REVIEW

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Challenges in the Management of Esophagogastric Varices and Variceal Hemorrhage in Cirrhosis — A Narrative Review

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ABSTRACT

Over the past decade, significant advancements in pharmacological, endoscopic, and radiographic treatments have emerged in the management of patients with cirrhosis and esophagogastric varices or variceal hemorrhage. These advances have been in several areas, including the role of screening and primary prophylaxis (preventing an initial variceal bleed), evaluation and management of acute esophagogastric variceal hemorrhage, and in preventing variceal rebleeding. Therefore, we believe there is a need for an updated, evidence-based "narrative review" on this important clinical topic that will be relevant for internists, hospitalists, intensive care unit physicians, and those in training. We believe the guidance presented in this narrative review will enhance daily medical practice of health care professionals and has the potential to improve quality of care for these complex patients.

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INTRODUCTION

Advanced chronic liver diseases can result in portal hypertension, which may lead to serious complications such as esophagogastric variceal hemorrhage requiring urgent evaluation and management. This review provides guidance on the evaluation and management of esophagogastric varices including screening/primary prophylaxis (preventing a first variceal bleed), acute variceal bleeding, and secondary prophylaxis (preventing recurrent variceal hemorrhage).

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SCREENING FOR HIGH-RISK ESOPHAGEAL VARICES AND PRIMARY PROPHYLAXIS

The rationale for conducting endoscopic screening in patients with cirrhosis is to detect patients that have esophageal varices at high risk for having a variceal hemorrhage, with the aim to treat them and thus prevent bleeding and improve patient survival. High-risk esophageal varices are those large in size or of any size and with red signs (eg, red wale markings, erythematous raised spots).[1]

The risk of having high-risk varices increases when liver function deteriorates and hepatic decompensation occurs (ie, presence of ascites, hepatic encephalopathy) or when the liver stiffness measurement (LSM, measured by

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transient elastography) is >20 kPa or platelet count is $<150 \times 10^9$/L. Transient elastography (TE) is a noninvasive method that measures liver stiffness using ultrasound waves and has been shown to accurately assess the severity of hepatic fibrosis and portal hypertension in patients with chronic liver disease. The results are given in kilopascals (kPa), and "normal" results are 2 kPa to 7 kPa. However, the accuracy of TE markedly decreases in obese patients, when measurements are not done after at least 4 hours of fasting, or in patients with hepatic congestion, cholestasis, or increased levels of transaminases. In these situations, the measured LSM values may be overestimated. The presence of high-risk varices is highly likely when LSM is >20 kPa. If TE is not locally available, patient referral to a medical center/hepatology specialist with this technology should be considered.

Consequently, endoscopic screening for high-risk esophageal varices is recommended in patients when liver function deteriorates, and hepatic decompensation occurs, or when LSM is >20 kPa or platelet count is $<150 \times 10^9$/L. Patients with compensated cirrhosis and LSM ≤20 kPa and platelet count $>150 \times 10^9$/L are unlikely to have high-risk varices (<5%) and therefore, endoscopic screening for esophageal varices can be avoided[2,3] (Figure 1). In patients with cirrhosis who are already on a nonselective beta-blocker (NSBB), and because NSBB is the treatment of choice in high-risk varices, screening endoscopy is not indicated because the presence of esophageal varices would not alter patient management.[2,3] A recent randomized study demonstrated that the administration of NSBB to patients with compensated cirrhosis and clinically significant portal hypertension (CSPH, defined as a hepatic venous pressure gradient ≥10 mm Hg) without esophageal varices or with small, non-high-risk varices, prevents the development of hepatic decompensation, including variceal hemorrhage.[4] This has led to the proposal that NSBB treatment could be administered to all patients with compensated cirrhosis and CSPH, diagnosed either invasively (hepatic venous pressure gradient ≥10 mm Hg) or noninvasively (eg, LSM ≥25 kPa),[5] irrespective of the presence of esophagogastric varices. If this proposal is confirmed/demonstrated, then all patients with CSPH should be treated with NSBB regardless of whether they have esophageal varices (endoscopy would then not be required), and the aim of NSBB treatment would not only be to prevent bleeding, but to prevent any complication of portal hypertension.[2,3]

CLINICAL SIGNIFICANCE

- In patients with compensated cirrhosis and liver stiffness measurement ≤20 kPa and platelet count $>150 \times 10^9$/L, endoscopic screening for esophageal varices can be avoided.
- Nonselective beta-blockers (NSBB) are the first line option for preventing an initial variceal bleed.
- In suspected variceal bleed, gentle hemodynamic resuscitation, a restrictive red blood cell transfusion policy, initiation of vasoactive medication and prophylactic antibiotic, and endoscopy within 12 hours is recommended.
- In secondary prophylaxis, carvedilol should be the NSBB of choice.

PRIMARY PROPHYLAXIS

Primary prophylaxis should prevent variceal bleeding and other potential complications of portal hypertension (ie, ascites, spontaneous bacterial peritonitis, hepatic

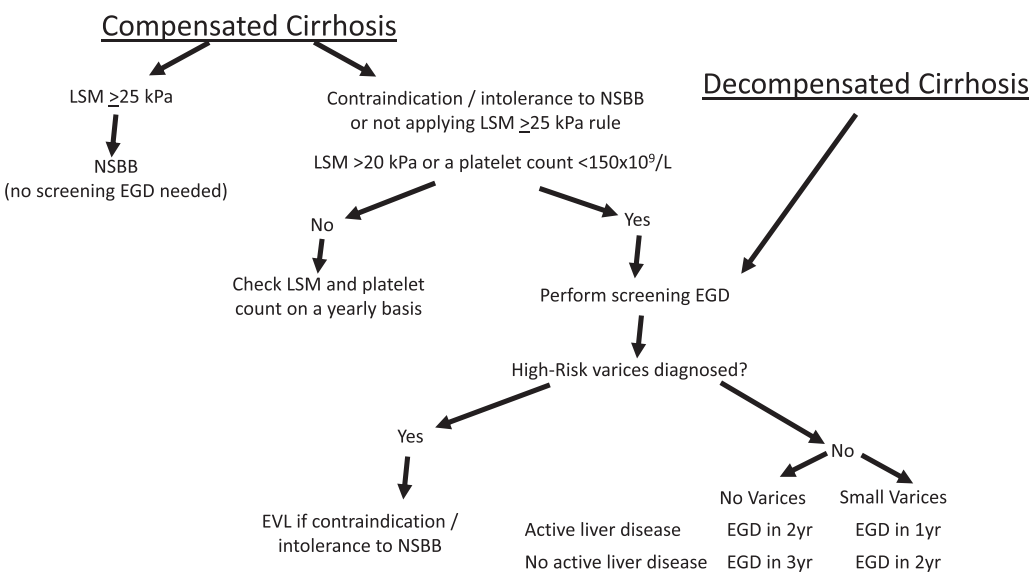

Figure 1 Where and when endoscopic screening is indicated.

encephalopathy) and improve patient survival. Primary prophylaxis modalities include NSBB or endoscopic therapy.

NONSELECTIVE BETA-BLOCKERS (NSBB)

NSBB is the first-line treatment option for primary prophylaxis as it is the only treatment shown to change the natural history of the disease. Propranolol, nadolol, and carvedilol reduce portal venous inflow by β_1 and β_2 adrenergic receptor blockade and have been shown to be effective in preventing a first variceal bleeding event. Carvedilol also has mild anti-alpha 1 adrenergic activity and is a nitric oxide donor that lowers hepatic vascular tone and hepatic resistance, thereby further reducing portal pressure.[6] Carvedilol is the preferred NSBB in patients with compensated cirrhosis because its portal pressure-lowering effect is more potent than that of traditional NSBB, and it has been shown to be more effective in preventing hepatic decompensation and improving survival.[4,6,7]

ENDOSCOPIC VARICEAL LIGATION

In patients with intolerance or contraindication to NSBB (eg, hypotension, shortness of breath, fatigue, bronchoconstriction, heart failure, sexual dysfunction) and high-risk varices, endoscopic variceal ligation (EVL) is indicated for primary prophylaxis for esophageal varices with the aim of variceal eradication.[2,3,8,9] Once esophageal varices are eradicated, surveillance endoscopy should be performed every 3 to 6 months for 1 year and then annually thereafter to assess for variceal recurrence[2,3,8,9] requiring retreatment.

GASTRIC VARICES

Gastric varices are classified, following Sarin's classification, as esophagogastric type 1 (gastroesophageal varix type 1 [GOV1]: an extension of esophageal varices along the lesser curvature of the stomach), esophagogastric type 2 (GOV2: an elongation of esophageal varices into the gastric fundus), isolated gastric varices type 1 (IGV1: cardio-fundal varices) and isolated gastric type 2 (IGV2: varices located in any other gastric location).[10,11] There are very limited data about primary prophylaxis of gastric varices. A randomized controlled study suggested that cyanoacrylate injection is more effective than propranolol or therapeutic abstinence (no treatment) in preventing an initial gastric variceal bleed.[12] However, there were no significant differences in survival among the 3 treatment arms. Based on the potential higher risks of adverse events (ie, pulmonary embolization) of cyanoacrylate injection and because NSBB reduces portal hypertension, which can, in turn, lower the risk of portal hypertension-related hepatic decompensation, NSBB is the preferred option for primary prophylaxis for gastric varices.[2,3,8,9] In patients with intolerance or contraindication to NSBB, management (endoscopic treatment, therapeutic abstinence), should be decided on a case-by-case basis.[8]

INITIAL EVALUATION AND TREATMENT OF SUSPECTED ACUTE VARICEAL HEMORRHAGE

Variceal hemorrhage is a severe and life-threatening complication of cirrhosis with portal hypertension. At the time of patient presentation, urgent assessment of hemodynamic status should be performed. If hemodynamic instability exists, prompt, yet careful intravascular volume replacement using crystalloid fluids should be initiated to avoid a paradoxical increase in portal hypertension and subsequent bleeding risk.[13,14] Moreover, for patients with cirrhosis, a liberal red blood cell (RBC) transfusion strategy has been shown to increase portal pressures, which can directly mediate rebleeding. A systematic review/meta-analysis of randomized controlled trials (RCTs), comparing restrictive vs liberal RBC transfusion for acute upper gastrointestinal bleeding, reported that a restrictive RBC transfusion strategy was associated with a significant overall reduction in mortality and rebleeding, with no difference in the risk of ischemic events.[15] The treatment effect on mortality was greatest in patients with cirrhosis, with a 48% reduction in the risk of death using a restrictive RBC transfusion policy. Moreover, there was an almost 6% absolute risk reduction for rebleeding in the cirrhosis group, with the number needed to treat to prevent one rebleeding event using a restrictive RBC transfusion strategy equaling 17.[15] A hemoglobin of <7-8 g/dL to initiate RBC transfusion is recommended.[16] For patients with ischemic vascular comorbidities (eg, coronary artery disease) a hemoglobin of <8-9 g/dL to initiate RBC transfusion is recommended.[8,15]

In patients with suspected variceal hemorrhage, current international, evidence-based guidelines recommend endoscopic evaluation as soon as safely possible (within 12 hours from the time of patient presentation) provided the patient has been hemodynamically resuscitated.[2,3,8,9]

Vasoactive medications (eg, terlipressin, octreotide, or somatostatin) reduce splanchnic blood flow and portal pressure, rapidly reducing variceal pressure and helping in the control of hemorrhage.[17] RCTs and systematic reviews/meta-analyses have demonstrated the efficacy and safety of vasoactive agents in variceal hemorrhage.[18] They should be initiated at the time of patient presentation, yet the exact duration of treatment remains without consensus. For many years it was considered necessary for vasoactive agents to be maintained for 5 days because this is the time that rebleeding is more frequent. More recent data suggest that 48 hours may be adequate.[2,3,8,9]

Patients with cirrhosis presenting with acute variceal hemorrhage are at high risk for bacterial infection, which can lead to a higher risk of rebleeding and increased mortality.[19,20] In this clinical scenario, antibiotic prophylaxis reduces the risk of bacterial infection as well as overall mortality, the rate of variceal rebleeding, and length of hospital stay.[21,22] Ceftriaxone (1 g IV/24 hours) has been shown to be superior to norfloxacin in the prevention of bacterial infections, bacteremia, and spontaneous bacterial peritonitis in cirrhotic patients with variceal hemorrhage.[23]

Table 1 Pre-Endoscopy Management of a Patient with Suspected Acute Esophagogastric Variceal Hemorrhage

- Initiate hemodynamic resuscitation (using IV crystalloid fluids with gentle infusion rate)
- Use restrictive RBC transfusion strategy
- Start vasoactive medication (eg, terlipressin, octreotide, somatostatin*)
- Give antibiotic prophylaxis (eg, ceftriaxone)
- Temporarily withhold antiplatelet agents and anticoagulants†
- Consider endotracheal intubation in selected patients‡
- Consider giving IV promotility agent prior to EGD (eg, erythromycin)
- Perform EGD within 12 hours of patient presentation following hemodynamic resuscitation

EGD = esophagogastroduodenoscopy; IV = intravenous; RBC = red blood cells.

*Terlipressin: Initial 48 hours: 2 mg IV every 4 hours until control of bleeding, then maintenance: 1 mg IV every 4 hours to prevent rebleeding for 2-5 days duration; Octreotide (Somatostatin analogue): Initial IV bolus of 50 ug (can be repeated in first hour if ongoing bleeding) then continuous IV infusion of 50 ug/h for 2-5 days duration; Somatostatin: Initial IV bolus 250 ug (can be repeated in the first hour if ongoing bleeding) then continuous IV infusion of 250-500 ug/h for 2-5 days duration.

†Restarting of antiplatelet agents/anticoagulants should be guided by patient risk of re-bleeding vs risk of thrombosis.

‡Endotracheal extubation should be performed as soon as clinically safe following EGD.

Ceftriaxone is the recommended antibiotic of choice for prophylactic therapy, but local antimicrobial policy should always be considered.[2,3,8,9] The general recommendation for duration of antibiotic prophylaxis is 7 days, although limited data suggest 3 days may suffice[24] (Table 1).

ACUTE ESOPHAGEAL VARICEAL HEMORRHAGE

The endoscopic diagnosis of esophageal variceal bleeding is made when there is active hemorrhage from an esophageal varix or an endoscopic sign of recent hemorrhage (eg, nipple sign, fibrin-platelet plug) is seen. Endoscopic variceal ligation has been shown to be superior to sclerotherapy (better control of bleeding and prevention of rebleeding, lower mortality, and fewer adverse events) and is the recommended first-line treatment in esophageal variceal hemorrhage, while injection sclerotherapy is used only when ligation is not possible.[2,3,8,9,25,26]

The use of hemostatic topical agents in the endoscopic treatment of gastrointestinal bleeding is relatively new, and there is very limited high-level evidence evaluating their role in acute variceal hemorrhage.[27] Current guidelines do not recommend topical agents as first-line endoscopic treatment of esophageal or gastric variceal hemorrhage.[2,8] These may be considered as a stop-gap measure or bridge to more definitive therapy and may allow for patient stabilization when standard endoscopic treatment is not effective or expertise in endoscopic hemostasis for variceal bleeding is not readily available.

It is crucial to note that even after successful initial endoscopic hemostasis in patients with acute esophageal variceal hemorrhage, 10%-15% may experience rebleeding, which is associated with a worse prognosis. Identification of these patients in whom a more effective therapy aimed at preventing rebleeding (pre-emptive transjugular intrahepatic portosystemic shunt [TIPS]) is recommended. This rebleeding risk is mainly seen in Child-Pugh C patients and Child-Pugh B >7 with active bleeding at the time of initial endoscopy despite the use of vasoactive medications (Table 2). In this subgroup of "high-risk patients," observational studies, RCTs and a meta-analysis have demonstrated that the placement of pre-emptive TIPS leads to significantly reduced esophageal variceal rebleeding, and significantly improved transplantation-free survival and overall survival, without an increase in adverse events, including hepatic encephalopathy.[28–31] Consequently, recent guidelines recommend performing risk stratification at the time of index endoscopy to identify patients at high risk and placement of pre-emptive TIPS within the first 72 hours in those patients meeting high-risk criteria.[2,8,31]

In patients presenting with *refractory/persistent* esophageal variceal bleeding despite vasoactive pharmacotherapy and endoscopic hemostasis, temporizing measures,

Table 2 Child-Pugh Score

Criteria	Points		
	1	2	3
Albumin g/dL	>35	28-35	<28
Ascites	None	Mild-moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin mg/dL	<2	2-3	>3
Encephalopathy (grade)	None	Mild-moderate (Grade 1 or 2)	Severe (Grade 3 or 4)
INR	<1.7	1.7-2.3	>2.3
Child-Pugh Class	Total Points*	Severity of Liver Disease	
A	5-6	Least severe	
B	7-9	Moderately severe	
C	10-15	Most severe	

INR = international normalized ratio.

*Calculated by adding the points for each of the 5 criteria.

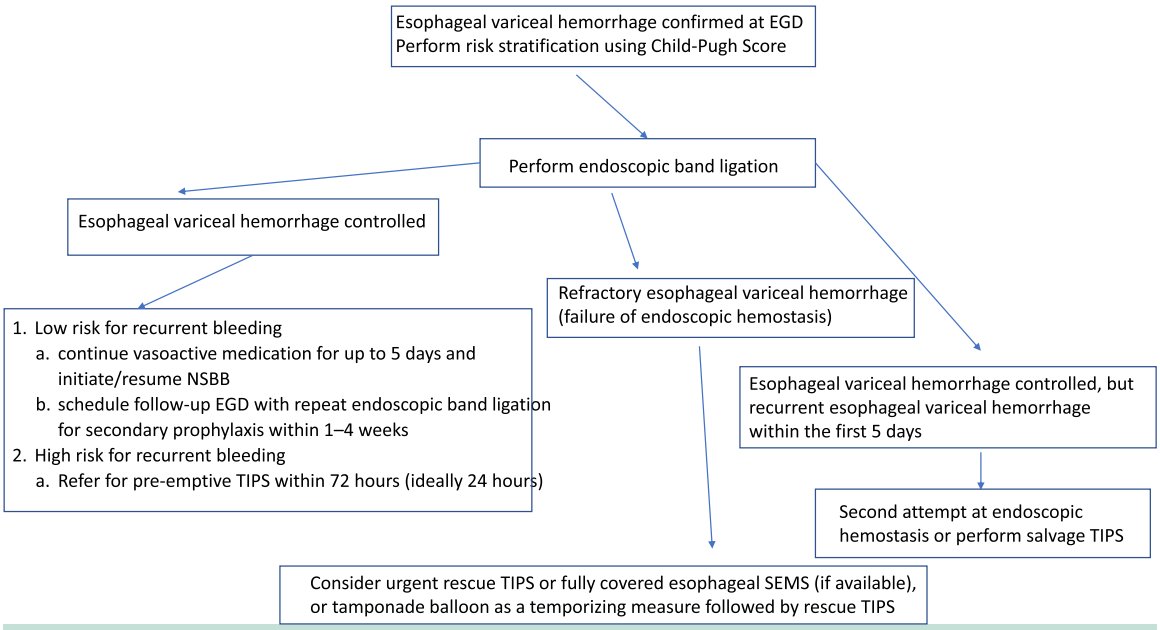

Figure 2 Algorithm for the management of acute esophageal variceal hemorrhage.

including balloon tamponade (eg, Sengstaken-Blakemore Tube) or fully covered self-expanding metal stents may be used to control bleeding.[8] These bridging therapies are utilized until definitive treatment with rescue TIPS can be performed.

Balloon tamponade as rescue therapy can control bleeding in up to 90% of patients, but is associated with potential adverse events including esophageal ulceration, perforation, and aspiration pneumonia.[32] Therefore, balloon tamponade tubes should not remain in place for more than 24 hours, by which time definitive treatment should be administered. Self-expanding fully covered metal stent deployment in the esophagus provides variceal tamponade and bleeding control and can remain in place for up to 14 days, allowing more time for further management decisions. Potential adverse events with self-expanding metal stents include stent migration and esophageal ulceration.[33]

In patients experiencing esophageal variceal rebleeding during hospitalization, a second attempt at endoscopic hemostasis or rescue TIPS placement is recommended (Figure 2).

ACUTE GASTRIC VARICEAL HEMORRHAGE

While not as prevalent as esophageal variceal hemorrhage, gastric variceal hemorrhage is more severe, with higher associated mortality and treatment failure.[11] It is important to note that because GOV1 gastric varices are endoscopically managed the same as esophageal varices, this section will refer exclusively to GOV2 and IGV1 gastric varices (also referred to as cardio-fundal varices).

Endoscopic treatments for gastric variceal hemorrhage include cyanoacrylate glue injection, injection sclerotherapy, thrombin injection, endoscopic ultrasound-guided embolization combined with cyanoacrylate glue injection, and band ligation. Interventional radiology techniques such as TIPS and obliteration of portosystemic shunts with balloon-occluded retrograde transvenous obliteration (BRTO) can also be used in selected cases.[2,8,31]

Although high quality data for the optimal endoscopic therapy of gastric variceal bleeding remain limited, there is consensus in recommending cyanoacrylate glue injection for acute cardio-fundal variceal (GOV2, IGV1) hemorrhage.[2,3,8,9,34] Although uncommon, potential adverse events associated with the use of cyanoacrylate injection include sepsis, distal embolic events (eg, pulmonary, cerebral), and ulceration at the varix injection site. Cyanoacrylate glue is not currently approved in the United States for the treatment of gastric variceal bleeding.

EUS-guided coil embolization combined with cyanoacrylate glue injection for treating gastric variceal hemorrhage has been reported to have high treatment efficacy, high gastric variceal obliteration rates, low gastric variceal recurrence, limited early and late rebleeding rates, and low adverse event rates.[35-37] A recent guideline from the European Society of Gastrointestinal Endoscopy suggests that EUS-guided management of bleeding gastric varices combining injection of coils and cyanoacrylate may be an option in centers with expertise in this technique.[8]

Emerging data from a small RCT reported that pre-emptive TIPS, performed within 1 to 5 days of hospital admission, may significantly improve rebleeding-free survival in Child-Pugh B and C patients with cardio-fundal variceal hemorrhage.[38] There are very limited high-level data

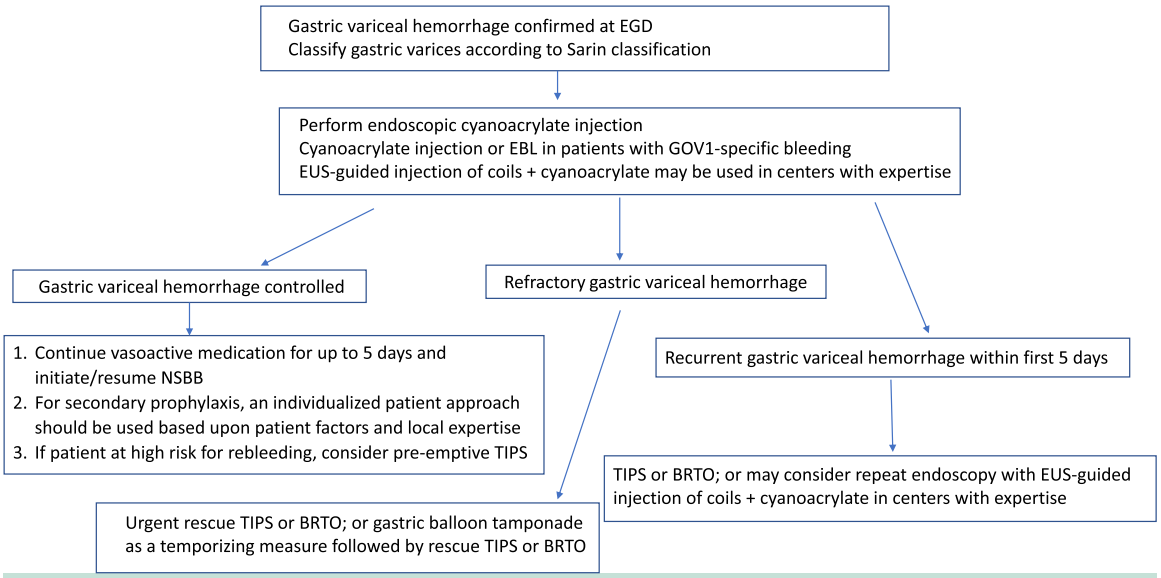

Figure 3 Algorithm for the management of acute gastric variceal hemorrhage.

directly comparing TIPS vs BRTO when endoscopic hemostasis has failed or early recurrent gastric variceal bleeding occurs.[32,39,40] BRTO accesses the gastric varices from systemic veins (ie, gastrorenal or gastrocaval shunts) and directly obliterates the collateral veins. However, although BRTO reduces rates of variceal rebleeding, it can further increase portal pressure.

Both TIPS and BRTO have similar technical success rates and adverse event rates. While TIPS is associated with higher rates of hepatic encephalopathy, BRTO requires a patent portal vein and the presence of a splenorenal shunt and can aggravate portal hypertension and esophageal varices. Patient selection and local technical expertise are important, yet given the limited quality of comparative data, specific selection criteria are not currently available (Figure 3).

SECONDARY PROPHYLAXIS (PREVENTION OF REBLEEDING) — ESOPHAGEAL VARICES

Following an initial episode of variceal bleeding, the risk of recurrent bleeding is as high as 60% during the first year if no treatment is administered.[41] Moreover, recurrent variceal bleeding represents further hepatic decompensation and portends a poor prognosis. Therefore, secondary prophylaxis is mandatory in all patients surviving an episode of acute variceal bleeding.

Combination Therapy (NSBB + EVL)

The combination of an NSBB and EVL is the treatment of choice in patients who do not meet the high-risk criteria for esophageal varices or are not candidates for pre-emptive TIPS. Combination therapy has been proven superior to any monotherapy.[42]

Is There a Preferred NSBB in Secondary Prophylaxis?

In secondary prophylaxis, observational data demonstrate that carvedilol plus EVL is associated with lower rates of rebleeding, liver-related mortality, and further nonbleeding liver decompensation when compared with classic NSBB.[43,44] Therefore, carvedilol should be the NSBB of choice.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) FOR SECONDARY PROPHYLAXIS

TIPS is an effective therapy in decreasing portal pressure and its complications, however, its use in secondary prophylaxis is not recommended as first-line therapy. Two studies comparing TIPS vs EVL + NSBB have demonstrated the benefit of TIPS in reducing variceal re-bleeding rates.[45,46] However, there was no reduction in mortality; yet it significantly increased rates of hepatic encephalopathy and therefore, cannot currently be recommended as first-line treatment.[31] TIPS is, however, recommended for patients who fail first-line therapy (eg, NSBB or NSBB + EVL) and have recurrent variceal bleeding,[2,8,31] and should be evaluated in patients with a contraindication or intolerance to NSBB.

SECONDARY PROPHYLAXIS (PREVENTION OF REBLEEDING) — GASTRIC VARICES

Patients with GOV1 varices should be managed similarly to esophageal varices, while the best strategy to prevent GOV2/IGV1 rebleeding has been less studied. TIPS has been compared with cyanoacrylate glue injection in one RCT demonstrating that patients treated with TIPS had

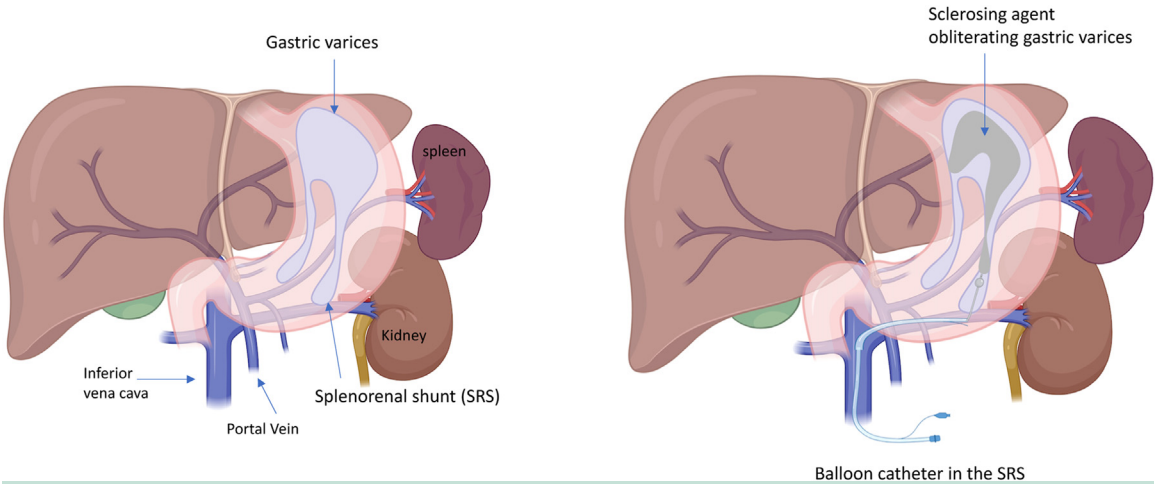

Figure 4 Balloon-occluded retrograde transvenous obliteration.

lower rates of gastric variceal rebleeding and no difference in survival or hepatic encephalopathy.[47]

BRTO has shown significantly higher efficacy in the prevention of gastric variceal rebleeding compared with repeated cyanoacrylate injection (2-year probability of rebleeding 7% vs 35% $P = .004$), but with no difference in survival[48] (Figure 4).

Even if both TIPS and BRTO have shown superiority to cyanoacrylate glue injection in the secondary prevention of gastric variceal hemorrhage, no RCT has compared TIPS with BRTO, and the choice of treatment should be taken based on local technical expertise and anatomical/pathophysiological considerations (ie, significant ascites or portal vein thrombosis would favor TIPS, whereas a history of recurrent hepatic encephalopathy or deteriorated liver function would favor BRTO).

In conclusion, progress has been made during the past decade in the evaluation and treatment of patients with esophagogastric varices and variceal hemorrhage secondary to cirrhosis. In patients with "compensated" cirrhosis and LSM $\leq$20 kPa and platelet count $>150 \times 10^9$/L, endoscopic screening for esophageal varices can now be avoided. Nonselective beta-blockers should be the first-line treatment option for preventing an initial variceal bleed (primary prophylaxis). In suspected variceal bleeding, gentle hemodynamic resuscitation, a restrictive RBC transfusion policy, initiation of vasoactive medication and prophylactic antibiotic, and endoscopy within 12 hours is recommended. The use of EUS-guided treatment of gastric varices can be considered at centers with expertise in this technique. Last, for preventing recurrent variceal bleeding (secondary prophylaxis), carvedilol should be the NSBB of choice. For patients not amenable or not responsive to endoscopic hemostasis, interventional radiographic techniques, including TIPS and BRTO, should be considered as preventive or rescue therapies.

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