Current endoscopic therapy of variceal bleeding

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Variceal ligation has proved more effective and safer than sclerotherapy and is currently the endoscopic treatment of choice for oesophageal varices. In acute bleeding, vasoactive drugs should be started before endoscopy and maintained for 2–5 days. The efficacy of drugs is improved when associated with emergency endoscopic therapy. Antibiotic prophylaxis should also be used. To prevent rebleeding, both endoscopic ligation and the combination of beta-blockers and nitrates may be used. Adding beta-blockers improves the efficacy of ligation. Haemodynamic responders to beta-blockers ± nitrates (those with a decrease in portal pressure gradient HVPG to <12 mmHg or by >20% of baseline) have a marked reduction in the risk of haemorrhage and will not need further treatment. Beta-blockers significantly reduce the risk of a first...
haemorrhage in patients with large varices, and they improve survival. As compared to beta-blockers, endoscopic ligation reduces the risk of first bleeding without affecting mortality, and should be used in patients with contraindications or intolerance to beta-blockers.

**Key words:** endoscopic therapy; sclerotherapy; endoscopic variceal ligation; portal hypertension; variceal bleeding.

Portal hypertension may develop in a variety of chronic liver diseases, although it frequently results from cirrhosis. It is associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastro-oesophageal varices. Variceal bleeding is a medical emergency associated with a mortality that is still in the order of 20% at 6 weeks in spite of recent progress.\(^1\)–\(^3\) Available therapy allows the control of bleeding in almost 85% of episodes at 5 days, with an incidence of early rebleeding of about 20% within the first 6 weeks.\(^1\),\(^4\) Late rebleeding occurs in around 60% of untreated patients within 1–2 years, and death occurs in 33%. Therefore, all patients surviving an acute variceal bleed should be treated for prevention of rebleeding.

Oesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease.\(^5\) The rate of formation of varices is about 5% per year, and consequently on long-term follow-up most patients will develop them.\(^6\) The strongest predictor for the development of varices in cirrhosis is an hepatic vein pressure gradient (HVPG) >10 mmHg.\(^6\) Once varices have developed, the overall incidence of variceal bleeding is around 25% at 2 years.\(^4\) Large variceal size is the most important predictor of haemorrhage. The endoscopic presence of red wale marks on the variceal wall and the severity of liver dysfunction also increase the bleeding risk.\(^7\)

**PATHOPHYSIOLOGY OF VARICEAL BLEEDING: RELEVANT ISSUES CONCERNING ENDOSCOPIC TREATMENTS**

Gastro-oesophageal varices, as well as other portosystemic collaterals, result from portal hypertension. Portal pressure is commonly assessed by measuring the HVPG, which accurately reflects the portal pressure gradient in alcoholic and viral cirrhosis.\(^8\) Although varices and ascites may develop when HVPG increases to \(>10\) mmHg, variceal bleeding does not appear until the HVPG increases to \(>12\) mmHg.\(^6\),\(^9\)–\(^11\) The complications of portal hypertension may be corrected by reducing the HVPG to below these thresholds.\(^8\) Similarly, preventing the HVPG from increasing above these values will prevent the development of the complications of portal hypertension.\(^6\),\(^11\)

Variceal wall tension is probably the key factor that determines variceal rupture and subsequent bleeding.\(^12\) Variceal wall tension is the force generated by the vessel wall opposing intravascular distension. A major determinant of variceal wall tension is the transmural variceal pressure, which is directly related to portal pressure.\(^12\) In fact, clinical studies have shown that variceal bleeding does not occur when the HVPG is reduced below 12 mmHg.\(^13\) Even if this threshold is not reached, the risk of bleeding decreases markedly (to 10–15% of cases or fewer) with reductions in HVPG \(>20\)% from baseline.\(^14\) Variceal wall tension also depends on vessel diameter (increasing when the size of the varix is larger), and is inversely proportional to the thickness of the vascular wall.\(^12\) Due to their location in the lamina propria, oesophageal varices have thin walls and lack tissue support, which may facilitate a progressive dilation and
eventual variceal rupture. The presence of red colour signs on the varices on endoscopy probably reflect a thin vascular wall. Oesophageal varices are supplied by the left gastric vein and drain into the azygos system. In the palisade zone, which starts at the gastro-oesophageal junction and extends cranially for 2–3 cm, the oesophageal venous plexus is more superficial and poorly buttressed by surrounding tissue, and most variceal bleeding occurs in this zone. The perforating zone is located as a continuation of the palisade zone and is 3–5 cm in length. In this zone, perforating vessels connect para-oesophageal and submucosal venous plexuses which become incompetent in portal hypertension, allowing retrograde and turbulent blood flow that contributes to the development (or reappearance) and dilation of oesophageal varices. Both the palisade and the perforating zones should be targets for endoscopic therapies in order to achieve eradication of varices and to avoid their reappearance.

EFFECTS OF ENDOSCOPIC THERAPY

Endoscopic therapies may influence variceal wall tension by reducing variceal size until obliteration, and by increasing the thickness of the vascular wall (Table 1). Endoscopic sclerotherapy (EST) consists of the injection of a sclerosing agent into the variceal lumen or adjacent to the varix, inducing thrombosis of the vessel and inflammation of the surrounding tissue. During active bleeding, sclerotherapy may achieve haemostasis-inducing variceal thrombosis and external compression by tissue oedema. With repeated sessions, the inflammation of the vascular wall and surrounding tissue leads to fibrosis, resulting in variceal obliteration. Furthermore, vascular thrombosis may induce ulcers that also heal, inducing fibrosis. Endoscopic variceal ligation (EVL) consists of the placement of rubber bands on the varices that completely interrupts blood flow into the ligated varix. This may induce haemostasis in the acute setting. Subsequently ischaemic necrosis of mucosa and submucosa develops, followed by granulation, with final sloughing of the rubber rings and necrotic tissue and replacement of varices by scar tissue. The whole process leaves shallow mucosal ulcerations that may heal, inducing fibrosis and replacement of vessels with maturing scar tissue. Sessions are repeated at 2–4-week intervals until complete obliteration of varices. Varices may recur after obliteration, and follow-up endoscopies are required with further treatment of recurrent varices.

<table>
<thead>
<tr>
<th>Table 1. Endoscopic treatment of varices.</th>
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<tr>
<td>• Variceal wall tension is the key factor that determines variceal rupture. Portal pressure is a determinant of wall tension. Variceal bleeding is markedly reduced when the HVPG decreases to &lt;12 mmHg or by &gt;20% from baseline</td>
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<tr>
<td>• Endoscopic therapy may influence variceal wall tension by reducing variceal size until obliteration and by increasing the thickness of the vascular wall. However, this treatment has no effect on portal pressure</td>
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<td>• EVL is at present the endoscopic method of choice to treat oesophageal varices. No beneficial effects have been observed combining EST and EVL. The association of proton pump inhibitors may enhance the safety of EVL</td>
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<tr>
<td>• Variceal obturation with tissue adhesives such as cyanoacrylates may be particularly effective in the treatment of gastric varices</td>
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HVPG, hepatic venous pressure gradient; EVL, endoscopic variceal ligation; EST, endoscopic sclerotherapy.
A wide variety of local and systemic complications associated with EST has been reported. Minor complications – such as chest pain, low-grade fever, temporary dysphagia or asymptomatic pleural effusion – are common and generally self-limiting. Mucosal ulceration is the most common oesophageal complication and may lead to stricture or bleeding in up to 20% of patients. Rarely, these ulcers may perforate or create fistulae into adjacent organs. Bacteraemia may also occur after EST, as may remote complications such as bacterial peritonitis, portal-vein thrombosis, transverse myelitis, or distal abscesses. EVL was designed to decrease the complications of EST. This mechanical method of obliterating varices may avoid the systemic effects that may be induced by injection methods. Since the amount of tissue ligated is limited, it should also result in fewer complications involving the oesophageal wall. In fact, in clinical trials EVL has proved safer than EST.

Endoscopic therapy is a local treatment that has no effect on the pathophysiological mechanisms that lead to portal hypertension and variceal rupture. However, a spontaneous decrease in HVPG occurs in around 30% of patients treated with either EST or EVL to prevent variceal rebleeding. It has been shown that patients with such a spontaneous haemodynamic response require fewer sessions of endoscopic therapy until variceal obliteration, and have a higher rate of variceal eradication than patients treated with endoscopic methods who have no spontaneous response. Furthermore, spontaneous responders have a significantly lower probability of rebleeding and better survival. These data suggest that adding beta-blockers to endoscopic therapy may enhance the efficacy of treatment by increasing the rate of haemodynamic responders.

TECHNICAL ASPECTS OF ENDOSCOPIC TREATMENTS

EST has been used for decades. It is performed with a flexible catheter with a needle tip, which is used to inject different sclerosing agents into or next to the varix. Flexible endoscopes with no special equipment are used (freehand method). There are different technical variations for performing EST, such as type and concentration of sclerosant, volume injected, interval between sessions, and number of sessions. The most widely used sclerosants are ethanolamine olate 5% or polidocanol 1–3% in Europe, and sodium morrhuate 5% or sodium tetracetylsulphate 1–3% in the United States. All these sclerosing agents have been used successfully in controlled trials. The sclerosant is injected, 1–5 mL at a time, at different levels within the lower oesophagus, and six to eight EST sessions at intervals of 1–2 weeks are necessary to obliterate the varices. EVL is at present the endoscopic method of choice to treat oesophageal varices in the great majority of cases, while EST is becoming increasingly uncommon.

EVL consist of the placement of rubber rings on variceal columns which are sucked into a plastic hollow cylinder attached to the tip of the endoscope. Multiple-shot devices have largely replaced the original single-shot ligators, since the procedure is much simpler and faster with multishot devices, and an overtube is not required, thus avoiding the severe complications related to its use. Furthermore, new transparent caps are available which improve the visibility (visibility with the old caps may be reduced by 30%). In most cases, endoscopic therapy is performed under light intravenous sedation. Usually the procedure is performed by starting the application of bands at the gastro-oesophageal junction and working upwards in a helical fashion to avoid circumferential placement of bands at the same level. The application of bands progresses for approximately 6–8 cm within the palisade and perforating zones. In actively
bleeding varices ligation is currently started at the site of bleeding. Up to 10–14 bands are usually applied in each session, and sessions are repeated at 2–4-week intervals until varices are obliterated.17 Eradication of varices usually requires two to four EVL sessions. However, more intensive ligation methods have been employed.28 Both the optimal number of bands placed in each session and the optimal time interval between sessions should be clarified to improve the efficacy of this treatment. Usually varices are considered eradicated when they have either disappeared or cannot be grasped and banded by the ligator. Variceal eradication is obtained in about 90% of patients, although recurrence is not uncommon.8,17 Consequently, follow-up endoscopies should be scheduled and recurrent varices should be treated with new EVL sessions.17 The optimal surveillance programme should also be clarified. Several technical refinements have been suggested, such as a combined variceal and paravariceal ligation, banding the surrounding mucosa with the aim of inducing widespread fibrosis and scarring, or using endoscopic ultrasound monitoring with miniprobes.28 Detachable nylon snares (miniloops) may be an alternative to banding, particularly for the ligation of large vessels such as gastric varices.27 Argon plasma coagulation has also been combined with EVL to prevent variceal recurrence.29 However, the value of all these approaches to enhance the efficacy of EVL should be clarified by controlled trials. A recent controlled trail supports the use of proton pump inhibitors in patients treated with EVL, showing that this achieves smaller post-EVL ulcers with a trend towards fewer bleeding episodes.30

Minor complications of EVL – such as transient dysphagia and chest discomfort or pain – are not uncommon and may occur in up to 45% of cases.31 Shallow ulcers at the site of bands are frequent and rarely bleed. Compared with EST, ulcers caused by EVL are more superficial and resolve faster, and bleeding is less common.17 Bacteraemia and infectious complications, such as spontaneous bacterial peritonitis (SBP), are also less frequent with EVL.23 Although complications related to the use of the overtube may be severe (such as bleeding or perforation), they are avoided with multiple-shot devices. However, severe complications – such as massive bleeding from ulcers or rarely from variceal rupture – may still occur with EVL.31

Variceal obturation consists of the injection of tissue adhesives (cyanoacrylates such as Histoacryl or Bucrylate) into the lumen of the varix to achieve the occlusion of the vessel given that adhesives harden within seconds of contact with blood.17 Human and bovine thrombin has also been used to obturate varices.27 The limited studies available suggest that variceal obturation may be particularly promising for treating gastric varices.17,27

ROLE OF ENDOSCOPIC THERAPY IN ACUTE VARICEAL BLEEDING

General management

Acute variceal bleeding is a medical emergency with high mortality and morbidity, and management should be undertaken in an intensive care setting.9 Current treatment strategies have significantly improved the outcome of acute variceal haemorrhage. However, it is still associated with a mortality of at least 20% at 6 weeks.1–3 Initial measures should be aimed at correcting hypovolaemia, preventing complications that may worsen prognosis, such as bacterial infections or acute renal failure, and achieving haemostasis. The specific haemostatic treatment should aim both at controlling acute haemorrhage and at preventing early rebleeding, which is particularly common within the first few days and is associated with increased mortality.32
Initial resuscitation involves basic measures, including obtaining an adequate peripheral venous access. A cautious and conservative blood volume restitution is currently recommended, using plasma expanders to maintain haemodynamic stability and packed red blood cells (PRBCs) to maintain the haemoglobin at approximately 8 g/dL, depending on other factors such as patients co-morbidities, age, haemodynamic status, and presence of ongoing clinical bleeding. Hypovolaemia should be avoided to prevent complications such as renal dysfunction. However, over-transfusion should also be avoided because of the risk inherent with blood transfusion, and also because it may induce an increase in portal pressure with a subsequent risk of precipitating further bleeding.

Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis (with or without ascites) presenting with variceal bleeding, and should be instituted from admission (Table 2). This measure decreases the rate of bacterial infections, decreases the incidence of early rebleeding, and significantly improves survival. Oral norfloxacin is the agent of first choice. Intravenous quinolones may be given when oral administration is not possible. A recent study suggests that in patients with advanced liver dysfunction, intravenous ceftriaxone may be more effective.

In patients who present or develop encephalopathy, this should be treated. There are no studies evaluating the usefulness of lactulose/lactitol for the prevention of hepatic encephalopathy.

Endoscopy should be performed as soon as possible after admission (within 12 h), especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis. Emergency endoscopy is the main method for diagnosing variceal haemorrhage and excluding other potential sources of bleeding (about 15% of patients with cirrhosis bleed from causes not related to portal hypertension). Resuscitation should precede endoscopy. Tracheal intubation may be required for airway protection before endoscopy, particularly in patients with encephalopathy.

Haemostatic treatment of acute variceal bleeding

In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before diagnostic endoscopy (Figure 1). This is supported by several randomised

<table>
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<th>Table 2. Treatment of acute variceal bleeding.</th>
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<tr>
<td>• When variceal bleeding is suspected, vasoactive drugs should be started as soon as possible, before diagnostic endoscopy, and maintained for 2–5 days when it is confirmed. The most effective and safe drugs are terlipressin and somatostatin</td>
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<td>• The efficacy of vasoactive drugs is improved when emergency endoscopic therapy is associated. The efficacy of emergency endoscopic therapy is also improved with associated vasoactive drugs</td>
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<td>• EVL is more effective and safer than EST as an emergency endoscopic treatment associated with vasoactive drugs</td>
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<tr>
<td>• Even combining vasoactive drugs and emergency EVL, and adding antibiotic prophylaxis, 5-day therapeutic failure occurs in 10–15% of patients. Failures are best managed by TIPS</td>
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EVL, endoscopic variceal ligation; EST, endoscopic sclerotherapy; TIPS, transjugular intrahepatic porto-systemic shunt.
controlled trials showing that early administration of vasoactive drugs reduces the rate of active bleeding during endoscopy, thus facilitating diagnostic and therapeutic endoscopy, and improves the control of bleeding and may decrease bleeding-related mortality.\cite{39-41} Vasoactive drug therapy should be maintained for 2–5 days.\cite{33} The most effective and safe drugs are terlipressin and somatostatin, and consequently either drug may be the first choice.\cite{4} Terlipressin is the only drug that has been shown to improve survival, while controlled trials comparing terlipressin and somatostatin have shown no significant differences between them.\cite{42} Results of meta-analysis of trials of octreotide used alone, without endoscopic therapy, are controversial.\cite{43}

A meta-analysis of 15 trials comparing emergency EST and vasoactive drugs, including more than 600 patients in each arm, has shown a similar efficacy with both treatments, and fewer side-effects with pharmacological therapy.\cite{44} The use of EST as first-line therapy for acute variceal bleeding has therefore come into question, and it has been claimed that a valid approach might be to add endoscopic therapy only when the pharmacological intervention fails.\cite{45} However, a randomised controlled trial has demonstrated that the efficacy of vasoactive drugs is significantly improved when associated with emergency EST, in patients with and without active haemorrhage.\cite{45} The main drawback to this approach is that EST also increases the incidence of side-effects.\cite{45}

Several randomised trials have compared emergency EST and EVL for actively bleeding varices without using vasoactive drugs.\cite{17,23} No significant differences were found between the endoscopic treatments in the majority of these studies, the main aim of which was to investigate the value of such therapies in the long-term prevention of variceal rebleeding.\cite{17,23} Two trials were specifically addressed to compare the two endoscopic therapies in actively bleeding varices, and conflicting results were found.\cite{46,47}
In one of the studies, EVL was more effective and safer than EST. In contrast, the other study, published only as an abstract, suggested that EST may be more effective. It has been claimed that emergency EVL may be difficult to perform due to factors such as a reduced field of view as a consequence of the attachment of the banding device which may fill with blood during active haemorrhage, hampering the appropriate placement of bands. The use of multiple-shot ligation devices with transparent cylinders may overcome these difficulties. The technical performance of emergency endoscopic therapy may further ameliorate associating vasoactive drugs. If vasoactive drugs are started as soon as possible before emergency endoscopy, the incidence of active variceal bleeding during the endoscopic procedure decreases from up to 50% of cases when drugs are not used to only 20–25% of cases when they are used. A recent randomised controlled trial has shown that adding emergency EVL to somatostatin (which was started before endoscopy and maintained for 5 days) significantly improves the efficacy and safety achieved with the addition of EST to somatostatin infusion. This strongly supports the combination of vasoactive drugs and emergency EVL as first-line therapy for acute variceal bleeding (Table 2). Several factors may account for the benefits observed using EVL instead of EST as emergency endoscopic therapy in addition to drugs for acute variceal bleeding. EVL produces mechanical strangulation of varices and may have a greater local haemostatic effect than EST. Indeed, oesophageal varices are eradicated more quickly and with fewer therapeutic sessions using EVL. It has also been observed that during acute variceal bleeding, EST but not EVL causes a sustained increase in portal pressure, which may be detrimental for successful treatment. Furthermore, the combination of both pharmacological and endoscopic therapy in the treatment of acute variceal bleeding is strongly supported by numerous trials showing that the efficacy of both emergency EST and EVL is significantly improved when they are associated with pharmacological treatment. The meta-analysis of these studies showed that combined therapy improved the initial control of bleeding and 5-day haemostasis with no differences in mortality or severe adverse events.

With the current recommended therapy combining vasoactive drugs and emergency EVL, and adding antibiotic prophylaxis, 5-day therapeutic failure occurs in only 10–15% of cases (Figure 1). Failures are best managed by TIPS (preferably with PTFE-covered stents). Shunt surgery may be an option in Child-A class patients. Balloon tamponade should only be used in massive bleeding as a temporary ‘bridge’ until definitive treatment can be instituted (for a maximum of 24 h, and preferably in an intensive care facility). When further bleeding is not severe, other rescue treatments may be considered. A second attempt at endoscopic therapy may be made. A recent haemodynamic study suggests that, in some cases, a more intensive pharmacological treatment may be considered. In this study, either doubling the dose of somatostatin or shifting to terlipressin achieved a reduction in HVPG in previous non-responders to the standard somatostatin dose (this effect was greater with terlipressin). An increased clinical efficacy has been observed using higher doses of somatostatin in patients with active bleeding. A recent study also suggested that early TIPS placement may improve efficacy in high-risk patients (defined by an HVPG >20 mmHg). Future trials should clarify the value of these approaches. The addition of recombinant factor VIIa to standard therapy did not improve the efficacy in a recent trial. However, it should be clarified whether it may be of some value in failures with severe coagulopathy and advanced liver disease (precluding other rescue therapies).
ROLE OF ENDOSCOPIC THERAPY IN THE PREVENTION OF REBLEEDING

Both non-selective beta-blockers and EST have shown efficacy in preventing variceal rebleeding as compared with untreated controls. In comparative studies, similar rates of rebleeding and survival have been achieved with both treatments, with a higher incidence of side-effects with EST than with beta-blockers. However, in more recent years other options have achieved better results, considering either pharmacological or endoscopic therapy (Table 3).

As compared with EST, EVL has been shown to improve both safety and efficacy in numerous studies. The meta-analysis of 13 randomised trials including more than 1000 patients shows that EVL significantly reduces the rebleeding rate and the number of sessions (and time) required to achieve eradication, as well as complications. However, EVL does not significantly improve survival. Therefore, EVL is the current endoscopic treatment of choice in the prevention of variceal rebleeding. It is unclear whether variceal recurrence after initial eradication may be more common with EVL than with EST, because perforating veins that feed the varices are less affected by ligation. Adding EST to EVL to obliterate such perforating veins was proposed to reduce variceal recurrence after EVL. However, in different randomised trials and in the meta-analysis of these studies, no beneficial effects have been observed combining both endoscopic treatments as compared with using EVL alone.

Pharmacological therapy has also improved in recent years. The combination of non-selective beta-blockers and isosorbide mononitrate (ISMN) enhances the reduction in portal pressure achieved using only beta-blockers. This combined therapy with beta-blockers and ISMN has been shown to be superior to beta-blockers alone and to EST. HVPG monitoring provides strong prognostic information for management of portal hypertension by adequately identifying patients who are effectively protected against the risk of bleeding. Numerous studies have shown that haemodynamic responders, that is those with a decrease in HVPG to <12 mmHg or by >20% of baseline, have a marked reduction in the risk of haemorrhage to below 10% of cases (which

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<td>- Both non-selective beta-blockers and EST are effective in preventing rebleeding as compared with untreated controls. However, other options have improved the results of both pharmacological and endoscopic therapy.</td>
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<tr>
<td>- As compared with EST, EVL improves both safety and efficacy and consequently is the current endoscopic treatment of choice.</td>
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<td>- The addition of beta-blockers enhances the efficacy achieved using EVL only.</td>
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<tr>
<td>- The combination of beta-blockers and ISMN enhances the reduction in portal pressure achieved with beta-blockers. This combined drug therapy has been shown to be superior to both beta-blockers alone and to EST.</td>
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<tr>
<td>- The results of trials comparing combined therapy with beta-blockers + ISMN versus EVL have shown that drug therapy is at least as effective as EVL.</td>
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<tr>
<td>- Haemodynamic responders (i.e. those with a decrease in HVPG to &lt;12 mmHg or by &gt;20% of baseline) have a marked reduction in the risk of haemorrhage. Responders to beta-blockers ± ISMN will not need any other treatment, while rescue therapies may be provided to non-responders.</td>
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<td>- TIPS is not recommended as a first-choice treatment to prevent rebleeding but as a rescue therapy.</td>
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EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; ISMN, isosorbide 5-mononitrate; HVPG, hepatic venous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.
is comparable to that achieved with shunt therapy. Furthermore, responders have a lower risk of developing other complications of portal hypertension (such as ascites) and better survival. In keeping with this, responders to beta-blockers + ISMN will not need any other treatment, while rescue therapies should be provided to non-responders who remain at a very high risk of bleeding.

The results of trials comparing pharmacological treatment with beta-blockers plus ISMN versus EVL have shown that combined drug therapy is at least as effective as EVL in preventing variceal rebleeding. No differences in mortality were observed, except in one trial showing an almost significantly better survival with drugs, despite the fact that this is the only study showing superiority of EVL in preventing variceal rebleeding. The addition of beta-blockers to EVL has shown efficacy as compared with EVL alone in two studies, although mortality did not change. On the other hand, the preliminary results of a recent multicentric trial suggest that the addition of EVL to combined drug therapy with beta-blockers plus ISMN may decrease variceal rebleeding as compared with drug therapy alone, although overall rebleeding was similar. These studies support the association of EVL and pharmacological therapy as first-line therapy to prevent variceal rebleeding (Table 3).

Numerous trials have compared endoscopic therapy with TIPS. The meta-analysis of these studies has shown that TIPS is more effective in preventing rebleeding but is also associated with a higher incidence of encephalopathy; survival is similar with

**Figure 2.** Algorithm for the prevention of variceal rebleeding. When available, HVPG monitoring (measuring HVPG at baseline and again within the first month of starting treatment with beta-blockers) provides strong prognostic information. Patients with a decrease in HVPG >20% from baseline or to <12 mmHg (responders) have a low risk of rebleeding, and no other therapy will be required. The best treatment to rescue non-responders has not yet been established. TIPS, transjugular intrahepatic portosystemic shunt; OLT, orthotopic liver transplantation.
both therapies.\textsuperscript{84,85} These results are similar in studies using either EST or EVL for the endoscopic treatment of varices.\textsuperscript{84,85} Furthermore, similar results have been observed in a trial comparing TIPS and combined drug therapy with beta-blockers plus ISMN.\textsuperscript{86} Therefore, TIPS is not recommended as a first-choice treatment to prevent rebleeding, but rather as a rescue therapy.\textsuperscript{87} The currently recommended treatment in patients who fail endoscopic and pharmacological therapies is TIPS or surgical shunts (distal splenorenal shunt or 8 mm H-graft) for those with cirrhosis of Child class A/B.\textsuperscript{88} In non-surgical candidates, TIPS is the only option. Transplantation provides good long-term outcomes in Child class B/C cirrhosis and should be considered. TIPS may be used as a bridge to transplantation.\textsuperscript{87}

**ROLE OF ENDOSCOPIC THERAPY IN THE PREVENTION OF THE FIRST BLEEDING EPISODE**

Since the first publication on the efficacy of beta-blockers,\textsuperscript{89} different randomised trials and the meta-analysis of these studies have shown that non-selective beta-blockers are useful in the primary prophylaxis of variceal bleeding, significantly reducing the risk of a first haemorrhage in patients with large varices and improving survival (Table 4).\textsuperscript{4,90} More recently, randomised controlled studies have also shown the efficacy of prophylactic EVL in this setting.\textsuperscript{91} Subsequently, different studies have compared the value of beta-blockers and EVL in preventing the first bleeding in patients with large varices.\textsuperscript{92} The meta-analysis of 12 trials, including more than 400 patients in each group, showed that EVL significantly reduce the risk of first variceal bleeding, with no differences in mortality.\textsuperscript{31} The rate of side-effects was higher with beta-blockers, although EVL events were more severe with treatment-related mortality in some cases.\textsuperscript{31} A recent small study does not support the idea that adding beta-blockers to EVL may improve the efficacy of EVL alone.\textsuperscript{93} Both beta-blockers and EVL, but not combination therapy, are currently recommended as first-line treatment to prevent first variceal bleeding in patients with large varices (Table 4).\textsuperscript{33,34} Present guidelines recommend classifying oesophageal varices in two grades, small and large, defining large varices as diameter >5 mm.\textsuperscript{34} In prophylactic studies, medium-sized varices have been usually grouped with large varices when three grades are used.\textsuperscript{8}

Around 30\% of patients with large varices have contraindications or intolerance to beta-blockers that preclude their use.\textsuperscript{94} EVL should clearly be offered to these

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<td>• As compared with beta-blockers, EVL reduces the risk of first variceal bleeding without affecting mortality. The rate of side-effects is higher with beta-blockers, although EVL events may be more severe with treatment-related mortality in some cases</td>
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<td>• Beta-blockers reduce portal pressure, achieving haemodynamic response in around 40% of cases. Responders, in addition to a very low risk of bleeding, also have other benefits such as a lower risk of developing ascites or SBP and better survival. These additional benefits should be further explored in future trials</td>
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</table>

EVL, endoscopic variceal ligation; SBP, spontaneous bacterial peritonitis.
patients (Figure 3). In the remaining patients other issues should also be considered. Non-selective beta-blockers reduce portal pressure, achieving an adequate haemodynamic response in around 40% of cases. In addition to a very low risk of bleeding, responders also have other benefits such as a lower risk of developing ascites or SBP. These additional benefits of beta-blockers should be explored in future studies assessing the value of prophylactic therapies. A recent study suggests that assessing acute response to beta-blockers in a single study may predict long-term outcome which clearly simplifies the use of HVPG monitoring to guide therapy. This may allow the possibility of using (or adding) EVL (or other treatments) in acute non-responders to beta-blockers to enhance the efficacy of treatment. Future trials should clarify these points.

Patients with small varices could be treated with non-selective beta-blockers to prevent progression of varices and bleeding, but further studies are recommended by experts due to the limited experience. Patients with small varices with red wale signs or with cirrhosis of Child C class have an increased risk of bleeding and may benefit from treatment (Figure 3). EVL should not be used for primary prophylaxis in patients with small varices. EVL has not been investigated in this setting due to the relatively low risk of bleeding of these patients and the invasive nature of the procedure with the risk of complications.

**GASTRIC VARICES**

In patients with cirrhosis, gastric varices are the source of 5–10% of bleeding episodes. Probably as a consequence of the relatively low incidence of haemorrhage, few randomised trials have been performed on the management of gastric variceal
bleeding. However, bleeding from this source may be more severe than that from oesophageal varices. Patients with gastric varices probably have a lower HVPG, and large gastric varices are often associated with gastrorenal shunts which can reduce portal pressure but not prevent bleeding. Gastric varices that constitute an extension of oesophageal varices along the lesser curvature of the stomach (GOV1) are treated as oesophageal varices.

Limited data are available on gastro-oesophageal varices that extend towards the fundus of the stomach (GOV2). Some endoscopic therapies have been used to treat bleeding from fundal varices, such as EST, glue injection, thrombin, EVL and ligation with large detachable snares. When using EST with conventional sclerosants, high rates of initial control of bleeding have been reported, although rebleeding is common. In randomised studies, endoscopic variceal obturation of gastric varices with tissue adhesives has been more effective than EVL and more effective than EST. Therefore, these glues are the current recommended endoscopic therapy for the management of fundal varices. TIPS may also be effective in this setting and should clearly be used when endoscopic therapy is not possible or fails. In these patients TIPS may be associated with the embolisation of collaterals feeding the varices. Balloon tamponade, with the Linton-Nachlas tube, may serve as a bridge to TIPS in massive bleedings. Trials comparing endoscopic therapy with TIPS and with drugs, both in acute bleeding and to prevent rebleeding, are required to clarify the best management for fundal varices. Isolated fundal varices (IGV1) may be secondary to splenic vein thrombosis, and thus splenectomy may be indicated. In the absence of specific controlled trials on primary prophylaxis of gastric variceal bleeding, endoscopic therapy should not be performed in this setting given the invasive nature of the procedure. Until these trials are available, non-selective beta-blockers may be used for the prevention of the first bleeding.

**Practice points**

- EVL is the endoscopic method of choice for treating oesophageal varices
- no beneficial effects have been observed by combining EST and EVL
- the association of vasoactive drugs and EVL is the first-line therapy in acute variceal bleeding
- combined therapy with EVL and beta-blockers with or without isosorbide mononitrate is best choice to prevent rebleeding
- EVL is effective in preventing a first variceal bleed and should be offered to patients with large varices and a contraindication or intolerance to beta-blockers
- variceal obliteration with tissue adhesives is the preferred treatment for gastric varices

**Research agenda**

- prognostic factors of failure of drugs in acute bleeding to be used for guided therapy to rescue patients at high risk
- best rescue therapies
EVL has proven more effective and safer than EST and is at present the endoscopic method of choice for treating oesophageal varices. No beneficial effects have been observed by combining EST and EVL as compared with EVL alone. Variceal obturation with tissue adhesives such as cyanoacrylates is effective in the treatment of gastric varices. In acute oesophageal variceal bleeding, vasoactive drugs (either terlipressin or somatostatin) should be started as soon as possible, before diagnostic endoscopy, and maintained for 2–5 days. The efficacy of drugs is improved associated with emergency endoscopic therapy. Adding EVL improves the efficacy and safety achieved with the addition of EST. Antibiotic prophylaxis should be an integral part of therapy in acute bleeding. To prevent rebleeding, both EVL and the combination of beta-blockers and ISMN may be a valid first-line choice. Adding beta-blockers improves the efficacy of EVL alone. Haemodynamic responders – that is, those with a decrease in HVPG to <12 mmHg or by >20% of baseline – have a reduction in the risk of haemorrhage to below 10% of cases. Responders to beta-blockers with or without ISMN will not need further treatment, while rescue therapies should be provided to non-responders. TIPS is the recommended rescue therapy when EVL with or without drugs fails. Beta-blockers significantly reduce the risk of a first haemorrhage in patients with large varices and improve survival. As compared with beta-blockers, EVL reduces the risk of first bleeding with no differences in mortality, and should clearly be offered to patients with large varices and contraindications or intolerance to beta-blockers.

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