Communication from the ASGE Standards of Practice Committee

GUIDELINE

The role of endoscopy in the management of variceal hemorrhage

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this document, a search of the medical literature was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When limited or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Recommendations for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this document. This document may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[1]

This document is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. It is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these recommendations.

Variceal bleeding is a common and serious adverse event of portal hypertension. Mortality after an index hemorrhage in patients with cirrhosis had been previously reported to be as high as 50%, with a 30% mortality rate associated with subsequent bleeding episodes.[2] Although more recent data demonstrate improvement in mortality with the increasing use of vasoactive drugs, endoscopy, and antibiotic prophylaxis, bleeding from esophageal varices is still associated with 20% mortality rate at 6 weeks.[3-6] The optimal management of patients with variceal bleeding requires a multidisciplinary approach by a team that includes gastroenterologists, interventional radiologists, and surgeons. The purpose of this document is to update a previous ASGE Standards of Practice publication providing a practical strategy for the specific use of endoscopy in screening for esophageal and gastric varices, prevention of variceal bleeding, and the management of patients with variceal hemorrhage.[7]

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ESOPHAGEAL VARICES

Screening for esophageal varices

Effective prophylactic treatments exist for patients with esophageal varices to prevent variceal bleeding.[8] There are no reliable methods for predicting which cirrhotic patients will have esophageal varices without endoscopy.[9] The most recent American Association for the Study of Liver Disease (AASLD) and Baveno V consensus guidelines suggest that all patients who have been diagnosed with cirrhosis undergo screening endoscopy to assess for esophageal and gastric varices.[10,11] If esophageal varices are identified on endoscopy, they should be graded as small or large (>5 mm) and the presence of red wales or spots should be noted because these findings have been identified as risk factors for future bleeding.[2,12] The optimal surveillance intervals for esophageal varices have not been determined. For patients with compensated cirrhosis found to have no varices on initial screening endoscopy, repeat endoscopy every 2 to 3 years has been suggested, whereas patients with small varices should undergo repeat endoscopy every 1 to 2 years.[2,13] Esophageal varices may develop faster in patients with cirrhosis secondary to alcohol abuse, decompensated liver disease, and in those with small varices with high-risk stigmata (red wale marks or red spots) on endoscopic examination. This subgroup of patients should undergo yearly upper endoscopy, even when no or only small varices are seen on initial screening.[2,12,13]

Endoscopy and primary prophylaxis

Endoscopy plays an essential role in the management of patients with cirrhosis because it identifies patients who will benefit from primary prophylaxis to prevent initial variceal hemorrhage and helps guide specific therapies. Nonselective β-blockers (eg, propranolol or nadolol) have been shown to prevent or delay the first episode of variceal bleeding in patients found to have large varices and patients who have small varices with advanced liver disease (Child-Pugh class B or C) or the presence of high-risk stigmata on varices.[14-18]

Endoscopic variceal ligation (EVL) is highly effective in eradicating esophageal varices and has been shown

TABLE 1. GRADE system for rating the quality of evidence for guidelines[1]

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	⊕⊕⊕◯
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	⊕⊕◯◯
Very low quality	Any estimate of effect is very uncertain	⊕◯◯◯

Adapted from Guyatt et al.[1]

to be as effective as β-blockers in preventing first variceal hemorrhage in 3 large randomized, controlled trials.[19-21] A single randomized U.S. study in patients with cirrhosis and high-risk esophageal varices demonstrated that propranolol-treated patients had a significantly higher rate of first variceal hemorrhage (12.9% vs 0%, $P = .04$) and cumulative mortality (12.9% vs 0%, $P = .04$) than patients who underwent prophylactic EVL.[22] However, this study was criticized for premature discontinuation because of an interim analysis showing a significantly higher number of treatment failures (variceal bleeding and severe adverse effects) in the propranolol group compared with the EVL group, which limited the follow-up to a median of 18 months.[23] In a meta-analysis of 8 randomized, controlled trials involving 596 patients, EVL compared with β-blockers reduced the rate of first variceal bleed (relative risk [RR], 0.57; 95% CI, 0.38-0.85), although there was no effect on mortality.[24] In this meta-analysis, severe adverse events in the propranolol group were more common than in the EVL group (RR, 0.34; 95% CI, 0.17-0.69); however there were 2 fatalities from ligation-induced ulcer bleeding in the EVL group. A recent Cochrane review comparing EVL with nonselective β-blockers for primary prophylaxis in esophageal varices included 19 randomized trials and demonstrated that EVL reduced variceal bleeding compared with β-blocker therapy (RR, 0.67; 95% CI, 0.53-1.39) with no difference in mortality.[25] Despite the results of these meta-analyses, the consensus of experts is that the 2 treatments are likely to have similar efficacy.[10,11] It is recommended that in most cases, prophylactic EVL be reserved for patients who cannot tolerate or who have contraindications to β-blockers or patients who have large varices with high-risk stigmata or Child-Pugh class B or C cirrhosis.[10,11] In addition, if primary prophylaxis with EVL is performed, it is recommended that β-blocker therapy not be used because combination therapy does not appear to further decrease the risk of initial variceal bleeding or mortality and is associated with increased side effects.

Current guidelines recommend that patients undergoing EVL for primary prophylaxis have repeat endoscopy with EVL every 1 to 2 weeks until documentation of variceal obliteration.[10] However, studies evaluating EVL for primary prophylaxis have used variable intervals for repeat EVL, ranging from 1 to 8 weeks.[19-22,26-28] A randomized, controlled trial of bimonthly versus biweekly EVL in 63 cirrhotic patients for both primary and secondary prophylaxis, the majority of whom were enrolled for primary prophylaxis (87.5% in the biweekly arm, 81% in the bimonthly arm), found that 3 sessions of EVL bimonthly had a higher total eradication rate, lower recurrence rate, and lower rate of additional treatment than 3 sessions of biweekly EVL.[29] Thus, repeat EVL for primary prophylaxis can be safely performed at 1- to 8-week intervals until variceal eradication is achieved. Surveillance EGD should be performed 1 to 3 months after eradication, and every 6 to 12 months thereafter to assess for variceal recurrence.[10,26] If recurrent varices are noted on surveillance examinations, additional attempts at eradication should be undertaken.

A potential adverse event of EVL is ligation-induced ulcers, reported to occur in 0.5% to 3% of cases, and is a major cause of concern when considering EVL for prophylactic therapy.[30,31] Studies of EVL for primary prophylaxis have variably used a proton pump inhibitor (PPI) after EVL, and PPIs can be considered as adjunctive therapy.[22,32]

Endoscopic treatments for acute esophageal variceal hemorrhage

Initial management and therapy before endoscopy. Patients with acute esophageal variceal hemorrhage should be stabilized in an intensive care unit before undergoing endoscopy. Obtaining adequate intravenous (IV) access with cautious blood volume resuscitation should be performed to maintain hemodynamic stability and achieve a hemoglobin concentration of approximately 7 to 8 g/dL.[11] Aggressive resuscitation with blood products and crystalloid should be avoided as it theoretically can increase portal pressures, leading to increased risk of rebleeding and mortality.[33-35] In patients with significant coagulopathy or thrombocytopenia, transfusion of fresh frozen plasma and/or platelets should be considered.

In addition, prophylactic antibiotics (oral or IV quinolone or IV ceftriaxone) should be administered to cirrhotic

patients with an upper GI bleed and should be administered for 7 days to decrease the risk of bacterial infections and increase survival.[36,37] Vasoactive pharmacological therapy with octreotide, somatostatin, terlipressin, or vasopressin should be initiated as soon as a patient is suspected of having an acute variceal hemorrhage. Of these agents, only octreotide and vasopressin are available in the United States. The most commonly used agent in the United States is octreotide, and the recommended dose of administration is a 50-μg IV bolus followed by a 50-μg/h infusion. If variceal hemorrhage is confirmed on endoscopy, pharmacological therapy should be continued for 3 to 5 days after the endoscopy.[10,11,38] Endoscopy should be performed urgently in patients with suspected acute variceal bleeding (within 12 hours of admission), and intubation of the patient before endoscopy should be strongly considered because of the high risk of aspiration of blood.[10]

Endoscopic variceal ligation. Endoscopic variceal ligation is the treatment of choice for both controlling esophageal variceal hemorrhage and secondary prophylaxis. The results of 6 randomized, prospective trials that directly compared EVL and endoscopic sclerotherapy (EST) reported that EVL is superior to EST for eradicating varices more rapidly, with less recurrent bleeding and fewer adverse events.[39-43] Two of the trials demonstrated a survival advantage in patients treated with EVL.[43,44] A meta-analysis also confirmed the superiority of EVL compared with EST for all major outcomes (recurrent bleeding, local adverse events including ulceration and stricture formation, time to variceal obliteration, and survival).[30] In conjunction with EVL therapy, treatment with a β-blocker should be considered as this has been reported to further decrease rebleeding from 38% to 14% ($P = .006$).[45]

After the treatment of an acute episode of esophageal variceal hemorrhage, endoscopy should be repeated until varices have been eradicated, which typically requires 2 to 4 sessions.[46] Optimal intervals for EVL for secondary prophylaxis have not been defined and range from 2 to 8 weeks in the studies evaluating EVL for secondary prophylaxis. Consensus guidelines recommend repeat endoscopy with EVL every 1 to 2 weeks until obliteration is observed.[10] However, studies evaluating EVL for secondary prophylaxis have used intervals of 10 to 12 days and 3 to 4 weeks.[29,45,47] A retrospective, case-control study of patients undergoing EVL for secondary prophylaxis compared patients in whom recurrent variceal bleeding developed with those who did not rebleed.[48] The overall median interval between EVL sessions was 3 weeks (interquartile range, 2-7 weeks), with a significantly shorter median interval in the rebleeding group (2 weeks, interquartile range 1-2 weeks) than in the nonbleeding group (5 weeks, interquartile range 3-7 weeks, $P = .004$). After adjusting for age, sex, and Child-Pugh class, a rebanding interval of 3 weeks or longer was associated with an increased likelihood of not rebleeding (adjusted hazard ratio, 3.84; 95% CI, 1.69-11.79; $P = .0007$).[48] Prospective trials are needed to clarify this issue. In the absence of prospective data, it is reasonable to consider 1- to 8-week intervals for EVL for secondary prophylaxis. Esophageal varices may recur in patients treated with EVL,[39] so endoscopic surveillance every 3 to 6 months should be performed and recurrent varices should be treated with EVL.[10]

The incidence of post-EVL band–induced ulcer bleeding appears to be higher in patients undergoing EVL after an episode of acute bleeding, with reports as high as 14%.[31,49-51] One randomized, placebo-controlled trial of 44 cirrhotic patients undergoing EVL for secondary prophylaxis found that pantoprazole (40 mg IV post-EVL, then 40 mg orally for 9 days) reduced postbanding ulcer size, but not number.[52] Of the 4 serious adverse events reported, 3 were post-banding ulcer bleeds and all occurred in the control group, although this finding did not reach statistical significance. A second randomized, controlled trial compared 5 days of IV PPI (pantoprazole 40 mg or omeprazole 40 mg) and IV vasoconstrictors (somatostatin 250 μg/h or terlipressin 1 mg/6 h) post-EVL in 118 cirrhotic patients with acute variceal bleeding.[53] Esophageal ulcers were noted in 86% of the vasoconstrictor group and 64% of patients in the PPI group ($P = .09$). Large ulcers (>1.5 cm) were noted more frequently in the vasoconstrictor group (29% vs 5%, $P \leq .04$), with 1 patient in the vasoconstrictor group and no patients in the PPI group experiencing esophageal ulcer bleeding ($P =$ not significant). Although prospective, randomized, controlled trial data for decreasing bleeding risk are lacking, PPI therapy can be considered adjunctive therapy post-banding.

Endoscopic sclerotherapy. Endoscopic sclerotherapy is successful in controlling active esophageal variceal bleeding in more than 90% of patients and has proven useful in reducing the frequency and severity of recurrent variceal hemorrhage.[54,55] EST may be performed in patients in whom EVL is technically difficult.[11] Gastric varices that are in continuity with esophageal varices may be treated with EST below the esophagogastric junction, whereas isolated gastric varices are less amenable to EST. Sclerotherapy may be performed by direct intravariceal injection of the sclerosant or via paravariceal injection adjacent to the varix. Several sclerosants (sodium tetradecyl sulfate, sodium morrhuate, ethanolamine oleate, polidocanol, and ethanol) have been used at varying concentrations, volumes, and treatment intervals. More frequent treatments achieve more rapid variceal obliteration than less frequent treatments, but are associated with greater frequency of mucosal ulceration.[56-58] Adverse events of EST include fever, retrosternal discomfort/pain, dysphagia, injection-induced bleeding, esophageal ulceration with delayed bleeding, esophageal strictures, esophageal perforation, mediastinitis, pleural effusion, bronchoesophageal fistula, acute respiratory distress syndrome, and infection.[59,60] EST-induced strictures usually respond to dilation.[59-62]

Management of treatment failures. In patients in whom initial endoscopic therapy fails to control acute esophageal variceal hemorrhage, balloon tamponade should be

performed to temporarily control bleeding until more definitive therapy can be performed. Balloon tamponade should not be maintained for more than 24 hours. After balloon tamponade, repeat endoscopy or transjugular intrahepatic portosystemic shunting (TIPS) should be performed. In the event of unsuccessful endoscopic therapy or recurrent bleeding despite combined pharmacological and endoscopic therapy, TIPS should be performed.[63,64] Case reports have also reported success with the use of self-expandable covered metal stents in controlling refractory variceal bleeding; however, no randomized studies have been performed comparing this strategy with balloon tamponade.[65-67]

GASTRIC VARICES

Gastric varices are most commonly continuations of esophageal varices and extend 2 to 5 cm below the gastroesophageal junction along the lesser curve of the stomach. Isolated gastric varices are most commonly located in the gastric fundus (type 1 isolated gastric varices) and can be seen in patients with cirrhosis and portal hypertension as well as in patients with splenic vein thrombosis (eg, from pancreatic disease) or portal vein thrombosis. Bleeding from gastric varices is typically high volume and can present with massive hematemesis.

Data regarding endoscopic therapy for the treatment of bleeding gastric varices are much more limited compared with endoscopic therapy for bleeding esophageal varices. Treatment options that have been studied in prospective trials include injection of cyanoacrylate-based tissue adhesives, fibrin glue, alcohol, sclerosants, and the use of band ligation.[68-73] Results from these small, prospective studies have had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another. Gastric variceal obturation (GVO) by using cyanoacrylate-based tissue adhesives or fibrin glue appears to be the most effective endoscopic intervention for initial hemostasis and prevention of recurrent bleeding from gastric varices compared with EST or EVL.[70,71] A randomized trial comparing *N*-butyl-2-cyanoacrylate injection with EVL in patients with acute gastric variceal hemorrhage demonstrated similar rates in controlling active bleeding with a decreased rate of rebleeding in patients treated with cyanoacrylate (22% vs 42%, $P = .044$).[74] Limited data comparing GVO with TIPS show no difference in mortality[75,76]; however, 1 study demonstrated that rebleeding of gastric varices was greater in patients treated with GVO compared with TIPS (38% vs 11%, $P = .014$).[75] Another retrospective cohort analysis demonstrated similar rates of rebleeding with significantly less long-term morbidity in patients treated with GVO compared with TIPS (1.6% vs 41.0%, $P < .001$), primarily because of encephalopathy after TIPS. Based on these data, the current recommendation for management of acute gastric variceal hemorrhage is to perform endoscopic GVO at centers that have experience with this procedure. Otherwise, EVL can be attempted. If gastric variceal hemorrhage cannot be controlled with endoscopic and pharmacological therapy, then TIPS or balloon-occluded retrograde transvenous obliteration should be performed. Balloon-occluded retrograde transvenous obliteration is a procedure performed by interventional radiologists in which the gastric varix is accessed via the outflow path of the varix by advancing a catheter up the femoral vein, into the inferior vena cava, then to the left renal vein and into the varix outflow tract. The varix is then occluded with a balloon-tip catheter followed by the delivery of coils and sclerosants to occlude and obliterate the varix.[77] Of note, cyanoacrylate-based compounds are available in the United States but are not approved by the U.S. Food and Drug Administration for the treatment of gastric varices. Injection of cyanoacrylate-based compounds has been associated with the development of thromboembolic events and bacteremia, and antibiotic prophylaxis should be administered.[78]

RECOMMENDATIONS

Recommendations regarding screening for esophageal varices:

- We recommend that all patients who have a diagnosis of cirrhosis undergo screening endoscopy to assess for esophageal and gastric varices. ⊕⊕⊕⊕
- In patients with compensated cirrhosis found to have no varices on initial screening endoscopy, we recommend repeat endoscopy every 2 to 3 years, whereas patients with small varices should undergo repeat endoscopy every 1 to 2 years. ⊕⊕⊕⊕
- We recommend yearly upper endoscopy in patients who have cirrhosis secondary to alcohol abuse or decompensated liver disease who are not found to have varices on screening EGD. ⊕⊕⊕⊕
- We recommend yearly upper endoscopy in patients with small varices accompanied by high-risk stigmata (red wale marks or red spots) on screening EGD. ⊕⊕⊕⊕

Recommendations for primary prophylaxis with EVL:

- We recommend EVL in patients who have large esophageal varices and cannot tolerate or have contraindications to nonselective β-blockers. ⊕⊕⊕◯
- We recommend primary prophylaxis with a nonselective β-blocker or EVL in patients who have large esophageal varices with high-risk stigmata or Child-Pugh class B/C cirrhosis. ⊕⊕⊕◯
- We suggest EVL for primary prophylaxis of esophageal varices be performed at 1- to 8-week intervals until variceal eradication is achieved. ⊕⊕◯◯
- We suggest surveillance EGD be performed 1 to 3 months after esophageal variceal eradication and every 6 to 12 months to check for recurrence. If recurrent varices are noted on surveillance examinations, additional attempts at eradication should be undertaken. ⊕⊕◯◯

Recommendations regarding endoscopic treatments for acute esophageal variceal hemorrhage:

- We recommend administration of prophylactic antibiotics for a period of 7 days in cirrhotic patients who present with variceal hemorrhage. ⊕⊕⊕⊕
- We recommend initiating pharmacological therapy with octreotide in patients in whom variceal hemorrhage is suspected and continuation of octreotide for 3 to 5 days after endoscopy if variceal hemorrhage is confirmed. ⊕⊕⊕○
- We recommend performing endoscopy urgently (within 12 hours of admission) in patients with suspected acute variceal hemorrhage. ⊕⊕⊕○
- We suggest intubation of patients before endoscopy to prevent aspiration during the procedure, especially in patients with encephalopathy. ⊕○○○
- We recommend EVL in patients with acute variceal hemorrhage or in patients with varices and stigmata of recent hemorrhage. ⊕⊕⊕○
- We suggest that EST be reserved for patients in whom EVL is technically difficult to perform. ⊕⊕⊕○
- We suggest that when initial endoscopic therapy fails to control acute variceal hemorrhage, balloon tamponade be performed to temporarily control bleeding until more definitive therapy can be performed. ⊕○○○
- We recommend that TIPS be performed in patients in whom combined endoscopic and pharmacological therapies have failed. ⊕⊕⊕○
- We recommend that after treatment of the acute episode of variceal hemorrhage, endoscopy with EVL be repeated until varices have been eradicated. ⊕⊕⊕○
- We suggest repeat endoscopy at 1- to 8-week intervals for EVL for secondary prophylaxis. ⊕⊕○○
- We recommend that endoscopic surveillance be performed every 3 to 6 months, and recurrent varices be treated with EVL. ⊕⊕⊕○

Recommendations regarding endoscopic treatments for gastric variceal hemorrhage:

- We suggest GVO with a cyanoacrylate-based compound for the treatment of acute gastric variceal hemorrhage at centers familiar with this technique. Otherwise, EVL can be attempted. ⊕⊕○○
- We recommend that when gastric variceal hemorrhage cannot be controlled with endoscopic and pharmacological therapy, alternative interventions should be performed. ⊕⊕⊕○

DISCLOSURES

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Abbreviations: EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; GVO, gastric variceal obturation; IV, intravenous; PPI, proton pump inhibitor; RR, relative risk; TIPS, transjugular intrahepatic portosystemic shunting.

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