubin, ascites, plasma urea, heart rate, 5 d failure	Cox regression	Yes (bootstrapping)
Moitinho *et al* (1999)[14]	65	No	EST or VAD	23 (35%)	HVPG ⩾ 20 mmHg	6 (9%)	Not reported	Logistic regression	No
D'Amico *et al* (2003)[6]	297	No	VAD, Endoscopy or combination	49 (15%)	Child, portal vein thrombosis, AST, active bleeding, transfusion volume	70 (21%)	Encephalopathy, bilirubin, HCC, albumin	Logistic regression	Yes (split sample)
Thomopoulous *et al* (2003)[15]	121	No	VAD + EVL	15 (10%)	Not reported	26 (18%)	Child, shock	Logistic regression	No
Lecleire *et al* (2005)[16]	275	No	Endoscopy	Not reported	Not reported	107 (23%)	Prothrombin time, digestive cancer, hematemesis, corticoids, age, in-patients	Logistic regression	No
Abraldes *et al* (2008)[14]	117	Yes	VAD + Endoscopy	18 (15%)	HVPG ⩾ 20 mmHg, shock, Child, non-alcoholic cirrhosis	7 (6%)	Not reported	Logistic regression	Yes (bootstrapping)
Bambha *et al* (2008)[12]	256	Yes	EVL + (VAD or placebo)	37 (15%)	MELD ⩾ 18, clot on varix	35 (14%)	MELD ⩾ 18, transfusion volume, active bleeding at endoscopy, early rebleeding	Bivariate cox analysis	No
Augustin *et al.* (2009)[5]	267	Yes	VAD + Endoscopy	55 (21%)	Not reported	63 (24%)	Child, infection, plasma creatinine, HCC	Logistic regression + CART analysis	Yes (split sample)

n: total number of patients (only those with variceal bleeding considered); EST: endoscopic sclerotherapy; EVL: endoscopic variceal ligation; VAD: vasoactive drug; HVPG: hepatic venous pressure gradient; AST: aspartate aminotransferase; HCC: hepatocellular carcinoma; CART: classification and regression tree; Ref: references.

efficacy of this "a la carte" strategy and the value of the different stratification approaches should be evaluated in future randomized controlled trials (RCTs). Finally, it seems important to remark that the relative weight of the different variables in the proposed prognostic models may be substantially affected by the treatments applied in the cohort. Therefore, new models drawn from cohorts receiving the current standard of care (i.e. combined vasoactive drug plus endoscopic ligation plus antibiotics) will be needed. A recent study by our group showed that when this standard of care is applied, renal dysfunction is the main modifiable indicator of bad prognosis in AVB[18].

GENERAL MANAGEMENT

There is evidence that current treatment strategies for AVB have improved survival in different countries[8,19,20]. However, early rebleeding and mortality rates remain high (15%-24%) in this scenario. For this reason, AVB is considered a medical emergency and therefore current guidelines state that it should be managed by a multi-disciplinary team of experienced staff including nurses,

hepatologists, endoscopists, interventional radiologists and surgeons, preferably in an intensive care unit (ICU). Diagnostic and therapeutic decisions should be driven by a written protocol developed to optimize the resources of each center. These recommendations have so far been based mainly on experts' opinion since objective data on the issue has been scarce. Nevertheless, over the last years, a number of studies published evaluating different aspects of the quality of general management of these patients may help to optimize current strategies.

On one hand it is clear that the management of patients with AVB and organ dysfunction can be extremely challenging. Admission of these patients to high-dependency or intensive care units is highly advisable. However, it is worth noting that the outcome of cirrhotic patients admitted to ICU correlates directly with the number of organs failing. Sepsis and multiorgan failure, especially if requiring renal replacement therapy, confer a dismal prognosis with over 90% mortality[21]. Therefore, consideration should be given to the futility of ICU admission and escalating organ support measures in this subset of patients, especially if they are not suitable for liver trans-

```
                    n = 138
                    Death
          No    121    79.8%
          Yes    43    26.2%
```

```
    Child score              Child score
       ≤ 7                      ≤ 7
      n = 66                   n = 98
    Death (6 wk)             Death (6 wk)
  No    61   92.4%         No    60   61.2%
  Yes    5    7.6%         Yes   38   38.8%
```

Low risk

```
        Bacterial                 Bacterial
        infection                 infection
           no                        no
         n = 72                    n = 26
       Death (6 wk)              Death (6 wk)
     No   53   73.6%           No    7   26.9%
     Yes  19   26.4%           Yes  19   73.1%
```

High risk

```
     Creatinine                Creatinine
     ≤ 1.35 mg/dL              ≤ 1.35 mg/dL
       n = 52                    n = 20
     Death (6 wk)              Death (6 wk)
   No   43   82.7%           No   10    50%
   Yes   9   17.3%           Yes  10    50%
```
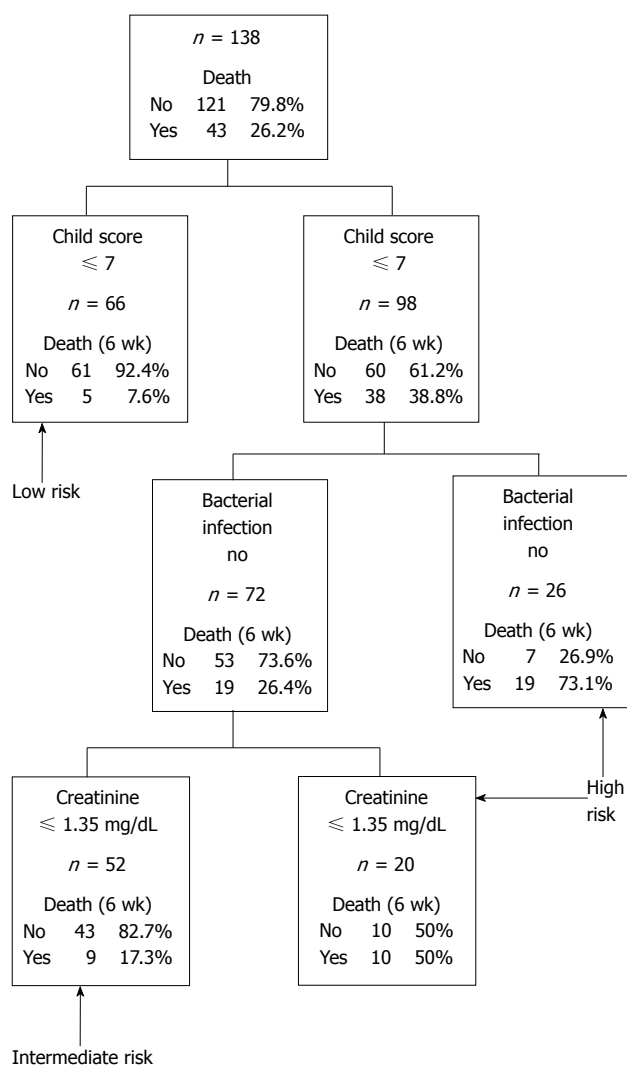
Intermediate risk

Figure 1 Prognostic model for 6 wk mortality based on an inductive tree generated by classification and regression tree analysis in a cohort of 164 consecutive patients after an episode of acute esophageal variceal bleeding.

plantation. Besides, recent studies have evaluated the influence of hospital volume and time of admission (week-days or weekends) as indirect measures of quality of care. Regarding the importance of hospital volume, a recent retrospective study was unable to show a direct relationship between hospital volume and better outcomes[22]. However, it still seems advisable that lack of the above mentioned facilities should require immediate referral to an experienced center until more data is available. Finally, a large cross-sectional study the USA identified a possible "weekend" effect leading to increased mortality for patients with non-variceal upper GI bleeding which did not reach statistical significance for variceal hemorrhages. This weekend effect may be attributable to many considerations including patients presenting later in the course of the disease or system issues (such as the availability and quality of supportive care with disparities in staff patterns on weekends).

The therapeutic approach to the cirrhotic patient with

AVB should include initial resuscitation and specific hemostatic measures aimed at correcting the hemorrhagic shock as well as early prevention of severe and frequent complications that worsen the prognosis of these patients (mainly bacterial infection and renal dysfunction).

Initial resuscitation

Initial resuscitation in AVB follows the general ABC (Airway, Breathing, Circulation) scheme and it is aimed at maintaining an appropriate delivery of oxygen to the tissues.

Extreme care of the airway should be maintained as the patient is at high risk of bronchial aspiration of gastric contents and blood. This risk is especially high in encephalopathic patients and is further exacerbated by endoscopic procedures. Endotracheal intubation is thus mandatory if there is any concern about the safety of the airway. Pulse oxymetry and oxygen administration are essential to maintain adequate blood oxygen saturation. Variceal bleeding is often massive; therefore, it is essential to obtain adequate peripheral venous access in order to administer fluids and blood products if required.

Optimal volume replacement remains controversial. Blood volume restitution should be undertaken as soon as possible with the goal of maintaining systolic blood pressure around 100 mmHg. Avoidance of hypovolemia and prolonged hypotension is particularly important in order to prevent renal failure and infection which are associated with increased risk of rebleeding and death[6,7,23]. Nevertheless, blood volume replacement and transfusion should be cautious and conservative since over-transfusion has been associated with rebound increases in portal pressure and more rebleeding and mortality, as suggested by experimental studies[24,25] and in a recent RCT published in abstract form[26]. Blood transfusion should be aimed at maintaining hemoglobin at 7-8 g/L[10,26] except in patients with rapid ongoing bleeding or ischemic heart or cerebral disease in which case this threshold should be raised. The use of vasoactive drugs has been shown to blunt the increase in portal pressure induced by volume expansion[27,28]. It has been suggested that volume replacement should be done with human albumin fraction or gelatin-based colloid which have been associated with less effect on clotting compared to dextran, although clinical data is lacking. Similarly, vigorous resuscitation with saline solution should be avoided because it can worsen or precipitate a recurrent variceal hemorrhage and accumulation of ascites and fluid at other extravascular sites.

Patients with cirrhosis often present with abnormalities in coagulation tests and platelet counts. The derangement of hemostasis in these patients has long been thought to play an important role in variceal hemorrhage. However, these abnormalities seem to be poorly correlated with bleeding[29]. Recent advancements in the pathophysiology of hemostasis in cirrhosis have led several authors to challenge these concepts and give new insights on potential new therapeutic approaches. The thrombocytopenia that is usually encountered in these

patients is now considered to impair not only primary hemostasis but also thrombin generation[30]. Transfusion of fresh frozen plasma and platelets can be considered in these patients although the exact role of these measures has not been evaluated appropriately. Another possibility still to be investigated in clinical trials is treatment with thrombopoietin[31]. Additionally, several drugs that act on coagulation and fibrinolytic pathways have been tested. Desmopressin (DDAVP), a drug that significantly decreases bleeding time in cirrhosis, has shown no clinical benefits in the setting of variceal bleeding[31,32]. The potential benefit of therapy with anti-fibrinolytic agents, useful in liver transplantation, has not been evaluated in clinical trials[33]. The use of recombinant activated factor VII which corrects prothrombin time in cirrhotics[34] has been assessed in two RCTs[35,36]. These studies failed to show a beneficial effect of this factor over standard therapy on preventing treatment failure and so this expensive therapy cannot be currently recommended.

Diagnostic endoscopy

The gold standard for the diagnosis of variceal hemorrhage is endoscopy. A diagnosis of bleeding varices is accepted if certain pre-specified criteria are met[37]. Current guidelines recommend performing an emergency endoscopy as soon as safely possible after admission[10,19,20] in order to confirm a variceal origin of the hemorrhage which represents the leading cause of upper GI bleeding in cirrhotics. However, these recommendations are based on experts' opinions and not on objective evidence drawn from adequately designed studies. On one hand, a certain amount of indirect data suggests that early performance of endoscopy may indeed be preferable. First, documentation of a non-variceal origin associates a much better prognosis and directly influences management. Second, endoscopic therapy clearly improves outcomes in AVB so the presumption is that early application of endotherapy may lower treatment failures and mortality. In fact, a recently published retrospective study[38] identified delayed endoscopy (defined as performed 15 h after admission) as a risk factor for in-hospital mortality although important methodological drawbacks hamper the external validity of these results. Finally, early endoscopy has proven to lower costs when performed in patients with non-variceal upper GI bleeding[39] so the assumption is that it may well be the same case for variceal bleeding. Unfortunately, these hypotheses remain unproven in RCTs so far.

On the other hand, several authors suggest that endoscopy-related complications (such as aspiration pneumonia) may compromise the potential benefits of early endotherapy[40]. Moreover, based on available evidence, it has been argued that early administration of vasoactive drugs might justify the delay of endoscopy and that endotherapy could be added only in case of failure of drugs to control bleeding[41]. Finally, since performing endoscopic therapy at the time of diagnostic endoscopy would spare the patient a second procedure, it is advisable that a skilled endoscopist is available. A recent retrospective study from Korea compared the outcomes of patients presenting with after-hours AVB according to the timing of initial endoscopy[42]. In the early endoscopy group (< 12 h after admission), the rate of finding the bleeding source was lower and 30 d mortality was higher than in the delayed endoscopy (12-24 h after admission) cohort. Another recent study with similar design showed that a shorter time to endoscopy was not associated with better outcomes[43]. Again, the retrospective nature of these studies limits the validity of these observations. In conclusion, although consensus seems to exist that an emergency endoscopy should be performed as soon as safely possible after admission, more studies are needed to adequately address the potential benefits and drawbacks of this strategy.

PREVENTION OF COMPLICATIONS AND DETERIORATION IN LIVER FUNCTION

Prophylaxis and treatment of infection

Up to 20% of cirrhotic patients who are hospitalized due to GI bleeding present with bacterial infections and an additional 50% will develop an infection while hospitalized[44]. This risk is especially high in those patients with poor liver function (i.e. Child B and C)[45,46]. The most frequent infections are spontaneous bacterial peritonitis and spontaneous bacteriemia (50%), followed by urinary tract infections (25%) and pneumonia (25%)[47]. Presence of these infections should be systematically ruled out in a bleeding cirrhotic patient (performing chest x-ray, urinary analysis and diagnostic paracentesis).

Infection is one of the strongest prognostic indicators in AVB and is associated with early rebleeding and greater mortality[5,48,49]. It has been proven that antibiotic prophylaxis significantly reduces the percentage of patients who develop infection and rebleeding[50] and that it increases survival[51]. Therefore, all cirrhotic patients (with or without ascites) with upper GI bleeding must receive prophylactic antibiotic therapy at admission. The current recommended antibiotic schedule is oral norfloxacin at dose of 400 mg BID for 7 d although ciprofloxacin could also be used[10,19,20]. When the oral route is not possible, quinolones can be administered intravenously. A recent RCT suggests that intravenous (IV) ceftriaxone (1 g/d) might be more effective than oral norfloxacin in preventing bacterial infections in Child B and C patients[52]. It seems advisable that the final choice of antibiotic should be nevertheless adjusted to the prevalence of quinolone-resistant microorganisms at each center. The potential beneficial effect of prophylactic schemes that cover the high risk 6 wk period after the bleeding remains unexplored.

Ascites and renal function

Tense ascites should be treated with paracentesis along with albumin replacement when indicated. This has been shown to decrease portal and variceal pressure[53].

The development of renal failure in cirrhotic patients after an AVB which occur in approximately 11% of cases is associated with a dismal prognosis[23]. Moreover, serum

creatinine level at admission of AVB has also proven to be a robust marker of severity in this setting, regardless of the evolution of renal function. Although current consensus set the creatinine level to define renal failure at 1.5 mg/dL, a lower cut-off (1.35 mg/dL) may allow an early identification of a high-risk population among variceal bleeders[5]. The need for aggressive management of renal dysfunction in cirrhotic patients is widely encouraged[10]. Renal function should be supported by adequate fluid and electrolyte replacement (saline solutions should be avoided), and should be closely monitored. Urine output should be maintained at a minimum of 40 mL/h; an output below 20 mL/h indicates poor renal function and impending renal failure[10]. In this case, active search and prompt treatment of potential (even non-apparent) precipitating factors (rebleeding, infection) is mandatory. Nephrotoxic drugs should be avoided, particularly aminoglycosides and non-steroidal anti-inflammatory drugs. The potential beneficial effect of specific strategies (e.g. short-term albumin infusion) aimed at preventing and/or treating renal dysfunction after AVB require evaluation in future studies.

Nutrition

Malnutrition is frequent in cirrhosis[54] and may contribute to an increased susceptibility to infections and renal dysfunction. Therefore, feeding should be resumed as soon as a 24 h interval free of rebleeding has been achieved. Enteral nutrition is always preferable due to lower cost and complications when compared to parenteral nutrition. There is currently no empirical evidence to continue recommending low protein diets which could further impair the nutritional status of these patients[55].

Encephalopathy

Variceal bleeding can precipitate hepatic encephalopathy. There is insufficient data to support the prophylactic use of lactulose or lactitol[10] although they can be given to patients who already present encephalopathy. It is important to be forewarned about the possibility of alcohol withdrawal. Judicious use of benzodiazepines or clomethiazole may be necessary to control an acute deprivation/withdrawal syndrome. Thiamine administration should also be considered to prevent Wernicke syndrome in alcoholic and/or malnourished patients.

HEMOSTATIC THERAPIES

The treatment of the AVB is aimed at controlling the acute hemorrhage, preventing early rebleeding and, ultimately, reducing mortality. Current recommended initial management is based on the combination of pharmacological and endoscopic therapy[10,19,20]. Rescue therapies such as local tamponade or portal-systemic shunts may be necessary in case of treatment failures.

Pharmacological therapy

Vasoactive drugs exert their action by reducing portal pressure. The rationale of the use of vasoactive drugs is the assumption that this reduction of portal pressure leads to a reduction in variceal pressure and a better control of hemorrhage[28,56]. Indeed, treatment with vasoactive drugs alone controls bleeding in up to 83% of patients[41].

Whenever a variceal bleeding is suspected, vasoactive drugs should be started as soon as possible, even before diagnostic confirmation, and ideally during transfer to the hospital since a quarter of deaths occur very early after bleeding onset[9]. Furthermore, a number of trials[57-59] have shown that early administration of these drugs reduces the rate of active bleeding during endoscopy thus facilitating endoscopic procedures. This might lead to a reduction of side effects, treatment failures and bleeding related mortality. The optimal duration of therapy with vasoactive drugs is not well established. Current guidelines recommend maintaining vasoactive treatment for 2-5 d since this is the time period in which rebleeding is more frequent[10,19,20].

Several drugs are available to treat AVB. Published data does not permit firm conclusions about the superiority of any of them over the rest and the choice should be based according to local resources[10,19,20,60].

Terlipressin: Terlipressin is a synthetic analogue of vasopressin with longer activity and fewer side effects. It reduces portal pressure and its effects are still significant 4 hours after administration[61-63]. The overall efficacy of terlipressin in controlling variceal bleeding is 75%-80% at 48 h[64] and 67% at 5 d[65]. Terlipressin has been shown to significantly improve control of bleeding and survival when compared to placebo[64,66-68] and is the only drug that has shown to improve survival. However, terlipressin can provoke ischemic complications and severe dysrhythmias. Therefore, it should be used with extreme caution or even avoided in those patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease or heart rhythm disorders.

Terlipressin is given as a 2 g bolus dose every 4 hours during the first 2 d. The dose is halved after bleeding is controlled and can be maintained for up to 5 d. Administration of terlipressin at low doses in continuous perfusion has been tested in cirrhotic patients with septic shock with promising results[69,70] but its use in AVB has not been explored yet and cannot be recommended.

Somatostatin: Natural somatostatin also causes splanchnic vasoconstriction at therapeutic doses and has proven to reduce portal pressure and HVPG during active bleeding[28,71-73]. Additionally, somatostatin blocks the postprandial increase in portal blood flow and portal pressure.

Randomized trials and meta-analyses[58,73,74] have demonstrated that somatostatin significantly improves control of bleeding when compared to placebo (63% *vs* 46%) but not survival[75]. On the other hand, its beneficial effect on control of bleeding, early rebleeding and mortality is similar to that of terlipressin with a better safety profile. Major side effects with somatostatin are extremely rare. Minor

side effects such as vomiting and hyperglycemia occur in up to 21% of patients and are usually easy to manage.

Somatostatin is usually given at a continuous perfusion dose of 250 mcg/h after an initial 250 mcg bolus (which can be repeated up to 3 times during the first hour). The infusion should be maintained for 5 d[76] or until a 24 h period free of rebleeding has been achieved. The use of 500 mcg/h doses has been associated with greater decreases in HVPG[71] and may be more effective in patients with more severe bleedings[77].

Octreotide and other somatostatin analogues: Octreotide is a synthetic analogue of natural somatostatin with similar mechanism of action and longer half life. However, this does not result in longer hemodynamic effects[78,79], probably due to the development of tachyphylaxis or rapid desensitization[80]. The effect of octreotide as single therapy in AVB is controversial. The only RCT addressing the issue did not show any benefit of octreotide over placebo in prevention of rebleeding or mortality[81]. On the other hand, octreotide appeared to be equivalent to terlipressin in two other trials which were nevertheless underpowered and not double-blinded[75]. Overall, the result of a recent meta-analysis suggests that the beneficial effect of octreotide as single therapy in AVB is negligible[82]. No placebo-controlled trials have been published using octreotide before endoscopy, the setting in which it is frequently used in clinical practice. However, results of another meta-analysis suggest that, when used on top of endoscopic sclerosis, octreotide is indeed effective in preventing early rebleeding with no apparent effect on mortality[83]. It has been speculated that this beneficial effect of octreotide may be related to its capacity of blunting postprandial increases in portal pressure[84]. The safety profile of octreotide is similar to that of somatostatin. The drug is usually given in continuous infusion of 25-50 mcg/h with an optional initial iv or subcutaneous bolus of 50 mcg. As for somatostatin, it can be given for up to 5 d to prevent early rebleeding. In summary, octreotide may be beneficial when used along with endoscopic therapy but has uncertain effects when used alone and therefore should be considered a second choice when terlipressin or somatostatin is available.

Vapreotide and lanreotide are two other synthetic analogues of somatostatin with comparable affinity for somatostatin receptors[84]. They both have been shown to reduce portal pressure in animals but their clinical hemodynamic effect in humans is controversial[85]. One study showed that, when used before endotherapy, vapreotide was more effective than placebo in controlling variceal bleeding[86]. Lanreotide did not improve the efficacy of endotherapy in a recent cooperative RCT that remains unpublished[12].

Vasopressin: Vasopressin is the most potent splanchnic vasoconstrictor. It reduces blood flow to all splanchnic organs, leading to a secondary decrease in portal venous inflow and portal pressure. However, these same potent vasoconstrictive properties limit the clinical usefulness of vasopressin. Its use is associated with multiple side effects, including cardiac and peripheral ischemia, dysrhythmia and hypertension, with an overall withdrawal rate of up to 25%[87]. Although the association with nitrates improves the efficacy and reduces complications of vasopressin, side effects are still significantly higher than those of terlipressin or somatostatin and its analogues[75]. Therefore, it remains the last choice among pharmacological therapy. It should not be used at maximal doses beyond the first 24 h after the bleeding. Vasopressin is given at continuous IV perfusion of 0.2-0.4 U/min that can be increased to a maximal dose of 0.8 U/min. It should always be associated to IV nitroglycerine at a 40-400 mcg/min dose, adjusted to maintain blood pressure above 90 mmHg.

In summary, vasoactive drugs are effective and safe and should be used as first line treatment of AVB as soon as variceal bleeding is suspected. Available data do not permit firm conclusions regarding the superiority of one drug over the others, although the efficacy and safety profile of either terlipressin or somatostatin seems to be the most adequate, rendering these two drugs as first choice. Octreotide and vapreotide could also be used if combined with endoscopy.

Endoscopic therapy
Endoscopic therapy versus placebo or non-active treatment: Endoscopic sclerotherapy (EST) alone controls active bleeding in at least 62% of patients[88]. A meta-analysis of the 5 available studies comparing EST with either sham or non-active treatment demonstrated a significant reduction in control of acute bleeding, early rebleeding and mortality[89]. There is no available data comparing endoscopic variceal ligation (EVL) with placebo.

Endotherapy versus drugs: A number of studies have compared EST with active drug treatment for AVB. A meta-analysis of these 13 studies (8 versus octreotide and 5 versus somatostatin) was not able to find significant differences between the two therapies regarding bleeding control or mortality[41]. However, differences of serious adverse events significantly favored somatostatin. No head-to-head comparisons with drugs have been conducted using EVL as endoscopic modality.

Combined therapy *vs* drugs or endotherapy alone: Available individual RCTs and meta-analysis have shown that combined endoscopic and pharmacological therapy improves initial control of bleeding and decreases treatment failure when compared with either one of them alone. A systematic review[90] comparing EST alone *vs* combined therapy showed a significant reduction in initial and 5 d hemostasis for combined therapy, with no significant effect on 5 d mortality (Risk ratio, *RR*: 0.73; 95% Confidence Interval, 95CI: 0.45-1.18). The rate of serious adverse events appeared to be similar for both therapeutic regimens. The only study comparing both strategies using exclusively EVL as endoscopic modality

	VAD + EVL *n/N* (%)	EVL *n/N* (%)
Calés *et al*[92]	14/98 (14)	21/98 (21)
Sung *et al*[91]	5/47 (11)	11/47 (23)
Total	19/145 (13)	32/145 (22)

Absolute risk difference for combined therapy: -9.0%, CI95 1.7%-17.7%; RR: 0.59, CI95 0.35-0.99, *P* = 0.045. In the study by Calés *et al*, EVL was not performed in all patients (the exact percentage of patients receiving EVL or EST is not provided). VAD: vasoactive drug; EVL: endoscopic variceal ligation; EST: endoscopic sclerotherapy; *n/N*: number of events/number of patients in each treatment arm; CI95: 95% confidence interval.

showed a significant reduction of early rebleeding (EVL alone 38% *vs* octreotide + EVL 9%, *P* = 0.0007) and a remarkable reduction in 30 d mortality (23% *vs* 11%, RR 0.45, 95CI 0.17-1.20), which nevertheless failed to reach statistical significance due to a lack of statistical power (total N: 94; β error for 50% risk reduction: 0.33; total N needed to make the observed RR 0.45 significant: 300 patients)[91]. When data from this study is pooled with data from the other available study in which EVL was used[92] (either EST or EVL where indistinctly performed in this study), combined therapy is significantly superior to endotherapy alone in reducing early mortality (Table 2).

Only two trials have been published comparing combined therapy (using EST) with vasoactive treatment alone: one with somatostatin[93], the other with octreotide[94] and the latter only as an abstract. Pooled results of these studies showed that combined therapy, despite causing more adverse effects, improved control of bleeding without apparent statistical influence on mortality (14% *vs* 21%, relative risk reduction 30%, RR 0.7 95CI 0.29-1.7, *P* = 0.4)[89]. Again, the study available as peer-reviewed article[93] was clearly underpowered to detect otherwise clinically relevant differences in mortality (total *n* = 100; total *n* needed to render this notable 0.7 RR statistically significant: 600).

Finally, the only trial comparing the current recommended combined therapy (using exclusively EVL) with drugs alone has been recently published[95]. In this study, combination of banding ligation and terlipressin infusion for 2 days was superior to only infusion of terlipressin for 5 days in the reduction of very early rebleeding (0% *vs* 15%, *P* = 0.006) and treatment failure (2% *vs* 24%, *P* = 0.002) in patients with inactive variceal bleeding at endoscopy.

In summary, combined endoscopic and vasoactive treatment is clearly more effective in controlling active bleeding and rebleeding than any of them alone but probably with the cost of more adverse effects. The net benefit on mortality might likely favor the combination but all available studies are clearly underpowered to address effect on mortality. More data are needed to draw firm conclusions on this key issue.

Sclerotherapy *vs* Ligation: Both EST and EVL (alone or combined with drugs) have proven to be effective to control AVB as explained above. Only two RCTs have specifically compared the efficacy of both endotherapies when used without vasoactive drugs. One of the studies, published only as an abstract[96], suggested that EST might be more effective, while the other study[96,97] showed that EVL was superior in terms of efficacy and safety. The only study comparing EST *vs* EVL as adjuvant therapy to drugs (somatostatin) has been recently published[96-98]. The study showed that the combination EVL-somatostatin was superior to EST-somatostatin in terms of bleeding control (treatment failure 10% *vs* 24%, RR 2.4, CI95 1.1-4.9, *P* = 0.02) and safety (overall side effects 14% *vs* 28%, RR 1.9, CI95 1.1-3.5, *P* = 0.03). Again, the beneficial effect of EVL on 6 wk mortality (13% *vs* 21%, RR 1.6, CI95 0.8-3.1, *P* = 0.17) did not reach statistical significance due to the small sample size (total *n* = 179; β error for 1.6 risk reduction: 0.48; total *n* needed to make the observed RR significant: 690 patients).

Additionally, a recent meta-analysis pooled data of 2 of these trials along with 8 other trials in which EST and EVL were compared both in acute bleeding and prevention of rebleeding[47]. The overall results of this review showed that EVL is better than EST in terms of controlling the initial bleeding and survival and is associated with less adverse events. Moreover, one of these studies also showed that EST but not EVL may induce sustained increases in HVPG which may affect control of bleeding and favor an early recurrence[99]. Finally, it has been claimed that emergency EVL may be more difficult to perform in the presence of massive bleedings due to a more reduced field of view compared to EST[100]. Nevertheless, the use of multi-shot ligation devices[48] as well as the reduction in the rate of active bleeding with early drug therapy have helped to overcome these difficulties[58,86,101]. In summary, all these data support the current consensus that EVL is the endotherapy of choice in AVB although some authors still consider EST acceptable if ligation is not available or technically not feasible.

Rescue therapies

Despite a careful observation of current recommended strategies, 10%-20% of patients will still experience treatment failure or early rebleeding[19,20]. Mortality of these patients is high (30%-50%)[102]. This section reviews the more recent advancements regarding rescue therapies for AVB.

Second endoscopy: Current guidelines[10] recommend that failure of the initial combined treatment can be managed with a second attempt at endoscopic therapy. However, this recommendation is based on experts' opinion since the exact role of a second attempt with endoscopy for uncontrolled bleedings has not yet been systematically evaluated.

Balloon tamponade and esophageal stents: Balloon tamponade is a very effective measure in controlling the

acute bleeding. The use of Sengstaken-Blakemore tube when a massive variceal bleeding is suspected allows initial control of bleeding in up to 80% of patients[103]. Nevertheless, its use is associated with potentially lethal complications such as aspiration, asphyxia due to balloon ligation and esophagus perforation which are associated with a high mortality. Besides, bleeding recurs after deflation in over 50% of cases. Therefore, its use should be restricted to patients with uncontrollable bleeding for a short period of time (< 24 h) as a bridge to a more definitive therapy[19,20]. Airway protection should be considered when balloon tamponade is used.

Recently, esophageal stents have been proposed as an alternative to balloon tamponade in the initial control of massive variceal hemorrhages. These removable self-expanding devices were able to control initially refractory bleedings in 70%-100% patients in 3 small non-controlled pilot studies[104-106]. Theoretically, they will have the advantage over tamponade of less severe complications and additional protection against early rebleeding since they can be left in place for up to 14 d. However, concerns do exist regarding the possibility of downstream migration (especially in patients with concomitant hiatus hernia). An ongoing multicentric RCT comparing balloon tamponade and self-expandable stents will hopefully provide useful information.

Shunting procedures: Both transjugular intrahepatic portosystemic shunts (TIPS) and surgical derivative procedures are extremely effective controlling variceal bleeding in patients who fail to respond to initial pharmacological and endoscopic therapies. However, the incidence of encephalopathy (which affects over 50% and worsens quality of life) and mortality (30% in the first month)[107] remain very high for shunt therapies[108,109], especially for patients with poor liver function (Child B or C).

Two studies by the same surgical group have shown almost universal control of bleeding and high long term survival after early (< 8 h from onset of bleeding) portocaval shunt. The first study was an uncontrolled report from a large cohort of non-selected cirrhotic patients over a 30-year period[110]. The second study[111], a RCT comparing emergency porto-caval shunt with EST (*n* = 211), yielded similar results, with universal control of bleeding in the surgical arm and clear superiority of shunt over EST in terms of survival and adverse effects for all Child-Pugh classes. Unfortunately, these impressive results have not been yet equaled by other groups. Although it has been suggested that surgical shunts may remain an option in Child A patients[10], its use as first choice rescue therapy is not currently supported.

TIPS have been proven to be extremely effective in controlling treatment failures in AVB[112,113]. Final hemostasis with TIPS is achieved in 90%-95% of patients with uncontrolled bleeding[19,20]. However, mortality remains high in these patients, mostly due to worsening of liver function (and frequently multiorganic failure), as a consequence of multiple transfusions, repeated endoscopic procedures, infections and deterioration of renal function. In patients with Child-Pugh score > 13, early mortality after TIPS is almost inevitable. Moreover, quality of life of patients surviving salvage TIPS is hampered by the high incidence of encephalopathy which affects half of the patients.

According to the most recent guidelines, the current place of TIPS in AVB is as second line treatment, applicable only for those patients in whom the combined pharmacological and endoscopic therapy has failed. However, technical advances and new studies have stimulated the interest on readdressing the role of TIPS in AVB. On one hand, the development of extended polytetra-fluoro-ethylene- covered stents have shown to significantly improve the stent long term patency and reduce the incidence of encephalopathy when compared with bare stents[114]. This may contribute to improve overall outcomes of patients receiving TIPS.

Besides, two other recent RCTs have reconsidered the place of TIPS in the management of AVB[115,116]. Both studies are based on the hypothesis that the benefits of TIPS may be enhanced if placed early before the patient deteriorates too much. To this aim, patients at higher risk of complication should be rapidly identified. The first RCT used hemodynamic criteria (HVPG $\geqslant$ 20 mmHg), uncovered TIPS as intervention arm and EST as control therapy[115]. The second study, still available only as abstract, used clinical criteria (Child-Pugh class B with active bleeding or Child C), covered TIPS and combined pharmacological and endoscopic therapy (either EST or EVL) for comparison[116]. In both studies, TIPS significantly reduced rebleeding and mortality without increasing the incidence of encephalopathy. Nevertheless, it should be noted that patients in the control arms of both studies presented mortality rates that were much higher than what would be expected if the current standard of care of AVB (i.e. drug + EVL + antibiotic treatment) had been universally applied so the actual relative benefits of TIPS could be overestimated.

CURRENT RECOMMENDATIONS FOR THE TREATMENT OF ACUTE ESOPHAGEAL VARICEAL BLEEDING (FIGURE 2)

Available data indicates that general management of the bleeding cirrhotic patient plays a major role in the final outcome of this complication. Advancements in this field are difficult due to inherent methodological issues (a variety of procedures performed by a multidisciplinary group influencing a single outcome). However, this growing body of evidence obtained from both RCTs and real-life data sources should help convince clinicians and decision makers alike that adequate resources need to be provided to allow for competent resuscitation, risk stratification, early endoscopy, the availability of timely skilled endoscopic intervention, as well as appropriate more specific therapy - all of which should be coordinated through a collaborative multidisciplinary group.

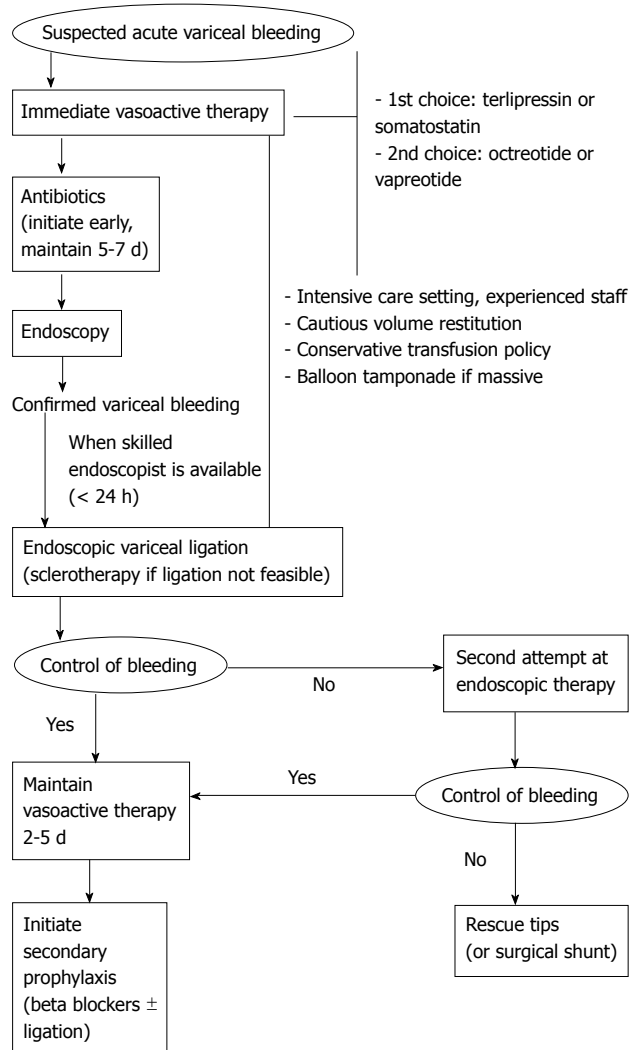It can be currently recommended to combine phar-

Figure 2 Current recommended management of patients with acute variceal bleeding.

macological and endoscopic therapies for the initial treatment of AVB. Vasoactive drugs (preferable somatostatin or terlipressin) should be started as soon as a variceal bleeding is suspected (ideally during transfer to hospital) and maintained afterwards for 2-5 d. After stabilizing the patient with cautious fluid and blood support, an emergency diagnostic endoscopy should be done and, as soon as a skilled endoscopist is available, an endoscopic variceal treatment (ligation as first choice, sclerotherapy if EVL not feasible) should be performed. Antibiotic prophylaxis must be regarded as integral part of the treatment of AVB and should be started at admission and maintained for at least 7 d. In case of failure to control the acute bleeding, rescue therapies should be immediately started. Shunt therapies (especially TIPS) are very effective at controlling treatment failures after AVB. In the near future, early identification of high-risk patients and use of covered TIPS may contribute to lower the high mortality of these patients. More studies are warranted to clarify which is the most rational management of patients presenting with a high risk of treatment failure.

CONCLUSION

Management of AVB has greatly improved over the past recent years. However, treatment failures and mortality remain high, especially in patients with poor liver function, even if the current standard of care is carefully applied. Therapeutic developments and increasing knowledge in the prognosis of this complication may allow optimization of the management strategy of AVB in the near future, adapting the different treatments to the expected risk of complications for each patient. Theoretically, this approach would allow the initiation of early aggressive treatments in high-risk patients and spare low-risk individuals unnecessary procedures. Current research efforts will hopefully clarify this hypothesis and help to further improve the outcomes of this severe complication of cirrhosis.

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