Evaluation and Management of Esophageal and Gastric Varices in Patients with Cirrhosis

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KEYWORDS

- Esophageal varices • Gastric varices • Nonselective beta-blocker
- Endoscopic variceal ligation • Variceal bleeding • Portal hypertension • Cirrhosis
- Decompensated cirrhosis

KEY POINTS

- Gastroesophageal varices can be seen endoscopically in patients with cirrhosis in the compensated and the decompensated stages but are more common in decompensated patients.
- In patients with compensated cirrhosis, the presence of gastroesophageal varices on endoscopy is indicative of the presence of clinically significant portal hypertension, the main predictor of decompensation.
- In patients with varices that have never ruptured, the use of nonselective beta-blockers is preferred, as they will not only prevent the first episode of variceal hemorrhage, but will also prevent the development of other decompensating events.
- Acute variceal bleeding is a life-threatening complication of cirrhosis, but the mortality associated with it has decreased with current management based on careful blood transfusion, vasoactive medications, antibiotics, and endoscopic and pre-emptive transjugular intrahepatic portosystemic shunts.
- Prevention of recurrent variceal hemorrhage is based on the combination of nonselective beta-blockers and endoscopic variceal ligation.

TYPES OF GASTROESOPHAGEAL VARICES

Esophageal varices are the most common type of gastroesophageal varices, with a prevalence of 50% to 60% among patients with cirrhosis, and up to 85% in patients with decompensated cirrhosis. Gastric varices are present in about 20% of patients with cirrhosis, and they can be of different types.[1] Sarin classification[2] is the most commonly classification used to define the type of gastric varices (**Fig. 1**). GOV type

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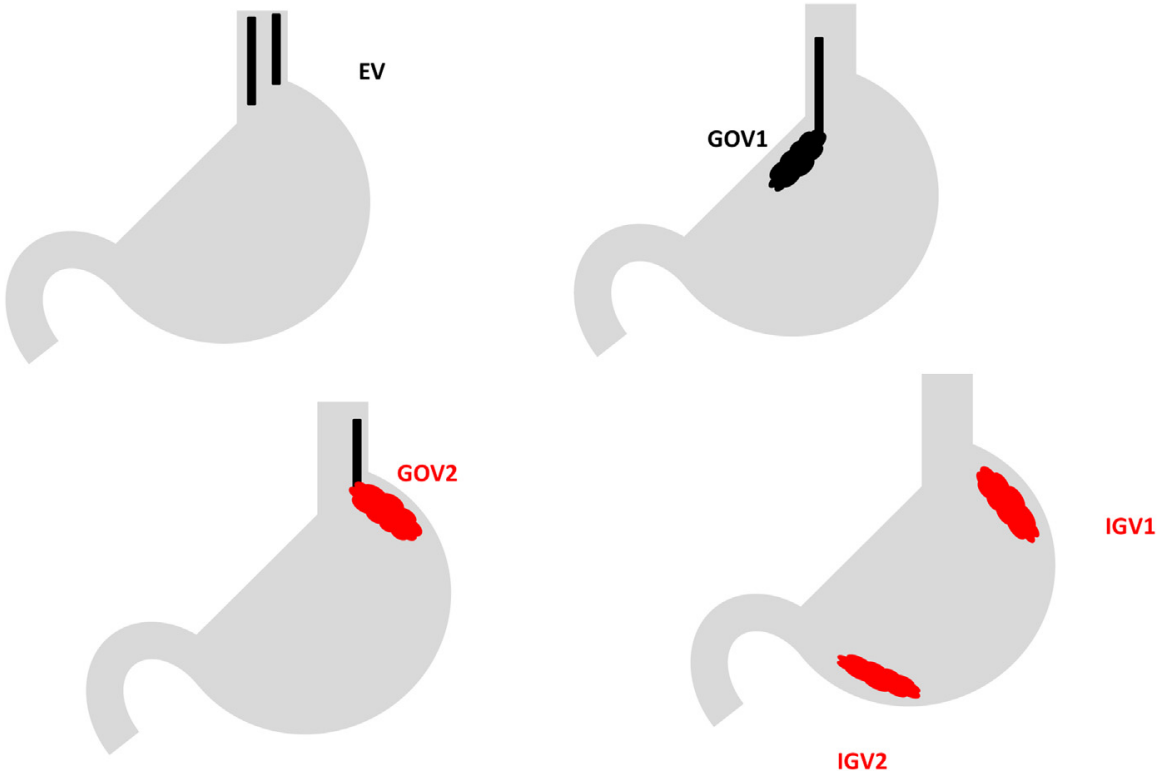

Fig. 1. Classification of gastroesophageal varices.

1 (GOV1) are esophageal varices extending below the cardia into the lesser curvature and are the most common (75% of gastric varices). GOV type 2 (GOV2) are esophageal varices extending into the fundus. Isolated GV type 1 (IGV1) are located in the fundus (IGV1). Isolated GV type 2 (IGV2) are located elsewhere in the stomach but are rare.

Esophageal varices and GOV1 will be considered together as gastroesophageal varices (GEV), because their management is the same. GOV2 and IGV1 will be referred to as fundal varices, and their specific therapeutic approach will be discussed separate from GEV.

In order to make an impact on the natural history of varices and improve clinical outcomes, specific interventions are recommended and will be discussed throughout this article. Variceal screening, surveillance, and prophylaxis of variceal bleeding are usually addressed in an outpatient setting, while acute variceal bleeding requires inpatient care and sometimes transfer to a tertiary center. Among the cirrhosis quality metrics developed by the American Association for the Study of Liver Diseases (AASLD),[3] 7 measures are applicable to the management of varices (**Table 1**). These measures aim to prevent variceal bleeding, but based on emerging data, the paradigm may change, with a focus on treating clinically significant portal hypertension rather than high-risk varices, and preventing any decompensations (eg, variceal bleeding, ascites, or hepatic encephalopathy) rather than just variceal bleeding (**Fig. 2**).

This new paradigm is based on a large randomized controlled trial (PREDESCI trial)[4] showing that nonselective beta-blockers (NSBBs) prevent decompensation (not only variceal hemorrhage, but mainly ascites) in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH). In this trial, CSPH was diagnosed using invasive measures: hepatic venous pressure gradient (HVPG) of 10 mm Hg or higher. However, CSPH can be diagnosed noninvasively by liver stiffness measurement/platelet count, presence of gastroesophageal varices (any size) and/or presence of large collaterals on cross-sectional imaging. Therefore, in patients with compensated

Table 1
American Association for the Study of Liver Diseases cirrhosis quality metrics regarding gastroesophageal varices

Variceal screening	• Patients with cirrhosis, with platelet count < 150,000/mm^3 or liver stiffness measurement > 20 kPa, and no documentation of previous gastrointestinal (GI) bleeding, should have EGD to screen for varices within 12 months of cirrhosis diagnosis. • Patients with decompensated cirrhosis and no documented history of previous GI bleeding should have EGD to screen for varices within 3 mo of cirrhosis diagnosis.
Primary prophylaxis of variceal bleeding	• Patients with cirrhosis, no documented history of previous GI bleeding, and medium/large varices on endoscopy should receive either NSBBs or EVL within 1 mo of varices diagnosis.
Variceal bleeding	• Patients who are admitted with or develop GI bleeding should receive antibiotics within 24 h of admission or presentation. Antibiotics should be continued for at least 5 d. • Patients with cirrhosis who present with upper GI bleeding should have EGD within 12 h of presentation. • Patients with cirrhosis who are found to have bleeding esophageal varices should receive EVL or sclerotherapy at the time of index endoscopy.
Secondary prophylaxis of variceal bleeding	• Patients with cirrhosis who survive an episode of acute variceal hemorrhage should receive a combination of EVL and NSBBs.

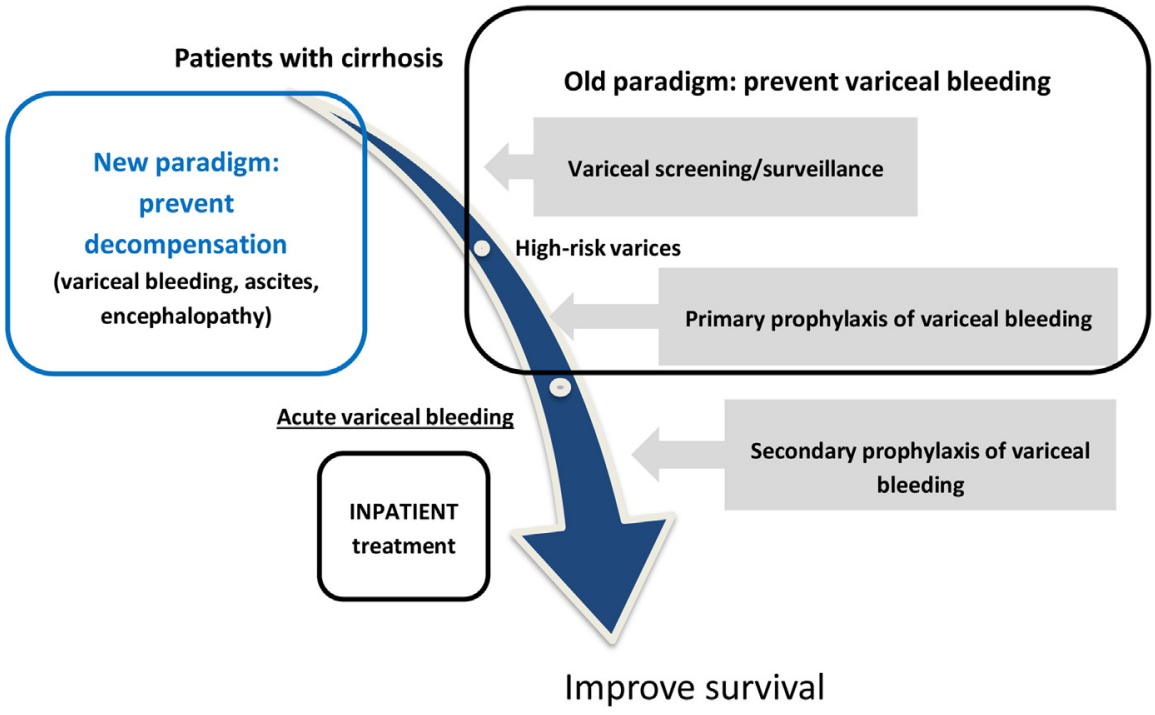

Fig. 2. Management of varices and points of intervention.

cirrhosis and varices, NSBBs would be preferred over endoscopic variceal ligation (EVL). In a patient who has obvious collaterals on imaging, esophagogastroduoendoscopy (EGD) may not even be necessary.

OUTPATIENT MANAGEMENT OF GASTROESOPHAGEAL VARICES

The most common scenario in an outpatient setting requiring gastroenterologists to think about GEV is when a patient presents for management of cirrhosis. A practical 3-pronged approach includes: establishing the stage of cirrhosis, deciding if or when to proceed with upper endoscopy, and determining if treatment is needed or what what type of treatment is necessary.

Establishing the Stage of Cirrhosis

The first step in the assessment of GEV is establishing the stage of cirrhosis: compensated or decompensated. Patients can transition from one stage to another, and the stage of cirrhosis is essential when deciding the management of GEV. When using Child–Turcotte–Pugh (CTP) classification, patients in CTP-A class are compensated, and patients in CTP-B/C class are mostly decompensated.

Compensated cirrhosis

Compensated cirrhosis is asymptomatic, and its diagnosis is based on:

- Clinical findings (eg, firm and/or enlarged left liver lobe, splenomegaly, spider angioma, or palmar erythema)
- Laboratory data (eg, thrombocytopenia, liver synthetic dysfunction with abnormal albumin, international normalized ratio [INR], bilirubin)
- Imaging (eg, nodular liver, with or without portal hypertension suggested by recanalized umbilical vein, portosystemic collaterals, splenomegaly)
- Liver elastography, if available (based on Baveno VI consensus,[5] patients with 2 separate liver stiffness measurements [LSM] > 15 kPa on transient elastography [TE] have severe fibrosis or compensated cirrhosis and are at risk to develop GEV)
- Liver biopsy, when data are discordant

Decompensated cirrhosis

Decompensated cirrhosis is easier to diagnose, as it is defined by the presence of any overt complications of cirrhosis such as ascites, hepatic encephalopathy, and/or variceal hemorrhage. In addition to the suggestive history and physical examination, laboratory and imaging data confirm the diagnosis, and liver biopsy is rarely needed.

Determining If and When an Upper Endoscopy Is Indicated

In patients with compensated cirrhosis, the severity of portal hypertension correlates with the development of GEV and risk of variceal bleeding.[6] Patients with compensated cirrhosis and without clinically significant portal hypertension (CSPH) are at a low risk of having or developing varices in the next 5 years. GEV usually occur once patients develop CSPH, and patients with CSPH not only have a higher risk of developing varices but also have a higher risk of decompensation.[7] The presence or absence of CSPH is determined by measuring the hepatic venous pressure gradient through transjugular hepatic vein catheterization, and is useful in research but impractical in routine clinical care. Noninvasive tests such as imaging showing portosystemic collaterals or recanalized umbilical vein or reversal of portal flow, liver stiffness measurement, platelet count,

and spleen diameter can help identify patients with a high risk of CSPH across cohorts of patients with different etiology of cirrhosis or posthepatitis C eradication.[8–16]

Compensated cirrhosis

In the case of no EGD in patients with LSM greater than 20 to 25 kPa by TE or recanalized umbilical vein/portosystemic collaterals on imaging, it should be noted that these patients are likely to have CSPH. They benefit from NSBBs, with the goal of preventing decompensation (based on PREDESCI trial,[4] they should receive carvedilol or propranolol).

If there is EGD in patients with compensated cirrhosis with likely CSPH but who cannot tolerate or have contraindications to NSBBs, patients should be monitored for development of large varices that would benefit from EVL.

Decompensated cirrhosis

Screening EGD in patients with decompensated cirrhosis is still recommended to be performed at the time of diagnosis of cirrhosis decompensation, followed by annual surveillance EGD if no varices were seen on prior EGD.

Given the presence of decompensation, all these patients have CSPH. Turco and colleagues[17] showed in a meta-analysis including patients with and without ascites that those who respond to treatment with NSBBs (based on reduction of HVPG) have a reduced risk of events, death, or liver transplantation. These data suggest that patients with decompensated cirrhosis have additional benefits from NSBBs regardless of presence of varices at high risk of bleeding, and EGD may not be required in the future to initiate NSBB.

Of note, for patients already on NSBBs, either for primary prophylaxis of variceal bleeding or for other indications, as long as their heart rate is 55 to 60 beats per minute (on nadolol or propranolol) or carvedilol is dosed at least 12.5 mg/d regardless of heart rate, screening or surveillance EGD is no longer required, as it will not change their current regimen based on EGD findings. For patients in whom endoscopic variceal ligation is used for primary prophylaxis for variceal bleeding, EGD interval is discussed. If TIPS (transjugular intrahepatic portosystemic shunt) was inserted for ascites, having obtained a portosystemic gradient less than 12 mm Hg, and TIPS has remained patent, EGD for screening or surveillance of varices is not necessary, as the pressure reduction achieved by TIPS is sufficient to make variceal bleed unlikely or even to make varices disappear. Importantly, TIPS should not be placed with the purpose of preventing first variceal hemorrhage, as this portosystemic shunting has been associated with a higher mortality in this setting.

Are Nonselective Beta-Blocker and Endoscopic Variceal Ligation Indicated?

In patients without prior variceal bleeding, the current recommendations address solely the prevention of the first variceal bleeding in patients with high-risk varices (HRV) considered to have a high risk of bleeding (>15% per year): patients with medium or large varices (which constitute the largest group), patients with small varices with red wale marks, or CTP-class C patients with any size varices. Studies on primary prophylaxis of variceal bleeding, spanning almost 3 decades, have reported on the benefits of NSBBs such as propranolol, nadolol, and more recently carvedilol.[18–24] The other therapy with a proven beneficial effect in preventing first variceal bleeding in patients with HRV is EVL. Either one or the other should be used (**Table 2**), as combination therapy has no advantages and can increase adverse effects. Shared decision making considering patients' preference when choosing between NSBB and EVL should be strongly considered, to ensure patients' adherence.

Table 2
For patients with cirrhosis and no prior variceal bleeding: nonselective beta-blocker or endoscopic variceal ligation (also see Fig. 3)

Therapy	No Ascites	Ascites	Goal
Propranolol	20–160 mg twice daily	20–80 mg twice daily	Titrate to HR 55–60 or SBP <90
Nadolol	20–160 mg daily	20–80 mg daily	Titrate to HR 55–60 or SBP <90
Carvedilol	3.125–12.5 mg daily	Avoid	Titrate to *12.5–25* mg/d or SBP<90
EVL	EGD every 2–8 wks until EV eradication → repeat EGD at 3–6 mo → EGD every 6-12 mo if no large varices		Variceal eradication; if recurrent large varices → resume banding every 2-8 wks

In the PREDESCI trial, patients with compensated cirrhosis and CSPH but without HRV treated with propranolol (titrated to 160 mg twice daily or maximum dose tolerated) or carvedilol (titrated to 25 mg/d or maximum dose tolerated) had an increased decompensation-free survival, especially a delayed development of ascites.[4] Of note, this effect was seen after 2 years of follow-up, and most patients had untreated chronic hepatitis C. Based on PREDESCI trial, the new paradigm will aim to prevent any decompensation in patients with CSPH, not just the first variceal bleeding in patients with HRV. As such, in patients with compensated cirrhosis, NSBB will be initiated earlier without the requirement of finding HRV on EGD, as the decision will be based on noninvasive testing suggestive of CSPH. In patients with decompensated cirrhosis, recommendations may change as well to favor initiation of NSBBs without EGD, given the high prevalence of small varices in these patients, the difficulty to perform EVL for small varices, and possible additional benefits from NSBBs.[17] EGD may be reserved for patients who cannot tolerate NSBBs, with the goal to perform EVL if large varices are detected.

After initiating NSBBs, patients need to be carefully monitored for adverse effects while titrating the dose to goal (see **Table 2**) or to the maximally tolerated dose. For propranolol and nadolol, the treatment goal is to achieve a resting heart rate of 55 to 60 beats per minute, in the absence of hypotension or adverse effects. For carvedilol, a dose of 12.5 mg/d was found to prevent first variceal bleed, without a specific heart rate goal.[25,26] NSBBs have the advantage of decreasing portal pressure and therefore have the potential of reducing not only variceal hemorrhage, but other complications of cirrhosis.

Safety concerns have been raised regarding the use of NSBBs in patients with decompensated cirrhosis, particularly in patients with refractory ascites or after an episode of spontaneous bacterial peritonitis.[27,28] These earlier reports finding increased kidney dysfunction and mortality secondary to NSBBs have been challenged by subsequent studies.[29,30] It seems that the harmful effect is dose-dependent and related to a low mean arterial pressure.[31] Therefore, NSBBs are not contraindicated in patients with ascites, but they require careful use or interruption in the event of severe circulatory dysfunction (eg, hypotension, hyponatremia, or hepatorenal syndrome). Avoid high doses (not to exceed 80 mg propranolol orally twice a day or 80 mg nadolol orally daily); avoid carvedilol given its additional vasodilating effect and therefore higher likelihood to decrease blood pressure. Titrate NSBBs to

avoid systolic blood pressure of less than 90 mm Hg, and temporarily discontinue NSBBs in the setting of bleeding, infection, or kidney dysfunction.[1]

EVL is a local therapy without an effect on portal pressure and carries the risk of bleeding from ligation-induced ulcers.[32,33] Additionally, EVL is not recommended in patients with high-risk small varices, because small varices are difficult to ligate. Importantly, if NSBBs are chosen as primary prophylactic therapy, there is no need for surveillance endoscopies. If EVL is chosen, endoscopy is done every 2 to 8 weeks if varices are large enough for band ligation; once variceal eradication is achieved, repeat endoscopy for surveillance is indicated at 3 to 6 months, followed by EGD every 6 to 12 months until large varices are detected, and band ligation is required again.[1]

SPECIAL CONSIDERATIONS REGARDING PRIMARY PROPHYLAXIS OF BLEEDING FROM FUNDAL VARICES

There is no specific approach regarding primary prophylaxis of variceal bleeding from fundal varices, given limited data in these patients.[1] The use of NSBBs or endoscopic obliteration with cyanoacrylate glue was evaluated in patients with large fundal varices (GOV2 or IGV1) and no prior bleeding.[34] There was a lower bleeding rate observed with endoscopic obliteration, but the small number of patients could support a firm recommendation. AASLD guidance suggests that NSBBs can be used for primary prophylaxis of bleeding from GOV2/IGV1, as this is the least invasive treatment, and it could also prevent decompensation of cirrhosis.[1] As discussed for esophageal varices, the issues regarding preventing decompensation in patients with compensated cirrhosis with fundal varices would favor the use of NSBBs.

SECONDARY PROPHYLAXIS OF VARICEAL BLEEDING: NONSELECTIVE BETA-BLOCKERS OR ENDOSCOPIC VARICEAL LIGATION

In patients who have bled from varices, the 1-year risk of recurrent variceal bleeding can be as high as 60% in the absence of secondary prophylaxis. The recommended treatment to prevent recurrent hemorrhage consists of combination therapy NSBB plus EVL.

Nonselective Beta-Blockers Used for Secondary Prophylaxis of Variceal Bleeding Are Nadolol or Propranolol

In this setting (dose and goals as per **Table 2**), there are not enough data to recommend carvedilol, as there are no randomized controlled trials, and patients may have more severe liver disease and are more prone to be more vasodilated. NSBBs should be started during hospitalization, once octreotide is discontinued, to allow monitoring of blood pressure, heart rate, and occurrence of any clinical adverse effects prior to discharge.

Endoscopic Variceal Ligation

In this setting, EVL is done every 2 to 8 weeks until varices are eradicated, followed by surveillance endoscopy at 3 to 6 months after variceal eradication, and every 6 to 12 months indefinitely. When large varices recur, EVL is resumed every 2 to 8 weeks until variceal eradication.

The key element of combination therapy is NSBBs, particularly in CTP-B/C class patients in whom a higher mortality has been shown when patients are on EVL alone compared with combination therapy NSBBs plus EVL.[35]

Patients who have had TIPS placed during the episode of acute variceal bleeding should not receive NSBB or EVL, as the shunt resolves portal hypertension and

varices. However, they will require Doppler ultrasound of the TIPS every 6 months (at the time of HCC surveillance) to assess TIPS patency.

SPECIAL CONSIDERATIONS REGARDING SECONDARY PROPHYLAXIS OF BLEEDING FROM FUNDAL VARICES

If the initial bleeding resolved or it was controlled with cyanoacrylate glue obliteration, strategies to decrease the risk of rebleeding from fundal varices include repeat cyanoacrylate glue, TIPS, or intravascular obliteration with sclerosant (balloon-occluded retrograde transvenous obliteration or BRTO).[36–39] To allow retrograde access to the fundal varices, BRTO requires the presence of a spontaneous gastrorenal or splenorenal shunt, which actually occurs in 60% to 80% of patients with fundal varices. Because it does not divert the portal blood flow from the liver but actually increases it, BRTO does not cause hepatic encephalopathy, but it may cause worsening ascites or bleeding from esophageal varices. TIPS and BRTO are recommended by AASLD as first-line treatments to prevent rebleeding, reserving the use of cyanoacrylate glue injections for situations when TIPS and BRTO are not feasible.[1]

Fig. 3 presents a stepwise approach for the outpatient management of patients with cirrhosis to appropriately use NSBBs, EVL, and other interventions targeting gastroesophageal varices.

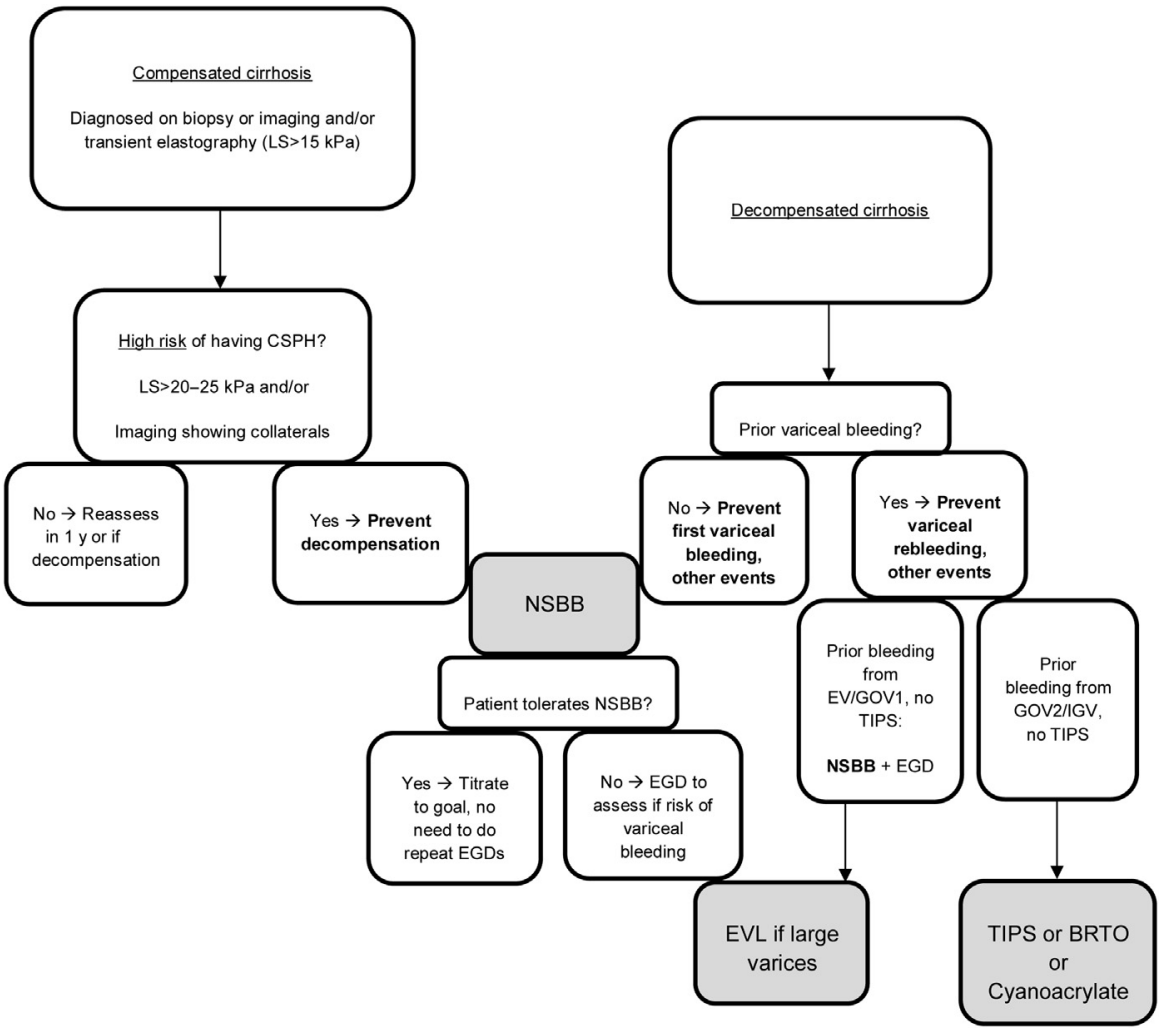

Fig. 3. NSBBs, EVL, and other interventions targeting gastroesophageal varices in the outpatient management of patients with cirrhosis.

INPATIENT MANAGEMENT OF GASTROESOPHAGEAL VARICES

Treatment of acute variceal bleeding is the most important aspect of inpatient management of GEV, but it is important to note that most hospital admissions for patients with cirrhosis are complications not related to variceal bleeding. These hospitalizations are opportunities to ensure patients receive appropriate management of GEV.

ACUTE VARICEAL BLEEDING

Advances in the management of acute variceal bleeding are associated with improved survival, but the 6-week mortality rate remains high, up to 20%.[40,41] Several therapies, including vasoactive medications, antibiotics, endoscopic methods (eg, EBL or sclerotherapy, glue injection, balloon tamponade, esophageal stent, and hemostatic powder), and interventional radiology treatments (TIPS, coil embolization, balloon-occluded retrograde transvenous obliteration) are currently used to treat acute variceal bleeding. **Fig. 4** summarizes the inpatient management of GEV, including interventions recommended by AASLD as quality metrics in cirrhosis care.

General management should focus on

- Resuscitation (intravenous access: airway/breathing/circulation) and orotracheal intubation, especially in patients with massive hematemesis or mental status changes
- Restrictive transfusion of packed red blood cells - transfuse when hemoglobin is less than 7 g/dL, with the goal of 7 to 9 g/dL[42]

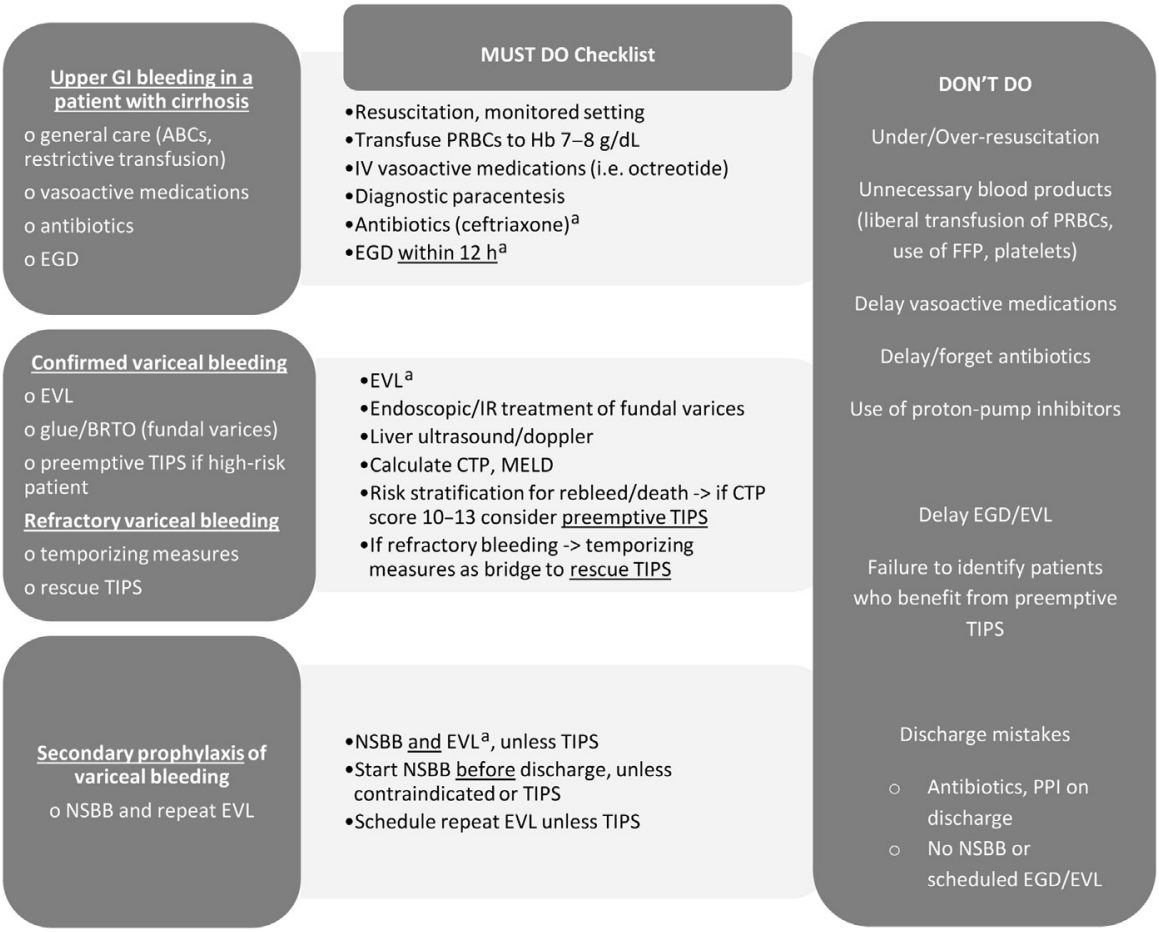

Fig. 4. Inpatient management of varices ([a] measures included in AASLD quality metrics).

- Avoid unnecessary correction of coagulopathy, as there is no evidence that correcting platelet count or INR are of benefit in variceal hemorrhage[1]
- Discontinue outpatient medications (diuretics, NSBBs) if low blood pressure in the setting of bleeding; of note, NSBBs could blunt the sympathetic response to hemorrhage

Specific pharmacologic therapy for acute variceal hemorrhage should be initiated as soon as diagnosis is suspected and while planning for an urgent upper endoscopy. This includes

- Vasoactive therapy causes splanchnic vasoconstriction and reduction in portal pressure - octreotide, terlipressin or somatostatin, with similar efficacy,[43] or vasopressin, which is less commonly used
  - Octreotide: intravenous bolus of 50 μg followed by a continuous infusion of 50 μg/h (2–5 days)
  - Terlipressin: 2 mg intravenously every 4 hours (initial 48 hours), followed by 1 mg intravenously every 4 hours (2–5 days)
  - Somatostatin: intravenous bolus of 250 μg followed by a continuous infusion of 250 to 500 μg/h (2–5 days)
- Antibiotic prophylaxis to decrease the variceal rebleeding rate and mortality by decreasing the risk of bacterial infection (in particular spontaneous bacterial peritonitis)[44]
  - Intravenous ceftriaxone 1 g/24 h, 5 to 7 days (stop once off vasoactive therapy, or at the time of discharge)

Proton pump inhibitors (PPIs) have no effect on variceal bleeding. While it is reasonable to start intravenous PPIs while awaiting EGD, they should be discontinued once variceal bleeding is confirmed. If used briefly to help with postbanding ulcer, although the evidence is limited, PPIs should not be continued after discharge.

EGD needs to be performed within 12 hours of admission, with EVL if a diagnosis of variceal hemorrhage is established based on several criteria[1]:

- Active bleeding from a varix
- Stigmata of recent hemorrhage are observed on a varix (clot, white nipple)
- Only nonbleeding varices are seen and there is no other source of bleeding

For patients in whom bleeding is brisk and banding cannot be performed, or if refractory bleeding not controlled with medical and endoscopic therapy, several temporizing measures may help. Balloon tamponade involves using a tube with an esophageal and a gastric balloon. It requires training and following a specific protocol, to avoid complications. It is effective in controlling bleeding temporarily, as a bridge to TIPS or, less likely, liver transplantation. It can cause lethal complications such as aspiration, esophageal ulceration, and perforation. Recently, self-expandable esophageal stents were found to have greater efficacy and less complications than balloon tamponade in the control of EVH in treatment failures.[45] Early application of hemostatic powder was also evaluated for acute variceal bleeding,[46] but it requires follow-up EGD for EVL after 24 hours, and more data are needed to establish its role. Balloon tamponade and esophageal stents are temporary bridge therapies, as ultimately, patients with refractory bleeding require TIPS placement (rescue TIPS). Because patients who rebleed despite standard therapy and require rescue TIPS are mostly Child C patients, the mortality after rescue TIPS is high.

Pre-emptive (early) TIPS (pTIPS) placement is a strategy that anticipates treatment failure and death by pre-emptively placing TIPS soon after therapeutic EVL in patients

at high risk of failing standard therapy. In a randomized trial including patients with a CTP score of 10 to 13 (excluding those with score 14 or 15) and CTB-B patients with active bleeding at endoscopy, pTIPS was associated with a 25% absolute risk reduction in mortality.[47] Subsequent studies have confirmed lower mortality with pTIPS in CTB-C (10–13 points),[48–50] despite which pTIPS is placed in only a minority of these patients.[51] The indication for pTIPS in CTP-B patients still requires further investigation. Interestingly, when using MELD score, pTIPS was found to be associated with improved survival in patients with MELD of at least 19, with no survival benefit if MELD less than 12.[52]

Other Considerations to Help Plan for Further Treatment

Diagnostic paracentesis to evaluate for spontaneous bacterial peritonitis that could have precipitated variceal bleeding should be performed before starting antibiotics.

Doppler ultrasound to assess the presence of hepatocellular carcinoma and portal vein patency should be performed prior to TIPS. Portal vein thrombosis can further increase portal pressure, and anticoagulation is of benefit to prevent recurrent variceal hemorrhage, but should not be initiated in the setting of active or recent hemorrhage. In fact, a recent trial showed that TIPS placement was more effective than EVL plus propranolol in preventing variceal rebleeding in patients with cirrhosis and PVT occluding greater than 50% of the lumen.[49]

For patients with GEV requiring enteral feeding, there is reluctance to insert nasogastric or enteric tubes, especially early after endoscopic treatment, out of fear that it may precipitate variceal (re)bleeding. While the mere presence of varices is not considered a contraindication, most hepatology/gastroenterology providers wait 24 to 48 hours after endoscopic treatment, although there are limited data in this regard. A recent retrospective chart review on patients requiring enteric feeding with known EV but no recent bleeding or endoscopic treatment reported that 14% of patients developed hematemesis, bloody nasogastric aspirate, or melena within 48 hours from tube placement,[53] but it did not offer details regarding the source of bleeding. A small randomized study[54] looked at enteral feeding versus no feeding after variceal hemorrhage and found no differences in outcomes, including gastrointestinal hemorrhage; however, the study was underpowered to detect a statistically significant difference.

Risk stratification of early rebleeding or death using CTP score and MELD score is essential, as it modifies the therapeutic strategy for high-risk patients.

TIPS considerations include

- Adjunctive embolization of esophageal and/or gastric collaterals at the time of TIPS placement is routinely performed by many interventional radiologists, as it was shown to decrease short-term rebleeding rate[55,56]
- Discontinue vasoactive medication (once TIPS is in place, octreotide or other vasoactive medication is of no benefit, as pressure reduction achieved by TIPS is much greater than reduction with pharmacologic therapy)
- Secondary prophylaxis with NSBBs and EVL is not recommended as long as TIPS remains patent with a gradient less than 12 mm Hg (the threshold associated with complications secondary to portal hypertension)
- TIPS will need evaluation with ultrasound Doppler every 6 months to check for patency; if suspicion for stenosis, TIPS interrogation/revision is necessary to make sure the gradient remains less than 12 mm Hg

ACUTE VARICEAL BLEEDING FROM FUNDAL VARICES

Although the general management is similar, endoscopic treatment of bleeding fundal varices does not rely upon EVL as complete suction of the varix into the ligator is

difficult (fundal varices are usually larger than esophageal varices and the gastric mucosa is thicker), and postbanding ulcers can lead to severe hemorrhage.[1] More efficient endoscopic methods to control bleeding from GOV2/IGV1 include obliteration with cyanoacrylate glue or endoscopic ultrasound with combined coil insertion and cyanoacrylate or other adjuncts such as Gelfoam,[57–62] although not approved in the United States and currently used off-label. Interventional radiology treatments include TIPS and BRTO.[63–66] TIPS has a greater than 90% success rate in achieving initial hemostasis,[67] and it is recommended by the AASLD as the treatment of choice for bleeding from fundal varices.[1] As fundal varices may bleed at lower portosystemic pressure gradient than esophageal varices and may persist post-TIPS, BRTO is an attractive alternative in patients with a patent gastro- or splenorenal shunt. Furthermore, combining TIPS and BRTO may be an effective approach in selected patients with bleeding gastric varices.[68,69] Given the complexity of care and the high expertise required for optimal treatment, patients with bleeding fundal varices should be treated in a tertiary center by a multidisciplinary team.

In conclusion, several interventions are recommended for the outpatient and inpatient management of esophageal and gastric varices. Although a select group of patients is best served by a multidisciplinary portal hypertension treatment team in a tertiary center, most patients can and should receive optimal treatment from practicing gastroenterologists.

DISCLOSURE

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REFERENCES

1. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310–35.
2. Sarin SK, Kumar A. Gastric varices: profile, classification, and management. Am J Gastroenterol 1989;84:1244–9.
3. Kanwal F, Tapper EB, Ho C, et al. Development of quality measures in cirrhosis by the practice metrics committee of the American Association for the Study of Liver Diseases. Hepatology 2019;69:1787–97.
4. Villanueva C, Albillos A, Genesca J, et al. Beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393:1597–608.
5. De Franchis R, Abraldes JG, Bajaj J, et al. Expanding consensus in portal hypertension report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–52.
6. North Italian Endoscopic Club for the S, Treatment of Esophageal V. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983–9.
7. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–8.

8. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the "Anticipate" study. Hepatology 2016;64:2173–84.
9. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66:1980–8.
10. Thabut D, Bureau C, Layese R, et al. Validation of Baveno VI criteria for screening and surveillance of esophageal varices in patients with compensated cirrhosis and a sustained response to antiviral therapy. Gastroenterology 2019;156:997–1009.e5.
11. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144:102–11.e1.
12. Takuma Y, Nouso K, Morimoto Y, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology 2013;144:92–101.e2.
13. Petta S, Sebastiani G, Bugianesi E, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. J Hepatol 2018;69:878–85.
14. Patanwala I, McMeekin P, Walters R, et al. A validated clinical tool for the prediction of varices in PBC: the Newcastle varices in PBC score. J Hepatol 2013;59:327–35.
15. Colecchia A, Ravaioli F, Marasco G, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol 2018;69:308–17.
16. Jangouk P, Turco L, De Oliveira A, et al. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. Liver Int 2017;37:1177–83.
17. Turco L, Villanueva C, La Mura V, et al. Lowering portal pressure improves outcomes of patients with cirrhosis, with or without ascites: a meta-analysis. Clin Gastroenterol Hepatol 2020;18(2):313–27.e6.
18. Yang J, Ge K, Chen L, et al. The efficacy comparison of carvedilol plus endoscopic variceal ligation and traditional, nonselective β-blockers plus endoscopic variceal ligation in cirrhosis patients for the prevention of variceal rebleeding: a meta-analysis. Eur J Gastroenterol Hepatol 2019;31(12):1518–26.
19. Zacharias AP, Jeyaraj R, Hobolth L, et al. Carvedilol versus traditional, nonselective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database Syst Rev 2018;(10):CD011510.
20. Schwarzer R, Kivaranovic D, Paternostro R, et al. Carvedilol for reducing portal pressure in primary prophylaxis of variceal bleeding: a dose-response study. Aliment Pharmacol Ther 2018;47:1162–9.
21. Abd ElRahim AY, Fouad R, Khairy M, et al. Efficacy of carvedilol versus propranolol versus variceal band ligation for primary prevention of variceal bleeding. Hepatol Int 2018;12:75–82.
22. Gupta V, Rawat R, Shalimar, et al. Carvedilol versus propranolol effect on hepatic venous pressure gradient at 1 month in patients with index variceal bleed: RCT. Hepatol Int 2017;11:181–7.
23. Reiberger T, Ulbrich G, Ferlitsch A, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62:1634–41.

24. Poynard T, Cales P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. N Engl J Med 1991;324:1532–8.
25. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009;50:825–33.
26. Shah HA, Azam Z, Rauf J, et al. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol 2014;60:757–64.
27. Mandorfer M, Bota S, Schwabl P, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146:1680–16890.e1.
28. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010;52:1017–22.
29. Bossen L, Krag A, Vilstrup H, et al. Nonselective beta-blockers do not affect mortality in cirrhosis patients with ascites: post hoc analysis of three randomized controlled trials with 1198 patients. Hepatology 2016;63:1968–76.
30. Mookerjee RP, Pavesi M, Thomsen KL, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol 2016;64:574–82.
31. Tergast TL, Kimmann M, Laser H, et al. Systemic arterial blood pressure determines the therapeutic window of non-selective beta blockers in decompensated cirrhosis. Aliment Pharmacol Ther 2019;50:696–706.
32. Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database Syst Rev 2012;(8):CD004544.
33. Sharma M, Singh S, Desai V, et al. Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology 2019;69:1657–75.
34. Mishra SR, Sharma BC, Kumar A, et al. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. J Hepatol 2011;54:1161–7.
35. Albillos A, Zamora J, Martinez J, et al. Stratifying risk in the prevention of recurrent variceal hemorrhage: results of an individual patient meta-analysis. Hepatology 2017;66:1219–31.
36. Fukuda T, Hirota S, Sugimura K. Long-term results of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy. J Vasc Interv Radiol 2001;12:327–36.
37. Hung HH, Chang CJ, Hou MC, et al. Efficacy of non-selective beta-blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: a randomized controlled trial. J Hepatol 2012;56:1025–32.
38. Lo GH, Liang HL, Chen WC, et al. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. Endoscopy 2007;39:679–85.
39. Mishra SR, Chander Sharma B, Kumar A, et al. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial. Gut 2010;59:729–35.

40. Ardevol A, Ibanez-Sanz G, Profitos J, et al. Survival of patients with cirrhosis and acute peptic ulcer bleeding compared with variceal bleeding using current first-line therapies. Hepatology 2018;67:1458–71.
41. Vuachet D, Cervoni JP, Vuitton L, et al. Improved survival of cirrhotic patients with variceal bleeding over the decade 2000-2010. Clin Res Hepatol Gastroenterol 2015;39:59–67.
42. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11–21.
43. Seo YS, Park SY, Kim MY, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60:954–63.
44. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. Aliment Pharmacol Ther 2011;34:509–18.
45. Escorsell A, Pavel O, Cardenas A, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: a multicenter randomized, controlled trial. Hepatology 2016;63:1957–67.
46. Ibrahim M, El-Mikkawy A, Abdel Hamid M, et al. Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial. Gut 2019;68:844–53.
47. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362:2370–9.
48. Hernandez-Gea V, Procopet B, Giraldez A, et al. Preemptive-TIPS improves outcome in high-risk variceal bleeding: an observational study. Hepatology 2019;69:282–93.
49. Lv Y, Qi X, He C, et al. Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial. Gut 2018;67:2156–68.
50. Lv Y, Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4:587–98.
51. Thabut D, Pauwels A, Carbonell N, et al. Cirrhotic patients with portal hypertension-related bleeding and an indication for early-TIPS: a large multicentre audit with real-life results. J Hepatol 2017;68:73–81.
52. Lv Y, Zuo L, Zhu X, et al. Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study. Gut 2019;68:1297–310.
53. Al-Obaid L, Bazarbashi AN, Cohen ME, et al. Enteric tube placement in patients with esophageal varices: Risks and predictors of postinsertion gastrointestinal bleeding. JGH Open 2019;4(2):256–9.
54. de Ledinghen V, Beau P, Mannant PR, et al. Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study. Dig Dis Sci 1997;42:536–41.
55. Gaba RC. Transjugular intrahepatic portosystemic shunt creation with embolization or obliteration for variceal bleeding. Tech Vasc Interv Radiol 2016;19:21–35.
56. Qi X, Liu L, Bai M, et al. Transjugular intrahepatic portosystemic shunt in combination with or without variceal embolization for the prevention of variceal rebleeding: a meta-analysis. J Gastroenterol Hepatol 2014;29:688–96.
57. Al-Ali J, Pawlowska M, Coss A, et al. Endoscopic management of gastric variceal bleeding with cyanoacrylate glue injection: safety and efficacy in a Canadian population. Can J Gastroenterol 2010;24:593–6.

58. Kahloon A, Chalasani N, DeWitt J, et al. Endoscopic therapy with 2-octyl-cyanoacrylate for the treatment of gastric varices. Dig Dis Sci 2014;59:2178–83.
59. Rios Castellanos E, Seron P, Gisbert JP, et al. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. Cochrane Database Syst Rev 2015;(5):CD010180.
60. Bhat YM, Weilert F, Fredrick RT, et al. EUS-guided treatment of gastric fundal varices with combined injection of coils and cyanoacrylate glue: a large U.S. experience over 6 years (with video). Gastrointest Endosc 2016;83:1164–72.
61. Weil D, Cervoni JP, Fares N, et al. Management of gastric varices: a French national survey. Eur J Gastroenterol Hepatol 2016;28:576–81.
62. Lee HA, Chang JM, Goh HG, et al. Prognosis of patients with gastric variceal bleeding after endoscopic variceal obturation according to the type of varices. Eur J Gastroenterol Hepatol 2019;31:211–7.
63. Imai Y, Nakazawa M, Ando S, et al. Long-term outcome of 154 patients receiving balloon-occluded retrograde transvenous obliteration for gastric fundal varices. J Gastroenterol Hepatol 2016;31:1844–50.
64. Lee SJ, Kim SU, Kim MD, et al. Comparison of treatment outcomes between balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt for gastric variceal bleeding hemostasis. J Gastroenterol Hepatol 2017;32:1487–94.
65. Chu HH, Kim M, Kim HC, et al. Long-term outcomes of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices: a comparison of ethanolamine oleate and sodium tetradecyl sulfate. Cardiovasc Interv Radiol 2018;41:578–86.
66. Stein DJ, Salinas C, Sabri S, et al. Balloon retrograde transvenous obliteration versus endoscopic cyanoacrylate in bleeding gastric varices: comparison of rebleeding and mortality with extended follow-up. J Vasc Interv Radiol 2019;30:187–94.
67. Chau TN, Patch D, Chan YW, et al. "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998;114:981–7.
68. Lakhoo J, Bui JT, Lokken RP, et al. Transjugular intrahepatic portosystemic shunt creation and variceal coil or plug embolization ineffectively attain gastric variceal decompression or occlusion: results of a 26-patient retrospective study. J Vasc Interv Radiol 2016;27:1001–11.
69. Saad WE. Combining transjugular intrahepatic portosystemic shunt with balloon-occluded retrograde transvenous obliteration or augmenting tips with variceal embolization for the management of gastric varices: an evolving middle ground? Semin Intervent Radiol 2014;31:266–8.