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Endoscopic diagnosis and management of esophagogastric variceal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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MAIN RECOMMENDATIONS

1 ESGE recommends that patients with compensated advanced chronic liver disease (ACLD; due to viruses, alcohol, and/or nonobese [BMI < 30 kg/m^2] nonalcoholic steatohepatitis) and clinically significant portal hypertension (hepatic venous pressure gradient [HVPG] > 10 mmHg and/or liver stiffness by transient elastography > 25 kPa) should receive, if no contraindications, nonselective beta blocker (NSBB) therapy (preferably carvedilol) to prevent the development of variceal bleeding.
Strong recommendation, moderate quality evidence.

2 ESGE recommends that in those patients unable to receive NSBB therapy with a screening upper gastrointestinal (GI) endoscopy that demonstrates high risk esophageal varices, endoscopic band ligation (EBL) is the endoscopic prophylactic treatment of choice. EBL should be repeated every 2–4 weeks until variceal eradication is achieved. Thereafter, surveillance EGD should be performed every 3–6 months in the first year following eradication.
Strong recommendation, moderate quality evidence.

3 ESGE recommends, in hemodynamically stable patients with acute upper GI hemorrhage (UGIH) and no history of cardiovascular disease, a restrictive red blood cell (RBC) transfusion strategy, with a hemoglobin threshold of ≤ 70 g/L prompting RBC transfusion. A post-transfusion target hemoglobin of 70–90 g/L is desired.
Strong recommendation, moderate quality evidence.

4 ESGE recommends that patients with ACLD presenting with suspected acute variceal bleeding be risk stratified according to the Child–Pugh score and MELD score, and by documentation of active/inactive bleeding at the time of upper GI endoscopy.
Strong recommendation, high quality of evidence.

5 ESGE recommends the vasoactive agents terlipressin, octreotide, or somatostatin be initiated at the time of presentation in patients with suspected acute variceal bleeding and be continued for a duration of up to 5 days.
Strong recommendation, high quality evidence.

6 ESGE recommends antibiotic prophylaxis using ceftriaxone 1 g/day for up to 7 days for all patients with ACLD presenting with acute variceal hemorrhage, or in accordance with local antibiotic resistance and patient allergies.
Strong recommendation, high quality evidence.

7 ESGE recommends, in the absence of contraindications, intravenous erythromycin 250 mg be given 30–120 minutes prior to upper GI endoscopy in patients with suspected acute variceal hemorrhage.
Strong recommendation, high quality evidence.

8 ESGE recommends that, in patients with suspected variceal hemorrhage, endoscopic evaluation should take place within 12 hours from the time of patient presentation provided the patient has been hemodynamically resuscitated.
Strong recommendation, moderate quality evidence.

9 ESGE recommends EBL for the treatment of acute esophageal variceal hemorrhage (EVH).
Strong recommendation, high quality evidence.

10 ESGE recommends that, in patients at high risk for recurrent esophageal variceal bleeding following successful endoscopic hemostasis (Child–Pugh C ≤ 13 or Child–Pugh B > 7 with active EVH at the time of endoscopy despite vasoactive agents, or HVPG > 20 mmHg), pre-emptive transjugular intrahepatic portosystemic shunt (TIPS) within 72 hours (preferably within 24 hours) must be considered.
Strong recommendation, high quality evidence.

11 ESGE recommends that, for persistent esophageal variceal bleeding despite vasoactive pharmacological and endoscopic hemostasis therapy, urgent rescue TIPS should be considered (where available).
Strong recommendation, moderate quality evidence.

12 ESGE recommends endoscopic cyanoacrylate injection for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage.
Strong recommendation, high quality evidence.

13 ESGE recommends endoscopic cyanoacrylate injection or EBL in patients with GOV1-specific bleeding.
Strong recommendations, moderate quality evidence.

14 ESGE suggests urgent rescue TIPS or balloon-occluded retrograde transvenous obliteration (BRTO) for gastric variceal bleeding when there is a failure of endoscopic hemostasis or early recurrent bleeding.
Weak recommendation, low quality evidence.

15 ESGE recommends that patients who have undergone EBL for acute EVH should be scheduled for follow-up EBLs at 1- to 4-weekly intervals to eradicate esophageal varices (secondary prophylaxis).
Strong recommendation, moderate quality evidence.

16 ESGE recommends the use of NSBBs (propranolol or carvedilol) in combination with endoscopic therapy for secondary prophylaxis in EVH in patients with ACLD.
Strong recommendation, high quality evidence.

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ABBREVIATIONS

ACLD	advanced chronic liver disease
AE	adverse event
BMI	body mass index
BRTO	balloon-occluded retrograde transvenous obliteration
BSG	British Society of Gastroenterology
DOAC	direct oral anticoagulant
EBL	endoscopic band ligation
EGD	esophagogastroduodenoscopy
EGVH	esophagogastric variceal hemorrhage
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
EVH	esophageal variceal hemorrhage
FFP	fresh frozen plasma
GI	gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GVH	gastric variceal hemorrhage
HVPG	hepatic venous pressure gradient
INR	international normalized ratio
NSBB	nonselective beta blocker
PCC	prothrombin complex concentrate
PPI	proton pump inhibitor
OR	odds ratio
RBC	red blood cell
RCT	randomized controlled trial
RR	relative risk or risk ratio
SEMS	self-expanding metal stent
SHR	summary hazard ratio
TIPS	transjugular intrahepatic portosystemic shunt
UGIH	upper gastrointestinal hemorrhage
VCE	video capsule endoscopy
TEG	thromboelastography

SCOPE AND PURPOSE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE) and addresses the role of gastrointestinal endoscopy in the diagnosis and management of esophagogastric variceal hemorrhage.

1 Introduction

Portal hypertension caused by increased sinusoidal (i. e. advanced chronic liver disease [ACLD]), presinusoidal (i. e. schistosomiasis, portal vein thrombosis), or post-sinusoidal (i. e. Budd–Chiari syndrome) pressure can lead to significant complications including esophagogastric variceal hemorrhage (EGVH). EGVH is a medical emergency that requires urgent evaluation and management. This ESGE Guideline provides evidence-based guidance on EGVH including screening/primary prophylaxis (preventing a first variceal hemorrhage), management of an acute bleeding episode, and guidance on secondary prophylaxis (preventing recurrent EGVH) in patients with ACLD.

2 Methods

The ESGE commissioned this Guideline (ESGE Guideline Committee chair, K.T.) and appointed a guideline leader (I.M.G.). The guideline leader (I.M.G.) established six task forces, each with its own leader (J.C.G.-P., M.C.D., L.F., T.H., J.G.K., and I.J.). Key questions were prepared by the coordinating team (I.M.G., J.C.G.-P., M.C.D., L.F., T.H., J.G.K., and I.J.) and divided amongst the six task forces (**Appendix 1 s**, see online-only Supplementary material).

A professional health sciences librarian (R.R.) performed a structured systematic literature search using keywords of English-language articles limited from 1 January 2000 to 30 September 2021, in Ovid MEDLINE, Embase (Elsevier), the Cochrane Database of Systematic Reviews (CDSR), and Cochrane Center Register of Controlled Trials (CENTRAL). Free-text keywords, MeSH terms, and other database-specific controlled vocabulary were searched; terms included esophageal/oesophageal varices, gastric varices, gastrointestinal, hemorrhage/haemorrhage, bleeding, and other related words (**Appendix 2 s**). The hierarchy of studies included in this evidence-based guideline was, in decreasing order of evidence level: published systematic reviews/meta-analyses, randomized controlled trials (RCTs), prospective and retrospective observational studies, and case series.

Evidence on each key question was summarized in tables, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1] (**Table 1 s**). Grading of the evidence depends on the balance between the benefits and risk or burden of any health intervention. Further details on ESGE guideline development have been previously reported [2].

The results of the literature search and answers to the PICO (patient, intervention, comparator, outcome) questions were presented to all guideline group members during two online face-to-face meetings conducted on 18 and 19 February 2022. Subsequently, drafts were written by each task force leader and distributed between the task force members for revision and online discussion. In June 2022, a draft prepared by the guideline leader and the six task force leaders was sent to all guideline group members. After the agreement of all members had been obtained, the manuscript was reviewed by two independent external reviewers. The manuscript was then sent for further comments to the 51 ESGE member societies and individual members. It was subsequently submitted to the journal *Endoscopy* for publication. The final revised manuscript was agreed upon by all the authors.

This ESGE Guideline was issued in 2022 and will be considered for update in 2027. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

The evidence statements and recommendations in this Guideline have in general been grouped according to the different task force topics (**Appendix 1 s**). Each statement is followed by the strength of evidence based on the GRADE system and the discussion/consensus of the evidence that occurred during

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the two 4-hour online meetings. All recommendations in this guideline are summarized in ▶**Table 1**. The definitions used throughout the guideline are shown in ▶**Table 2**.

3 Endoscopic screening for high risk esophagogastric varices and primary prophylaxis for EGVH

3.1 Screening for high risk esophagogastric varices

RECOMMENDATION

ESGE recommends that, for patients with compensated ACLD and liver stiffness measurement < 20 kPa and platelet count ≥ 150×10^9/L, screening upper gastrointestinal (GI) endoscopy can be avoided because these patients are thought to have a low probability for having high risk varices.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends that patients with decompensated ACLD (liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤ 150×10^9/L) should be screened by upper GI endoscopy to identify high risk esophagogastric varices (esophageal varices that are medium or large in size; or small-sized esophageal varices with red wale markings).

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that patients with compensated ACLD, but with liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤ 150×10^9/L who are not receiving nonselective beta blocker therapy, should be screened by upper GI endoscopy to identify high risk esophagogastric varices (esophageal varices that are medium or large in size; or small-sized esophageal varices with red wale markings).

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that esophageal varices be documented in the endoscopy report according to the Baveno criteria as small, medium, or large varices, with or without the presence of red wale markings.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that gastric varices be documented in the endoscopy report according to the Sarin classification.

Strong recommendation, low quality evidence.

In 2015, the Baveno VI consensus conference challenged the dogma that all patients with cirrhosis/ACLD should undergo upper gastrointestinal (GI) endoscopy to screen for high risk varices [3]. With the use of noninvasive testing, it has been reported that patients with a liver stiffness < 20 kPa and a platelet count ≥ 150×10^9/L are at low risk (< 5 %) of having high risk varices [3]. These parameters, known as the Baveno VI criteria, have subsequently been validated by numerous studies in multiple settings, including in various compensated ACLD patient populations [4–7]. A recent systematic review assessing the performance of the Baveno VI criteria showed a pooled negative predictive value of 99 % (95 %CI 99 % to 100 %) for ruling out high risk varices, with criteria performance not affected by the cause of cirrhosis, so appearing to confirm that the Baveno VI criteria can be safely used to avoid endoscopy in a substantial proportion of patients with compensated cirrhosis [8].

RECOMMENDATION

ESGE does not recommend video capsule endoscopy (VCE) for screening of esophageal varices.

Strong recommendation, high quality evidence.

A multicenter randomized trial and two meta-analyses investigating the diagnostic performance of esophageal video capsule endoscopy (VCE) compared with esophagogastroduodenoscopy (EGD) for the detection and grading of esophageal varices in patients with ACLD have been published [9–11]. Sacher-Huvelin et al. reported on the diagnostic performance of VCE compared with EGD in 300 patients with cirrhosis [9]. Esophageal varices were identified by VCE in 121 patients (40.3 %) and by EGD in 140 (46.6 %). The overall sensitivity, specificity, and positive and negative predictive values of VCE were 76 %, 91 %, 88 %, and 81 %, respectively, and the overall accuracy was 84 % [9].

Colli et al. performed a systematic review/meta-analysis on the diagnostic accuracy of VCE for the diagnosis of esophageal varices in children or adults with chronic liver disease or portal vein thrombosis [10]. In the 15 included studies (936 patients with cirrhosis), 68.4 % had varices of any size. The sensitivity of VCE to diagnose esophageal varices of any size ranged from 65 % to 100 % and the specificity from 33 % to 100 %. The pooled estimate of sensitivity was 84.8 % and of specificity 84.3 % of VCE for diagnosing esophageal varices of any size [10]. In a subsequent systematic review/meta-analysis including 17 studies (1328 patients with portal hypertension) comparing VCE with

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▶ **Table 1** Summary of recommendations made in this Guideline.

Endoscopic screening for high risk esophagogastric varices and primary prophylaxis for EGVH
ESGE recommends that, for patients with compensated ACLD and liver stiffness measurement < 20 kPa and platelet count ≥ 150×10^9/L, screening upper GI endoscopy can be avoided since these patients are thought to have a low probability for having high risk varices Strong recommendation, high quality evidence
ESGE recommends that patients with decompensated ACLD (liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤ 150×10^9/L) should be screened by upper GI endoscopy to identify high risk esophagogastric varices (esophageal varices that are medium or large in size; or small-sized esophageal varices with red wale markings) Strong recommendation, moderate quality evidence
ESGE recommends that patients with compensated ACLD, but with liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤ 150×10^9/L who are not receiving NSBB therapy, should be screened by upper GI endoscopy to identify high risk esophagogastric varices (esophageal varices that are medium or large in size; or small-sized esophageal varices with red wale markings) Strong recommendation, moderate quality evidence
ESGE recommends that esophageal varices be documented in the endoscopy report according to the Baveno criteria as small, medium, or large varices, with or without the presence of red wale markings Strong recommendation, low quality evidence
ESGE recommends that gastric varices be documented in the endoscopy report according to the Sarin classification Strong recommendation, low quality evidence
ESGE does not recommend VCE for screening of esophageal varices Strong recommendation, high quality evidence
ESGE recommends that patients with compensated ACLD (due to viruses, alcohol, and/or nonobese [BMI < 30 kg/m^2] nonalcoholic steatohepatitis) and clinically significant portal hypertension (HVPG > 10 mmHg and/or liver stiffness by transient elastography > 25 kPa) should receive, if no contra-indications, NSBB therapy (preferably carvedilol) to prevent the development of variceal bleeding Strong recommendation, moderate quality evidence
ESGE recommends that, in those patients who are unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates high risk esophagogastric varices, prophylactic endoscopic treatment should be performed Strong recommendation, moderate quality evidence
ESGE recommends that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates high risk esophageal varices, EBL is the endoscopic prophylactic treatment of choice. EBL should be repeated every 2–4 weeks until variceal eradication is achieved. Thereafter, surveillance EGD should be performed every 3–6 months in the first year following eradication Strong recommendation, moderate quality evidence
ESGE suggests that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates gastric varices (Sarin GOV-2 or IGV-1), no treatment, cyanoacrylate injection alone, or EUS-guided coil plus cyanoacrylate injection can be considered. EUS-guided injection therapy should be decided on a case-by-case basis and limited to centers with expertise in this endoscopic technique Weak recommendation, low quality evidence
ESGE recommends that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that does not demonstrate high risk varices, surveillance endoscopy should be performed every 2 years if there is ongoing active liver disease or every 3 years if the underlying liver disease is quiescent Weak recommendation, low quality evidence
Pre-endoscopy management of acute EGVH
ESGE recommends urgent assessment of the hemodynamic status in patients presenting with suspected acute EGVH Strong recommendation, low quality evidence
ESGE recommends prompt, yet careful, intravascular volume replacement, initially using crystalloid fluids, if hemodynamic instability exists, to restore tissue perfusion while avoiding intravascular volume overexpansion Strong recommendation, low quality evidence
ESGE does not recommend the transfusion of FFP as part of the initial management of EGVH Strong recommendation, low quality evidence
ESGE does not recommend the use of recombinant factor VIIa as part of the initial management of EGVH Strong recommendation, high quality evidence
ESGE suggests endotracheal intubation prior to upper GI endoscopy in patients with suspected variceal hemorrhage and ongoing hematemesis, encephalopathy, and/or with agitation and inability to control their airway to protect against the potential aspiration of gastric contents Weak recommendation, low quality evidence
ESGE recommends that, if prophylactic endotracheal intubation is performed, extubation should occur as soon as clinically safe following upper GI endoscopy Strong recommendation, very low quality evidence

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▶ **Table 1** (Continuation)

ESGE does not recommend routine platelet transfusion or a specific minimum platelet count threshold for triggering platelet transfusion. If variceal bleeding is not controlled, the decision to transfuse platelets should be made on a case-by-case basis Strong recommendation, moderate quality evidence
ESGE recommends, in hemodynamically stable patients with acute UGIH and no history of cardiovascular disease, a restrictive RBC transfusion strategy, with a hemoglobin threshold of ≤ 70 g/L prompting RBC transfusion. A post-transfusion target hemoglobin of 70–90 g/L is desired Strong recommendation, moderate quality evidence
ESGE recommends, in hemodynamically stable patients with acute UGIH and a history of acute or chronic cardiovascular disease, a more liberal RBC transfusion strategy with a hemoglobin threshold of ≤ 80 g/L prompting RBC transfusion Strong recommendation, low quality evidence
ESGE recommends that patients with ACLD presenting with suspected acute variceal bleeding be risk stratified according to the Child–Pugh score and MELD score, and by documentation of active/inactive bleeding at the time of upper GI endoscopy Strong recommendation, high quality of evidence
ESGE recommends the following risk stratification definitions: a) patients with Child–Pugh A or Child–Pugh B without active bleeding at upper GI endoscopy or MELD < 11 points are at low risk of poor outcome b) patients with Child–Pugh B with active bleeding at upper GI endoscopy despite vasoactive agents or Child–Pugh C are at high risk of poor outcome c) patients with MELD ≥ 19 points are considered at high risk of poor outcome Strong recommendation, high quality evidence
ESGE recommends the vasoactive agents terlipressin, octreotide, or somatostatin be initiated at the time of presentation in patients with suspected acute variceal bleeding and be continued for a duration of up to 5 days Strong recommendation, high quality evidence
ESGE suggests, following successful endoscopic hemostasis, vasoactive agents may be stopped 24–48 hours later in selected patients Weak recommendation, moderate quality evidence
ESGE recommends antibiotic prophylaxis using ceftriaxone 1 g/day for up to 7 days for all patients with ACLD presenting with acute variceal hemorrhage, or in accordance with local antibiotic resistance and patient allergies Strong recommendation, high quality evidence
ESGE recommends that antiplatelet agents be temporarily withheld in patients presenting with acute variceal hemorrhage Strong recommendation, low quality evidence
ESGE recommends that the restarting of antiplatelet agents be determined on the basis of the patient's risk of rebleeding versus their risk of thrombosis Strong recommendation, low quality evidence
ESGE recommends that anticoagulants be temporarily withheld in patients presenting with suspected acute variceal hemorrhage and appropriate reversal agents be used in patients with hemodynamic instability Strong recommendation, low quality evidence
ESGE recommends that the restarting of anticoagulants should be guided by the patient's risk of rebleeding versus their risk of thrombosis Strong recommendation, low quality evidence
ESGE recommends, in the absence of contraindications, intravenous erythromycin 250 mg be given 30–120 minutes prior to upper GI endoscopy in patients with suspected acute variceal hemorrhage Strong recommendation, high quality evidence
Endoscopic management of EGVH
ESGE recommends that, in patients with suspected variceal hemorrhage, endoscopic evaluation should take place within 12 hours from the time of patient presentation, provided the patient has been hemodynamically resuscitated Strong recommendation, moderate quality evidence
ESGE recommends that the timing of upper GI endoscopy in patients with suspected acute variceal hemorrhage should not be influenced by the INR level at the time of patient presentation Strong recommendation, low quality evidence
ESGE recommends EBL for the treatment of acute EVH Strong recommendation, high quality evidence
ESGE does not recommend the use of hemostatic sprays/powders for the definitive endoscopic treatment of acute esophageal or gastric variceal hemorrhage. Hemostatic sprays/powders may be considered as a bridge to definitive therapy when standard endoscopic treatment is not effective or is not available Strong recommendation, high quality evidence

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▶ **Table 1** (Continuation)

ESGE recommends that, in patients at high risk for recurrent esophageal variceal bleeding following successful endoscopic hemostasis (Child–Pugh C ≤ 13 or Child–Pugh B > 7 with active EVH at the time of endoscopy despite vasoactive agents, or HVPG > 20 mmHg), pre-emptive TIPS within 72 hours (preferably within 24 hours) must be considered Strong recommendation, high quality evidence
ESGE recommends that, for persistent esophageal variceal bleeding despite vasoactive pharmacological and endoscopic hemostasis therapy, urgent rescue TIPS should be considered (where available) Strong recommendation, moderate quality evidence
ESGE suggests that, for persistent esophageal variceal bleeding despite vasoactive pharmacological and endoscopic hemostasis therapy, self-expandable metal stents (where available) are preferred over balloon tamponade for bridging to definitive hemostasis therapy Weak recommendation, low quality evidence
ESGE suggests that recurrent EVH in the first 5 days following successful initial endoscopic hemostasis be managed by a second attempt at endoscopic therapy or salvage TIPS Weak recommendation, low quality evidence
ESGE recommends classifying gastric or gastroesophageal varices according to the Sarin classification Strong recommendation, low quality evidence
ESGE recommends endoscopic cyanoacrylate injection for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage Strong recommendation, high quality evidence
ESGE makes no formal recommendation regarding the use of endoscopic thrombin injection in acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage because of the currently limited and disparate data
ESGE recommends endoscopic cyanoacrylate injection or EBL in patients with GOV1-specific bleeding Strong recommendations, moderate quality evidence
ESGE suggests that EUS-guided management of bleeding gastric varices combining injection of coils and cyanoacrylate may be used in centers with expertise and familiarity with this technique Weak recommendation, low quality evidence
ESGE suggests urgent rescue TIPS or BRTO for gastric variceal bleeding when there is a failure of endoscopic hemostasis or early recurrent bleeding Weak recommendation, low quality evidence
Post-endoscopy management of EGVH
ESGE recommends that patients who have undergone EBL for acute EVH should be scheduled for follow-up EBLs at 1- to 4-weekly intervals to eradicate esophageal varices (secondary prophylaxis) Strong recommendation, moderate quality evidence
ESGE recommends the use of NSBBs (propranolol or carvedilol) in combination with endoscopic therapy for secondary prophylaxis in EVH in patients with ACLD Strong recommendation, high quality evidence
ESGE recommends an individualized approach for secondary prophylaxis of cardiofundal variceal hemorrhage (GOV2, IGV1) based upon patient factors and local expertise owing to the current lack of definitive high level evidence regarding specific eradication therapies for cardiofundal varices (e. g. endoscopic cyanoacrylate injection ± NSBB, EUS-guided injection of coils plus cyanoacrylate, TIPS, or BRTO) and appropriate treatment intervals Strong recommendation, low quality evidence
ESGE suggests against the routine use of PPIs in the post-endoscopic management of acute variceal bleeding and, if initiated before endoscopy, PPIs should be discontinued Weak recommendation, low quality evidence
ESGE recommends the rapid removal of blood from the GI tract, preferably using lactulose, to prevent or to treat hepatic encephalopathy in cirrhotic patients with acute variceal hemorrhage Strong recommendation, moderate quality evidence

ACLD, advanced chronic liver disease; BMI, body mass index; BRTO, balloon-occluded retrograde transvenous obliteration; EBL, endoscopic band ligation; EGD, esophagogastroduodenoscopy; EGVH, esophagogastric variceal hemorrhage; EUS, endoscopic ultrasound; EVH, esophageal variceal hemorrhage; FFP, fresh frozen plasma; GI, gastrointestinal; GOV, gastroesophageal varices; HVPG, hepatic venous pressure gradient; IGV, isolated gastric varices; INR, international normalized ratio; NSBB, nonselective beta blocker; PPI, proton pump inhibitor; TIPS, transjugular intrahepatic portosystemic shunt; UGIH, upper gastrointestinal hemorrhage; VCE, video capsule endoscopy.

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▶ **Table 2** Definitions used in this Guideline.

Compensated ACLD	Liver stiffness measurement by transient elastography < 20 kPa and platelet count > 150×10^9/L
Decompensated ACLD	Liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤ 150×10^9/L
Clinically significant portal hypertension	HVPG > 10 mmHg and/or liver stiffness by transient elastography > 25 kPa
High risk esophagogastric varices	Varices that are medium or large size or varices that are small size with red wale markings
High risk cirrhotic patients with variceal bleeding	HVPG ≥ 20 mmHg
Acute episode of variceal bleeding	Variceal bleeding events in the interval of 5 days from the time of patient presentation to a medical facility
Early variceal rebleeding	Variceal bleeding that occurs beyond 5 days but with 6 weeks from the time of patient presentation to a medical facility provided initial hemostasis was achieved
Late variceal rebleeding	Variceal bleeding that occurs ≥ 6 weeks from the time of patient presentation to a medical facility
Type 1 gastroesophageal varices (GOV1)	Extend below the gastroesophageal junction along the lesser curvature of the stomach
Type 2 gastroesophageal varices (GOV2)	Extend below the gastroesophageal junction into the gastric fundus
Type 1 isolated gastric varices (IGV1)	Are only located in the gastric fundus
Type 2 isolated gastric varices (IGV2)	Are located elsewhere in the stomach (e. g. antrum)

ACLD, advanced chronic liver disease; GOV, gastroesophageal varices; HVPG, hepatic venous pressure gradient; IGV, isolated gastric varices.

EGD, the diagnostic accuracy of VCE in diagnosing esophageal varices was 90 % [11]. The diagnostic pooled sensitivity and specificity were 83 % and 85 %, respectively. The diagnostic accuracy of VCE for the grading of medium-to-large sized esophageal varices was 92 %. The pooled sensitivity and specificity were 72 % and 91 %, respectively, for the grading of esophageal varices [11].

3.2 Primary prophylaxis for esophagogastric variceal hemorrhage

RECOMMENDATION

ESGE recommends that patients with compensated ACLD (due to viruses, alcohol, and/or nonobese [BMI < 30 kg/m^2] nonalcoholic steatohepatitis) and clinically significant portal hypertension (hepatic venous pressure gradient [HVPG] > 10 mmHg and/or liver stiffness by transient elastography > 25 kPa) should receive, if no contraindications, nonselective beta blocker (NSBB) therapy (preferably carvedilol) to prevent the development of variceal bleeding.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that, in those patients who are unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates high risk esophagogastric varices, prophylactic endoscopic treatment should be performed.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates high risk esophageal varices, endoscopic band ligation (EBL) is the endoscopic prophylactic treatment of choice. EBL should be repeated every 2–4 weeks until variceal eradication is achieved. Thereafter, surveillance EGD should be performed every 3–6 months in the first year following eradication.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE suggests that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that demonstrates gastric varices (Sarin GOV-2 or IGV-1; cardiofundal varices), no treatment, cyanoacrylate injection alone, or endoscopic ultrasound (EUS)-guided coil plus cyanoacrylate injection can be considered. EUS-guided injection therapy should be decided on a case-by-case basis and limited to centers with expertise in this endoscopic technique.

Weak recommendation, low quality evidence.

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RECOMMENDATION
ESGE recommends that, in those patients unable to receive NSBB therapy with a screening upper GI endoscopy that does not demonstrate high risk varices, surveillance endoscopy should be performed every 2 years if there is ongoing active liver disease or every 3 years if the underlying liver disease is quiescent.
Weak recommendation, low quality evidence.

Primary prophylaxis is universally recommended for patients with ACLD and high risk varices. Both NSBB therapy and endoscopic band ligation (EBL) are accepted primary prophylaxis options for esophageal varices, as they have both been shown to significantly reduce the risk of a first episode of esophageal variceal hemorrhage (EVH). A network meta-analysis (including 32 RCTs comparing NSBBs, isosorbide mononitrate, carvedilol, and EBL, alone or in combination with each other or placebo; 3362 adults who had cirrhosis with large esophageal varices and no prior history of bleeding) showed that both NSBB therapy and EBL have similar efficacy in reducing the risk of a first variceal bleed [12]. While serious and life-threatening adverse events (AEs) are more common in patients treated with EBL, discontinuation owing to AEs was more common in NSBB-treated patients. Moreover, NSBBs demonstrated a survival benefit over EBL. This observed beneficial effect may be a result of factors beyond the prevention of EVH and may be related to the effect of NSBBs on reducing portal hypertension.

Moreover, an individual patient data meta-analysis also reinforced the benefit of NSBBs in patients with compensated cirrhosis and high risk varices [13]. This meta-analysis included 11 RCTs (1400 patients with cirrhosis and high risk varices, of which 656 had compensated cirrhosis) comparing NSBB therapy against EBL, either as monotherapy or in combination, for the primary prevention of bleeding. In patients with compensated cirrhosis, the mortality risk was lower with NSBB therapy than with EBL (summary hazard ratio [SHR] 0.57, 95 %CI 0.36 to 0.90; $P=0.02$) and was similar with NSBB therapy and EBL compared with NSBBs alone ($P=0.10$). The benefit in patients with compensated cirrhosis treated with NSBBs was mainly because of a decrease in the risk of developing ascites (SHR 0.38, 95 %CI 0.19 to 0.73; $P=0.004$), while the risk of a first variceal bleed was similar (SHR 0.94, 95 %CI 0.47 to 0.87; $P=0.86$) between the groups. Additionally, neither the risk of variceal bleeding nor the risk of developing ascites was improved by adding EBL to NSBBs as compared with treatment with NSBBs alone. These data suggest that NSBBs should be the treatment of choice in patients with high risk varices because, in addition to decreasing the variceal bleeding risk similarly to EBL, they decrease the risk of developing ascites and significantly improve survival.

The preferred NSBB for primary prophylaxis is carvedilol based on its greater portal pressure lowering effect compared with propranolol or nadolol, and the improvement in the outcome of nonresponders to propranolol [14]. The effects of carvedilol in preventing decompensation and improving survival in patients with compensated cirrhosis has been recently investigated in a meta-analysis. This study included 352 patients with compensated cirrhosis (181 treated with carvedilol and 171 controls) from four RCTs and showed a decreased risk of decompensation (SHR 0.506, 95 %CI 0.289 to 0.887; $P=0.02$) and mortality (SHR 0.417, 95 %CI 0.194 to 0.896; $P=0.03$) in patients treated with carvedilol, without significant heterogeneity [15].

There have been several systematic reviews/meta-analyses of RCTs evaluating the benefits and harms of EBL versus NSBBs as primary prophylaxis for esophageal variceal bleeding [16–18]. In a Cochrane systematic review, Gluud et al. reported that 176/731 of the patients randomized to EBL (24 %) and 177/773 of patients randomized to NSBBs (23 %) died. EBL reduced upper GI hemorrhage (UGIH) and variceal bleeding compared with NSBBs (relative risk [RR] 0.69 and 0.67, respectively). There was a beneficial effect of EBL on primary prevention of EVH, yet this did not reduce mortality [16]. In the most recent systematic review/meta-analysis evaluating carvedilol versus EBL, Tian et al. reported no significant difference in variceal bleeding between the carvedilol and EBL groups (RR 0.86, 95 %CI 0.60 to 1.23). Moreover, no significant difference was observed for all-cause mortality (RR 0.82, 95 %CI 0.44 to 1.53) or for bleeding-related deaths (RR 0.85, 95 %CI 0.39 to 1.87) [18].

4 Pre-endoscopy management of acute EGVH

4.1 Hemodynamic resuscitation

RECOMMENDATION
ESGE recommends urgent assessment of the hemodynamic status in patients presenting with suspected acute EGVH.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends prompt, yet careful, intravascular volume replacement, initially using crystalloid fluids, if hemodynamic instability exists, to restore tissue perfusion while avoiding intravascular volume overexpansion.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE does not recommend the transfusion of fresh frozen plasma as part of the initial management of EGVH.
Strong recommendation, low quality evidence.

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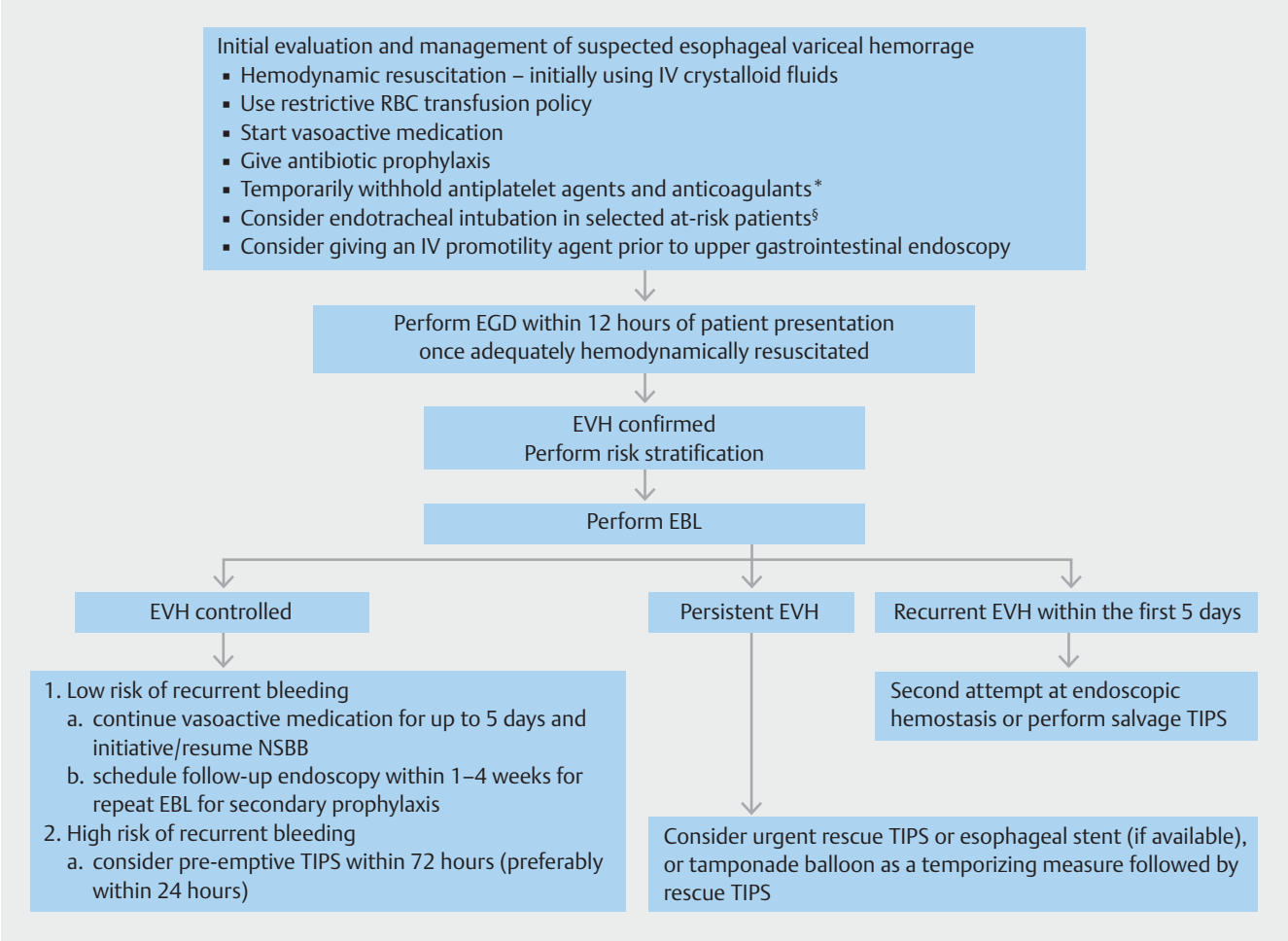
RECOMMENDATION

ESGE does not recommend the use of recombinant factor VIIa as part of the initial management of EGVH.
Strong recommendation, high quality evidence.

The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multiorgan failure. Early intensive hemodynamic resuscitation of patients with acute UGIH has been shown to significantly decrease mortality (▶ **Fig. 1** and ▶ **Fig. 2**) [19]. However, uncertainty remains regarding the optimal rate of fluid resuscitation (aggressive vs. restrictive), especially for EGVH.

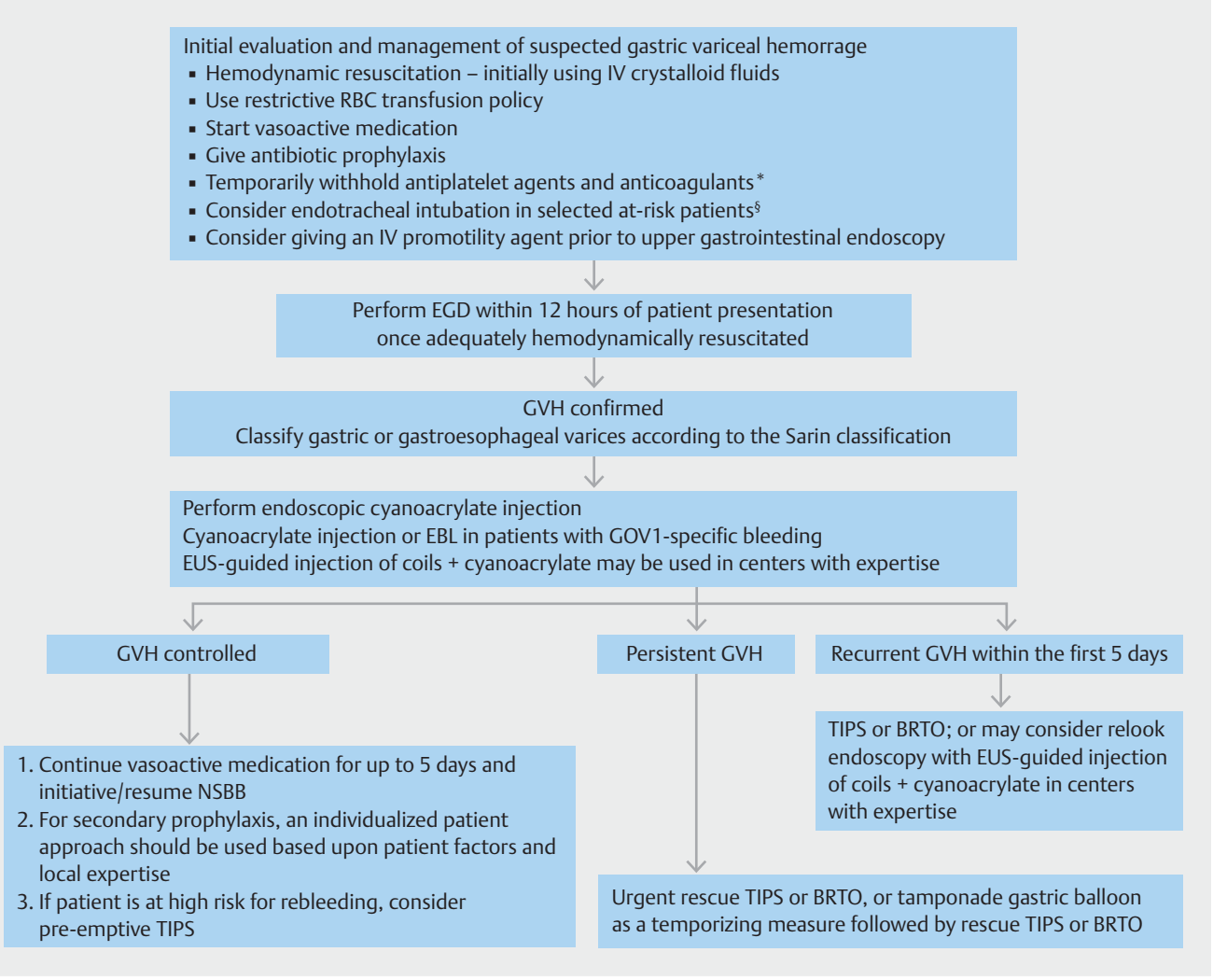
Existing limited evidence, derived from patients with hemorrhagic shock from all causes including trauma, suggest that, as compared with a conventional fluid resuscitation strategy, a restrictive fluid resuscitation regimen may lead to fewer AEs and may reduce mortality [20–23]. The optimal choice of intravenous fluid for initial resuscitation is unclear, with crystalloids or colloids often being used while the need for the transfusion of blood products is assessed [24–26]. In both a large RCT and a meta-analysis of critically ill patients, as compared with saline, use of a "balanced" crystalloid solution (e. g. lactated Ringer's solution) was shown to reduce both mortality and major adverse renal events [25, 26]. Whether these data can be fully extrapolated to patients with EGVH is uncertain. Care should be taken to avoid aggressive intravascular volume overexpansion in patients presenting with suspected EVGH in order to avoid a paradoxical increase in portal hypertension and subsequent bleeding risk.

Mohanty et al. in a retrospective study evaluating whether the transfusion of fresh frozen plasma (FFP) affected mortality and bleeding outcomes in patients with cirrhosis and acute variceal hemorrhage [27], reported that FFP transfusion was associated with significantly increased mortality at 42 days (odds ratio [OR] 9.41, 95 %CI 3.71 to 23.90), failure to control



▶ **Fig. 1** ESGE algorithm for the management of acute esophageal variceal hemorrhage (EVH).
EBL, endoscopic band ligation; EGD, esophagogastroduodenoscopy; IV, intravenous; NSBB, nonspecific beta blocker; RBC, red blood cell; TIPS, transjugular intrahepatic portosystemic shunt.
* The restarting of antiplatelet agents and/or anticoagulants should be guided by the patient's risk of rebleeding versus their risk of thrombosis.
§ Extubation should occur as soon as clinically safe following upper gastrointestinal endoscopy.

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▶ **Fig. 2** ESGE algorithm for the management of acute gastric variceal hemorrhage (GVH).
BRTO, balloon retrograde transvenous obliteration; EBL, endoscopic band ligation; EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; GOV1, gastroesophageal varices type 1; IV, intravenous; NSBB, nonspecific beta blocker; RBC, red blood cell; TIPS, transjugular intrahepatic portosystemic shunt.

bleeding at 5 days (OR 3.87, 95 %CI 1.28 to 11.70), and longer hospital stay (OR 1.88, 95 %CI 1.03 to 3.42). Lower volume factor replacements such as prothrombin complex concentrate (PCC) and recombinant factor VIIa appear to be more effective than FFP in decreasing international normalized ratio (INR) values in patients with cirrhosis [28], while not carrying the risk of intravascular volume overload. However, two RCTs failed to show any benefit for recombinant factor VIIa infusion in EGVH [29, 30].

4.2 Endotracheal intubation

RECOMMENDATION

ESGE suggests endotracheal intubation prior to upper GI endoscopy in patients with suspected variceal hemorrhage and ongoing hematemesis, encephalopathy, and/or with agitation and inability to control their airway to protect against the potential aspiration of gastric contents.

Weak recommendation, low quality evidence.

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RECOMMENDATION

ESGE recommends that, if prophylactic endotracheal intubation is performed, extubation should occur as soon as clinically safe following upper GI endoscopy.

Strong recommendation, very low quality evidence.

Studies evaluating the outcomes and safety of prophylactic endotracheal intubation prior to upper GI endoscopy in patients presenting with acute UGIH, including EGVH, are limited and of low quality. Their results have varied regarding important outcomes such as aspiration, pneumonia, and mortality [31–34]. Meta-analyses pooling these small observational studies show that prophylactic endotracheal intubation before upper GI endoscopy in all patients with acute UGIH may be associated with a higher risk of aspiration and pneumonia, longer hospital stays, and potentially higher mortality [35–37].

The most recent meta-analyses [36,37] conducted subgroup analyses stratified by the type of UGIH (variceal vs. other), hypothesizing that variceal bleeding would be associated with a greater benefit from prophylactic endotracheal intubation. These subgroup analyses included two observational studies (n = 172 patients) with more EGVH patients (62 %) in the prophylactic intubation group. Alshamsi et al. [36] reported that prophylactic endotracheal intubation in patients with variceal bleeding was associated with higher rates of aspiration (OR 4.60, 95 %CI 0.53 to 39.91), pneumonia (OR 5.31, 95 %CI 0.63 to 44.76), and longer hospital length of stay (mean difference 1.60 days, 95 %CI −0.66 to 3.86). Moreover, there was significantly increased mortality observed (OR 3.47, 95 %CI 1.24 to 9.74) in the variceal hemorrhage group [36]. Chaudhuri similarly reported that prophylactic intubation conferred increased mortality in patients presenting with variceal bleeding (OR 4.45; 95 %CI 1.46 to 13.56), with no study heterogeneity observed in the variceal group (I^2 0 %) [37]. Intubation prior to urgent EGD for EGVH did not improve clinical outcomes, suggesting against the use of routine prophylactic intubation in patients with EGVH who have only mild encephalopathy and no ongoing hemorrhage. The benefits and risks of prophylactic endotracheal intubation should be carefully weighed when considering airway protection before upper GI endoscopy in patients with EGVH.

4.3 Platelet and FFP transfusion

RECOMMENDATION

ESGE does not recommend routine platelet transfusion or a specific minimum platelet count threshold for triggering platelet transfusion. If variceal bleeding is not controlled, the decision to transfuse platelets should be made on a case-by-case basis.

Strong recommendation, moderate quality evidence.

Limited data are available on the requirement for platelet transfusion in acute variceal bleeding and thrombocytopenia [38]. There are no studies evaluating adequate platelet thresholds for the purpose of enhancing hemostasis in the bleeding cirrhotic patient. At steady state in cirrhosis, there is a balance in all phases of hemostasis that is marked by compensatory changes in both the prohemostatic and antihemostatic systems.

Some experts recommend the use of thromboelastography (TEG) to help determine the need for factor and platelet replacement therapy in patients with cirrhosis. TEG is a method of testing the efficiency of blood coagulation and is primarily used in surgery and anesthesiology, although increasingly it is used in emergency departments, intensive care units, and labor and delivery suites. There is one recently published open label RCT [38] comparing the use of TEG with routine blood tests (platelet count, prothrombin time, and fibrinogen) as a guide to platelet transfusion in patients with cirrhosis. In this study, 60 cirrhotic patients were randomized to either the TEG group (patients received FFP when the R time [reaction time] was > 15 minutes and 3 units of platelets over 30–60 minutes when the MA [maximum amplitude] was < 30 mm) or the conventional transfusion group (patients received FFP when the INR was > 1.8 and received 3 units of platelets when the platelet count was $< 50 \times 10^9$/L). The authors found that TEG findings were within the normal range in most cirrhotic patients, which led to a significant decrease in the use of both platelet and FFP transfusions in the TEG group. The use of TEG-guided blood product transfusion strategy reduced blood product transfusions and rebleeding at day 42 in cirrhotic patients with acute variceal bleeding and coagulopathy. These findings suggest that hemostatic competence is maintained, even in the bleeding cirrhotic patient.

4.4 Red blood cell transfusion strategy

RECOMMENDATION

ESGE recommends, in hemodynamically stable patients with acute UGIH and no history of cardiovascular disease, a restrictive red blood cell (RBC) transfusion strategy, with a hemoglobin threshold of ≤ 70 g/L prompting RBC transfusion. A post-transfusion target hemoglobin of 70–90 g/L is desired.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends, in hemodynamically stable patients with acute UGIH and a history of acute or chronic cardiovascular disease, a more liberal RBC transfusion strategy with a hemoglobin threshold of ≤ 80 g/L prompting RBC transfusion.

Strong recommendation, low quality evidence.

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For patients with cirrhotic liver disease, a liberal red blood cell (RBC) transfusion strategy has been shown to increase portal pressures, which can directly mediate rebleeding. In a systematic review/meta-analysis that included five RCTs comparing restrictive versus liberal RBC transfusion for acute UGIH (1965 patients [93 % from two RCTs], with 919 patients on the restrictive RBC transfusion strategy and 1064 on the liberal strategy), Odutayo et al. reported that a restrictive RBC transfusion policy was associated with a significant overall reduction in mortality (RR 0.65, 95 %CI 0.44 to 0.97) and rebleeding (RR 0.58, 85 %CI 0.40 to 0.84), and no difference in the risk of ischemic events [39].

The effect on rebleeding was consistent across subgroups. The treatment effect for mortality was greatest in patients with cirrhosis (413/1965; 21 %), with a 48 % reduction in the risk of death with a restrictive RBC transfusion policy (RR 0.52, 95 %CI 0.29 to 0.94; $P = 0.03$). Moreover, the absolute risk reduction was 4.21 % (95 %CI 1.44 % to 6.03 %) for overall rebleeding and 5.87 % (95 %CI 0.75 % to 8.74 %) for rebleeding in the cirrhosis group. The number needed to treat to prevent one rebleeding event using a restrictive transfusion strategy was 24 (95 %CI 17 to 70) in the group overall and 17 (95 %CI 11 to 134) in the subgroup of patients with cirrhosis [39].

4.5 Risk stratification

RECOMMENDATION

ESGE recommends that patients with ACLD presenting with suspected acute variceal bleeding be risk stratified according to the Child–Pugh score and MELD score, and by documentation of active/inactive bleeding at the time of upper GI endoscopy.

Strong recommendation, high quality of evidence.

RECOMMENDATION

ESGE recommends the following risk stratification definitions:

a) patients with Child–Pugh A or Child–Pugh B without active bleeding at upper GI endoscopy or MELD < 11 points are at low risk of poor outcome
b) patients with Child–Pugh B with active bleeding at upper GI endoscopy despite vasoactive agents or Child–Pugh C are at high risk of poor outcome
c) patients with MELD ≥ 19 points are considered at high risk of poor outcome.

Strong recommendation, high quality evidence.

In the setting of acute variceal hemorrhage in patients with ACLD, validated risk stratification scores evaluating the severity of the underlying liver disease can be used to predict patient outcomes including: mortality (at 6 weeks) related to the acute episode of variceal bleeding and rebleeding, and both failure to control the acute bleeding episode and early rebleeding (within 5 days of index endoscopy). The best predictor of poor outcome in cirrhotic patients with variceal bleeding is the hepatic venous pressure gradient (HVPG) measurement, which defines high risk patients as those with an HVPG ≥ 20 mmHg [40, 41]; however, HVPG measurement is an interventional procedure and is not usually readily available. Therefore, clinical scores have been validated as risk stratification tools including: the Child–Pugh score (▶ **Table 3**) [42–45] and the MELD score (▶ **Table 4**) [43, 46–50].

Patients with Child–Pugh C ≤ 13 points or Child–Pugh B > 7 points with active variceal bleeding at GI endoscopy (defined as variceal jet/oozing, despite the use of vasoactive drugs) are at high risk of a poor outcome, so may benefit from preemptive transjugular intrahepatic portosystemic shunt (TIPS) placement and these criteria have been validated in a recent meta-analysis of individual patient data [44]. Although there are concerns about the prognostic capacity of these variables because of the subjectivity of evaluating the presence/severity

▶ **Table 3** The Child–Pugh score.

Clinical and laboratory criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin, µmol/L	< 34	34–50	> 50
Albumin, g/L	> 35	28–35	< 28
INR	< 1.7	1.7–2.3	> 2.3

Class	Total points[1]	Severity of liver disease
A	5–6	Least severe
B	7–9	Moderately severe
C	10–15	Most severe

INR, international normalized ratio.
[1] Obtained by adding the points for each of the five parameters.

▶ **Table 4** The MELD score[a].

Components of the MELD score
$3.78 \times \log_e$ serum bilirubin (mg/dL)[b]
$11.20 \times \log_e$ INR[b]
$9.57 \times \log_e$ serum creatinine (mg/dL)[b, c]
6.43 (= constant for liver disease etiology)

INR, international normalized ratio.
[a] The MELD score is the sum of each of its four components, with scores ranging from 6 to 40.
[b] Any value < 1.0 is given the value 1, as $\log_e 1 = 0$ and values < 1.0 would give a negative result.
[c] For patients dialyzed twice within the last 7 days, a value of 4.0 is used.

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of ascites and/or hepatic encephalopathy, as well as the true risk of Child–Pugh B patients, recent studies have shown they are effective in classifying patient risk [45, 51]. MELD ≥ 19 also defines high risk ACLD patients and has been evaluated in several studies [43, 48,51].

4.6 Use of vasoactive agents

RECOMMENDATION

ESGE recommends the vasoactive agents terlipressin, octreotide, or somatostatin be initiated at the time of presentation in patients with suspected acute variceal bleeding and be continued for a duration of up to 5 days.
Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE suggests, following successful endoscopic hemostasis, vasoactive agents may be stopped 24–48 hours later in selected patients.
Weak recommendation, moderate quality evidence.

Several systematic reviews/meta-analyses, including numerous RCTs with thousands of patients, have evaluated the efficacy and safety of vasoactive agents in acute EGVH [52–57]. In summary, vasoactive agents are superior to no vasoactive treatment in terms of rates of in-hospital mortality, overall mortality, variceal bleeding control, variceal rebleeding, and blood transfusion requirement. Octreotide and somatostatin appear to have equal efficacy to terlipressin and vasopressin, and are associated with lower rates of AEs. Vasopressin is no longer used owing to its extrasplanchnic vasoconstrictive properties and high AE profile.

Vasoactive agents as adjuvant treatment following successful endoscopic hemostasis have also been shown to significantly reduce early rebleeding rates (within 5 days after index variceal hemorrhage). Moreover, following successful endoscopic hemostasis, an abbreviated course of vasoactive treatment may be equally as effective as a treatment duration of 3–5 days [56, 58, 59]. In their systematic review/meta-analysis, Yan et al. reported no significant difference in 42-day mortality rate (RR 0.95, 95 %CI 0.43 to 2.13) when comparing a 3- to 5-day vasoactive drug regimen with a shorter course. Moreover, when evaluating the very early rebleeding rate, a shorter course also appeared to be beneficial (RR 1.77, 95 %CI 0.64 to 4.89), although this difference was not statistically significant. Continuous infusion of terlipressin may be more effective than intermittent infusion [60].

4.7 Use of antibiotic prophylaxis

RECOMMENDATION

ESGE recommends antibiotic prophylaxis using ceftriaxone 1 g/day for up to 7 days for all patients with ACLD presenting with acute variceal hemorrhage, or in accordance with local antibiotic resistance and patient allergies.
Strong recommendation, high quality evidence.

Patients with ACLD presenting with acute EGVH are at high risk for bacterial infection, especially respiratory tract infection [61]. Bacterial infection leads to a higher risk of rebleeding and an increased overall mortality rate. In a multicenter retrospective cohort study including 371 adult patients with cirrhosis and acute EGVH, all of whom had received antibiotic prophylaxis, Lee et al. reported that 14 % of patients developed bacterial infection within 14 days despite antibiotic prophylaxis [61]. Respiratory infections accounted for more than 50 % of infections, and there was a high proportion of culture-positive infections caused by organisms resistant to the recommended fluroquinolones and third-generation cephalosporins [61].

Two systematic reviews/meta-analyses of RCTs investigated the benefits and outcomes of antibiotic prophylaxis in patients with ACLD and acute EGVH [62, 63]. In both studies, antibiotic prophylaxis was shown to reduce the risk of bacterial infection as well as overall mortality, risk of rebleeding, and length of hospital-stay, especially among patients with more advanced chronic liver disease.

Third-generation cephalosporins have been shown to be superior to fluoroquinolones in the prevention of bacterial infection. In an RCT (n = 111), Fernandez et al. reported that intravenous ceftriaxone was significantly better than norfloxacin in the prevention of bacterial infections, bacteremia, and spontaneous bacterial peritonitis in patients with ACLD and EGVH (11 % vs. 33 %, $P = 0.003$; 11 % vs. 26 %, $P = 0.03$; and 2 % vs. 12 %, $P = 0.03$, respectively) [64]. Ceftriaxone (1 g/24 hours) should be the first choice of treatment, especially considering the higher rates of microbial resistance to fluoroquinolones, which can lead to treatment failure [61].

Antibiotic stewardship programs recommend the critical use of antibiotics with the shortest possible duration of therapy. The duration of antibiotic prophylaxis in patients with ACLD and EGVH has been studied. The general recommendation for the duration of antibiotic prophylaxis is a maximum of 7 days; however, some data suggest that a 3-day duration of antibiotic treatment may suffice. Lee et al., in an RCT including 71 patients, compared a 3-day treatment regimen of ceftriaxone 500 mg every 12 hours to a 7-day regimen and reported no difference between the groups in the rate of variceal rebleeding, nor in 28-day mortality [65]. For patients with compensated Child–Pugh A liver disease, the rate of bacterial infection is low. Chang et al. evaluated the use of antibiotic prophylaxis in this subset of patients and compared antibiotic prophylaxis to an on-demand antibiotic regimen. The rate of bacterial

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infection within 14 days and the overall mortality rate within 42 days did not differ between the groups [66].

Antibiotic prophylaxis in patients with ACLD and acute EGVH reduces the overall mortality rate, rate of variceal rebleeding, and length of hospital stay. Third-generation cephalosporins, especially ceftriaxone 1 g/24 hours, appear superior to fluoroquinolones with a maximum treatment duration of 7 days.

4.8 Management of patients on antiplatelet agents

RECOMMENDATION
ESGE recommends that antiplatelet agents be temporarily withheld in patients presenting with acute variceal hemorrhage.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends that the restarting of antiplatelet agents be determined on the basis of the patient's risk of rebleeding versus their risk of thrombosis.
Strong recommendation, low quality evidence.

Coagulation disorders are common in patients with chronic liver disease; inappropriate clotting is now considered to be the main disorder and is attributed to changes in the hemostatic balance [67]. Antiplatelet agents (aspirin and P2Y12 receptor inhibitors) represent a severe aggravating factor for patients with ACLD and acute EGVH. Antiplatelet agents typically must be withheld at the onset of variceal bleeding; however, the restoration of normal platelet function is not observed until a minimum of 5–7 days later. Platelet transfusion has been suggested for patients with life-threatening active bleeding, but outcome data have not demonstrated a clinical benefit with this strategy [68]. In patients with coronary artery stents who are receiving dual antiplatelet therapy, management should be coordinated with an interventional cardiologist. In such cases, it is recommended that aspirin is continued with only temporary interruption of the P2Y12 receptor antagonist [69].

According to the recently published collaborative guideline from the British Society of Gastroenterology (BSG) and ESGE on the management of anticoagulants during endoscopy, low dose aspirin should not be resumed if it is used for primary prophylaxis [70, 71]. This is because low dose aspirin has a relatively small benefit, with no reduction in vascular mortality and an annual absolute risk reduction for any serious vascular event of only 0.06 % [70, 71].

In contrast, restarting low dose aspirin for secondary prophylaxis should be considered only in patients at very high individual risk for cardiovascular events, or if there is no further evidence of bleeding. Discontinuation of low dose aspirin in patients with known cardiovascular disease and GI bleeding is associated with an increase in death and acute cardiovascular events after hospital discharge [72–74]. The timing of the restarting of antiplatelet therapy for secondary cardiovascular prophylaxis following acute variceal bleeding should be determined by weighing the risk of variceal rebleeding and the risk of thrombosis. P2Y12 receptor antagonists in patients with coronary artery stents should be restarted within 5 days owing to the high risk of stent occlusion if further delayed. This timeframe represents an optimal balance between hemorrhage and thrombosis [69].

4.9 Management of patients on anticoagulation

RECOMMENDATION
ESGE recommends that anticoagulants be temporarily withheld in patients presenting with suspected acute variceal hemorrhage and appropriate reversal agents be used in patients with hemodynamic instability.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends that the restarting of anticoagulants should be guided by the patient's risk of rebleeding versus their risk of thrombosis.
Strong recommendation, low quality evidence.

The management of variceal bleeding occurring while on anticoagulant therapy is challenging. According to a multicenter retrospective case–control study, patients who have UGIH while on anticoagulant therapy are more likely to be hemodynamically unstable (i.e. have hypotension and/or shock) and present with lower hemoglobin and hematocrit values when compared with patients not taking anticoagulants [75]. However, anticoagulant therapy did not significantly influence treatment failure at 5 days (i.e. failure to control bleeding, early rebleeding, or death within 5 days), nor 6-week mortality, when anticoagulant therapy was provided for portal vein thrombosis. There was however an observed three- to four-fold increase in mortality when anticoagulants were administered to treat cardiovascular disease (i.e. prosthetic valves or atrial fibrillation) [75], suggesting that co-morbidity and not anticoagulation treatment was influencing survival.

According to the recently published collaborative guideline from the BSG and ESGE on the management of anticoagulants during endoscopy, in cases of acute variceal bleeding, anticoagulant therapy should be promptly withheld, and coagulopathy corrected according to the severity of hemorrhage and the patient's underlying thrombotic risk [70]. It should be stressed however that correction of coagulopathy, when required, should not delay endoscopic intervention because endoscopy can be safely performed at therapeutic levels of anticoagulation.

Briefly, in patients with hemodynamic instability who take vitamin K antagonists, it is recommended that intravenous vitamin K and four-factor PCC be administered, with FFP consid-

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ered if PCC is not available. The use of FFP has been questioned recently by a multicenter observational study which highlighted that FFP transfusion in patients with acute variceal bleeding was associated with poor clinical outcomes, in particular increased odds of mortality at 42 days, failure to control bleeding at 5 days, and length of hospital stay > 7 days [27].

In patients who are taking direct oral anticoagulants (DOACs), DOAC reversal agents should be considered only in those with hemodynamic instability and then in coordination with a local hematologist. Idarucizumab should be used in dabigatran-treated patients and andexanet in anti-factor Xa-treated patients (i. e. apixaban and rivaroxaban), or intravenous four-factor PCC if andexanet is not available. In patients who do not have hemodynamic instability, because of the short half-life of DOACs, withholding the drug is sufficient to manage most cases of UGIH.

The timing of the restarting of anticoagulation depends on the patient's underlying thrombotic risk. In patients at low thrombotic risk, it is suggested that anticoagulation be restarted 7 days after successful hemostasis of the acute variceal bleeding episode. In patients at high thrombotic risk, an earlier resumption of anticoagulation with heparin bridging, within 3 days, is recommended.

4.10 Use of a prokinetic agent

RECOMMENDATION

ESGE recommends, in the absence of contraindications, intravenous erythromycin 250 mg be given 30–120 minutes prior to upper GI endoscopy in patients with suspected acute variceal hemorrhage.

Strong recommendation, high quality evidence.

Blood in the esophagus and stomach in patients with variceal bleeding often obscures the endoscopic view and makes endoscopic intervention difficult to perform. The use of an intravenous prokinetic agent has been shown to be helpful in promoting gastric emptying of blood and clots, and providing improved endoscopic visualization. Barkun et al., in a meta-analysis, found that an intravenous infusion of different prokinetic agents administered up to 2 hours before endoscopy in patients with acute UGIH improved endoscopic visualization and significantly decreased the need for repeat endoscopy [76]. Most studies assessing the use of pre-endoscopy prokinetics in acute UGIH have used intravenous erythromycin.

Erythromycin, a macrolide antibiotic, is a potent motilin agonist that induces rapid gastric emptying when given intravenously in doses ranging from 1 to 3 mg/kg in healthy individuals [77]. The effect of erythromycin on endoscopic visibility and its outcome in patients with acute variceal bleeding was investigated in a randomized, double-blind placebo-controlled trial [78]. Patients received either 125 mg erythromycin or placebo administered intravenously 30 minutes before endoscopy. Erythromycin infusion significantly improved the quality of endoscopic visualization, shortened the duration of the index endoscopy, and decreased the length of hospital stay. Although there was a trend toward a decrease in the need for repeat endoscopy and endoscopy-related pulmonary complications, these clinical end points failed to reach statistical significance, perhaps because of the small sample size [79]. Insufficient data were identified to provide evidence-based recommendations for the use of metoclopramide [79, 80] in this clinical situation. However, if erythromycin is not available, metoclopramide may be considered as an alternative (10 mg intravenously 30–120 minutes prior to upper GI endoscopy) if there are no contraindications.

5 Endoscopic management

5.1 Timing of endoscopy

RECOMMENDATION

ESGE recommends that, in patients with suspected variceal hemorrhage, endoscopic evaluation should take place within 12 hours from the time of patient presentation, provided the patient has been hemodynamically resuscitated.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that the timing of upper GI endoscopy in patients with suspected acute variceal hemorrhage should not be influenced by the INR level at the time of patient presentation.

Strong recommendation, low quality evidence.

In patients with acute EGVH, the optimal timing of upper GI endoscopy is controversial, given that all published studies to date have been observational in nature, have disparate definitions of "early" and "late" endoscopy and study conclusions, meaning there is a lack of high level evidence on which to base guideline recommendations. A systematic review/meta-analysis by Jung et al. [81] of patients with acute variceal bleeding (843 urgent endoscopy patients [≤ 12 hours] and 453 nonurgent endoscopy patients [> 12 hours]) reported similar overall mortality (OR 0.72, 95 %CI 0.36 to 1.45; $P = 0.36$) and rebleeding rates (OR 1.21, 95 %CI 0.76 to 1.93; $P = 0.41$) between the groups. Other outcomes, including successful primary hemostasis, need for salvage therapy, length of hospital stay, and number of blood transfusions, were also similar; however, the investigators reported high heterogeneity between the included studies, and this may produce misleading results and conclusions.

In a more recent systematic review/meta-analysis by Bai et al. [82] that included 2824 patients with ACLD and acute variceal bleeding, overall mortality was significantly lower in the early endoscopy group (≤ 12 hours) as compared with the

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delayed endoscopy group (>12 hours; OR 0.56, 95%CI 0.33 to 0.95; $P=0.03$) [82].

Regarding the INR value at the time of patient presentation and its influence on the timing of upper GI endoscopy, we were unable to identify any high level evidence that has evaluated this specific question in the setting of acute variceal hemorrhage. Limited retrospective data often failed to include important baseline characteristics of patients (e.g. INR level at presentation) and their impact on decisions regarding the timing of upper GI endoscopy [83, 84]. However, extrapolating from the recent ESGE guideline on nonvariceal UGIH, it is recommended that the use of a predetermined INR cutoff value to define the timing of endoscopy be avoided in the setting of acute UGIH [85, 86].

5.2 Esophageal variceal hemorrhage

5.2.1 Initial management

RECOMMENDATION

ESGE recommends EBL for the treatment of acute EVH.
Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE does not recommend the use of hemostatic sprays/powders for the definitive endoscopic treatment of acute esophageal or gastric variceal hemorrhage. Hemostatic sprays/powders may be considered as a bridge to definitive therapy when standard endoscopic treatment is not effective or is not available.
Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends that, in patients at high risk for recurrent esophageal variceal bleeding following successful endoscopic hemostasis (Child–Pugh C ≤13 or Child–Pugh B >7 with active EVH at the time of endoscopy despite vasoactive agents, or HVPG >20 mmHg), pre-emptive TIPS within 72 hours (preferably within 24 hours) must be considered.
Strong recommendation, high quality evidence.

The endoscopic diagnosis of acute esophageal variceal bleeding is made when there is active hemorrhage from a varix or a sign of recent hemorrhage (nipple sign, platelet–fibrin plug) is seen. An esophageal variceal source of UGIH can also be inferred when there is blood in the stomach with no other source of bleeding except for esophageal varices.

There are two main endoscopic treatment modalities for acute EVH, EBL and injection sclerotherapy. Numerous RCTs have compared these modalities. In a seminal meta-analysis by Laine and Cook, EBL was shown to be superior to sclerotherapy in reducing both rebleeding (OR 0.47, 95%CI 0.29 to 0.78) and mortality (OR 0.67, 95%CI 0.46 to 0.98) [87]. Furthermore, EBL resulted in fewer AEs (esophageal strictures, OR 0.10, 95%CI 0.03 to 0.29) and required fewer endoscopic sessions to achieve variceal obliteration.

In an updated meta-analysis that included 36 RCTs with 3593 patients, Onofrio et al. [88] reported that EBL was associated with a significant improvement in bleeding control (RR 1.08, 95%CI 1.02 to 1.15), mortality (RR 0.72, 95%CI 0.54 to 0.97), and AEs (RR 0.29, 95%CI 0.20 to 0.44) when compared with sclerotherapy. Furthermore, the risk of rebleeding was greater with sclerotherapy (RR 1.41, 95%CI 1.03 to 1.94) [88]. Moreover, in a subanalysis, the authors evaluated five trials that compared EBL versus the combination of EBL and sclerotherapy. The risk of AEs was significantly lower with EBL alone (RR 0.58, 95%CI 0.39 to −0.88; $P=0.01$) when compared with the combination of EBL and sclerotherapy. There were no statistically significant differences in other outcomes [88]. Injection sclerotherapy has largely been replaced by EBL.

Typically, 5–10 bands are applied on esophageal varices starting at the site of active or recent bleeding if such a spot is identified. The remaining varices are then treated, beginning from the gastroesophageal junction and continuing in a spiral cephalad manner. An RCT suggested that placing more than six bands did not impact outcomes; however, it did result in a longer procedure time and a greater number of misfired bands [89]. Other studies have suggested that placing more bands than appropriate for the actual variceal size is associated with an increased risk of rebleeding [90, 91].

The use of hemostatic sprays/powders in GI bleeding is relatively new, with most studies being conducted in patients with nonvariceal UGIH. Ibrahim et al. performed an RCT evaluating TC-325, a hemostatic powder, in 86 patients with cirrhosis and acute variceal hemorrhage [92]. Patients were randomized to either TC-325 application within 2 hours of hospital admission followed by elective endoscopy within 24 hours or elective endoscopy within 24 hours. In the study group, TC-325 failed to achieve immediate hemostasis in five patients (11.6%), while the remaining 38 patients had no bleeding (active bleeding or blood in stomach) at the time of elective endoscopy. In the control group, 13 patients (30.2%) had a second episode of hematemesis within 12 hours and required rescue endoscopy and hemostasis therapy; all of the remaining 30 patients had active variceal bleeding at elective endoscopy. The 6-week survival was significantly improved in the TC-325 group (7% vs. 30%; $P=0.006$) [92]. The application of a hemostatic spray/powder may be considered as a bridge to definitive therapy and may allow for early patient stabilization when expertise in endoscopic hemostasis for variceal bleeding is not readily available.

Randomized trials have demonstrated the benefit of pre-emptive TIPS in patients at high risk of rebleeding. In a proof-of-concept study, Monescillo et al. demonstrated a reduction of treatment failure and a survival benefit of pre-emptive TIPS in high risk patients when compared with sclerotherapy [40]. In a study by Garcia-Pagan and colleagues, patients with

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Child–Pugh C ≤13 or Child–Pugh B and active bleeding at the time of endoscopy were randomly assigned to treatment with TIPS within 72 hours after randomization (TIPS group) or continuation of vasoactive pharmacological therapy with EBL (pharmacotherapy–EBL group) [42]. There were 63 patients with cirrhosis and endoscopically confirmed EVH included and all received initial treatment with endoscopic therapy plus vasoactive drugs. The 1-year probability of control of acute bleeding or prevention of severe bleeding was 50 % in the pharmacotherapy–EBL group versus 97 % in the TIPS group (P < 0.001). The 1-year survival was 61 % in the pharmacotherapy–EBL group versus 86 % in the early-TIPS group (P < 0.001). The early use of TIPS was not associated with an increase in severe hepatic encephalopathy [42].

These results were recently validated in two studies from China including patients with viral hepatitis as the predominant etiology of ACLD [43, 93]. In an observational study, a lower cumulative incidence of failure to control variceal bleeding or rebleeding at 6 weeks and 1 year were reported [43]. In an RCT, 132 consecutive patients with advanced cirrhosis (Child–Pugh B or C) and acute variceal bleeding who had been treated with vasoactive drugs plus endoscopic therapy were randomly assigned to receive either early TIPS (done within 72 hours after initial endoscopy; n = 86) or standard treatment (vasoactive drugs continued to day 5, followed by propranolol plus EBL for the prevention of rebleeding, with TIPS as rescue therapy when needed; n = 46). The investigators reported that transplantation-free survival was higher in the early TIPS group than in the control group (HR 0.50, 95 %CI 0.25 to 0.98; P = 0.04) [93]. Transplantation-free survival at 6 weeks was 99 % (95 %CI 97 % to 100 %) in the early TIPS group compared with 84 % in the standard treatment group (95 %CI 75 % to 96 %; absolute risk difference 15 % [95 %CI 5 % to 48 %]; P = 0.02) and at 1 year was 86 % (95 %CI 79 % to 94 %) versus 73 % (95 %CI 62 % to 88 %; absolute risk difference 13 % [95 %CI 2 % to 28 %]; P = 0.046). There was no significant difference in AEs between the groups [93].

In a recent meta-analysis of individual patient data (including 3 RCTs and 4 observational studies) comprising 1327 patients, pre-emptive TIPS significantly increased the proportion of high risk ACLD patients with acute variceal bleeding who survived for 1 year compared with pharmacological therapy and endoscopy (HR 0.44, 95 %CI 0.32 to 0.61; P < 0.001). Pre-emptive TIPS also significantly improved control of variceal bleeding and ascites without increasing the incidence of hepatic encephalopathy [45].

5.2.2 Management of failed endoscopic hemostasis in acute esophageal variceal hemorrhage

RECOMMENDATION

ESGE recommends that, for persistent esophageal variceal bleeding despite vasoactive pharmacological and endoscopic hemostasis therapy, urgent rescue TIPS should be considered (where available).

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE suggests that, for persistent esophageal variceal bleeding despite vasoactive pharmacological and endoscopic hemostasis therapy, self-expanding metal stents (where available) are preferred over balloon tamponade for bridging to definitive hemostasis therapy.

Weak recommendation, low quality evidence.

TIPS is an established salvage/rescue modality for patients with persistent/refractory EVH despite vasoactive pharmacological and endoscopic therapy. Although there are no high level RCTs, several retrospective studies have evaluated the role of salvage TIPS. In a review of 15 studies, therapeutic success was reported in up to 100 % of patients, with a variceal rebleeding rate up to 16 % and mortality up to 75 % [94]. In a recent retrospective study of 144 patients with refractory esophageal variceal bleeding, TIPS failure occurred in 16 % of patients. The 6-week and 12-month mortality rates were 36 % and 42 %, respectively. All patients with a Child–Pugh score >13 died [95].

Balloon tamponade tubes, including the Sengstaken–Blakemore tube (250 mL gastric balloon, an esophageal balloon, and a gastric suction port) or the Minnesota tube (a Sengstaken–Blakemore tube with an added esophageal suction port above the esophageal balloon) are effective as a temporizing measure in treating esophageal variceal bleeding in cases where endoscopic hemostasis has failed or is unavailable. Balloon tamponade as salvage/rescue therapy can control bleeding in up to 90 % of patients; however, it is associated with several potential AEs, including esophageal ulceration, esophageal perforation, and/or aspiration pneumonia, in up to 20 % of patients [96]. Therefore, balloon tamponade tubes should not remain in place for more than 24 hours, by which time definitive treatment should be administered because the rate of variceal rebleeding is approximately 50 % once the balloon tamponade tube is removed.

There are several small observational studies suggesting that the use of fully covered self-expanding metal stents (SEMSs) may be a viable alternative to balloon tamponade tubes. Stent deployment in the esophagus provides variceal tamponade and bleeding control. Stents can remain in place for up to 14 days, allowing more time for further management including definitive therapy. Potential AEs include stent migration and ulcer development [97, 98].

In a meta-analysis including 155 patients pooled from 12 studies (11 retrospective observational studies and 1 RCT), the pooled clinical success rate in achieving hemostasis within 24 hours was 96 % (95 %CI 90 % to 100 %) and technical success of SEMS placement was 97 % (95 %CI 91 % to 100 %). AEs (variceal rebleeding, ulceration and stent migration) were reported in 36 % (95 %CI 23 % to 50 %) of the patients. The pooled survival rate at 30 days and 60 days were 68 % (95 %CI 56 % to 80 %) and 64 % (95 %CI 48 % to 78 %), respectively [99].

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In the only randomized study in patients with esophageal variceal bleeding refractory to medical and endoscopic treatment, balloon tamponade was compared with placement of a fully covered SEMS. Stent therapy was shown to be superior in achieving esophageal variceal bleeding control (85 % vs. 47 %; $P = 0.04$), reducing the need for blood transfusion ($P = 0.08$), and AEs (15 % vs. 47 %; $P = 0.08$). However, no difference in 6-week survival was observed (54 % vs. 40 %; $P = 0.46$) [100].

It should be noted that there is no role for balloon-occluded retrograde transvenous obliteration (BRTO) in treating esophageal variceal bleeding. BRTO is indicated in patients with gastric variceal bleeding in the presence of a gastrorenal shunt [101]. BRTO may aggravate nongastric varices (esophageal and duodenal) [102].

5.2.3 Management of recurrent esophageal variceal bleeding after initial endoscopic hemostasis

RECOMMENDATION
ESGE suggests that recurrent EVH in the first 5 days following successful initial endoscopic hemostasis be managed by a second attempt at endoscopic therapy or salvage TIPS.
Weak recommendation, low quality evidence.

Recurrent esophageal variceal bleeding in the first 5 days may occur in 10 %–20 % of patients following endoscopic treatment. In such patients, a second attempt at endoscopic hemostasis may be made, although the optimal approach remains without consensus [3]. For patients with severe rebleeding or endoscopically uncontrollable bleeding, patients should be referred for TIPS. Balloon tamponade or a SEMS may be needed to bridge the patients while awaiting TIPS [3].

5.3 Acute gastric variceal hemorrhage

5.3.1 Initial management

RECOMMENDATION
ESGE recommends classifying gastric or gastroesophageal varices according to the Sarin classification.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends endoscopic cyanoacrylate injection for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE makes no formal recommendation regarding the use of endoscopic thrombin injection in acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage because of the currently limited and disparate data.

RECOMMENDATION
ESGE recommends endoscopic cyanoacrylate injection or EBL in patients with GOV1-specific bleeding.
Strong recommendations, moderate quality evidence.

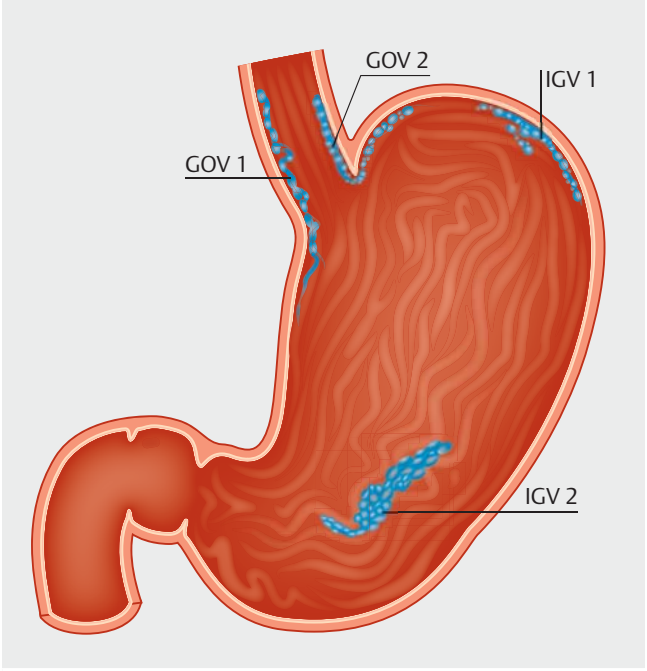
RECOMMENDATION
ESGE suggests that EUS-guided management of bleeding gastric varices combining injection of coils and cyanoacrylate may be used in centers with expertise and familiarity with this technique.
Weak recommendation, low quality evidence.

While acute gastric variceal hemorrhage (GVH) is not as prevalent as EVH, GVH is more severe, with higher associated mortality and treatment failure [103]. Sarin et al. categorized gastric varices into gastroesophageal varices (GOV), also sometimes referred to as "junctional varices," and isolated gastric varices (IGV; e. g. cardiofundal varices) [104]. Type 1 GOV (GOV1) extend below the gastroesophageal junction along the lesser curvature of the stomach. Type 2 GOV (GOV2) extend below the gastroesophageal junction into the gastric fundus. Type 1 IGV (IGV1) are located only in the fundus and type 2 IGV (IGV2) are located elsewhere in the stomach (e. g. the antrum) (▶ **Fig. 3**).

The currently available endoscopic options for treating acute GVH include injection sclerotherapy (e. g. using ethanol, ethanolamine, or polidocanol), EBL, and cyanoacrylate injection. However, high quality data for the optimal endoscopic therapy of acute gastric variceal bleeding remain limited, with there being inconsistencies between trials regarding mortality, and the incidence of rebleeding and AEs.

Several systematic reviews/meta-analyses have evaluated the efficacy of cyanoacrylate injection for the treatment of GVH [105–109]. Qiao et al. reported on three RCTs, which included 194 patients with active gastric variceal bleeding, comparing endoscopic cyanoacrylate injection versus EBL [106]. Control of active bleeding was achieved in 35/44 (79.5 %) in the EBL group and 46/49 (93.9 %) patients in the cyanoacrylate injection group ($P = 0.03$), with a pooled OR of 4.44 (95 %CI 1.14 to 17.30). Rebleeding was similar between the two interventions for GOV2 (35.7 % vs. 34.8 %, $P = 0.90$), but cyanoacrylate injection was superior for reducing rebleeding in both GOV1 (26.1 % vs. 47.7 %; $P = 0.04$) and IGV1 (17.6 % vs. 85.7 %; $P = 0.02$). Cyanoacrylate injection, as compared with EBL, was

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▶ **Fig. 3** An illustration of the different types of gastric varices according to the Sarin classification. GOV1/2, gastroesophageal varices type 1/2; IGV1/2, isolated gastric varices type 1/2.

also significantly better in preventing the recurrence of gastric varices (36.0 % vs. 66.0 %; *P* = 0.002). There was no difference in AEs or mortality between the two groups.

Also in 2015, in a Cochrane meta-analysis, Rios Castellanos et al. reported on six RCTs (including 493 patients) comparing cyanoacrylate injection versus other endoscopic methods (sclerotherapy using alcohol-based compounds or EBL) for acute GVH in patients with ACLD and portal hypertension [107]. Endoscopic cyanoacrylate injection was possibly more effective than EBL in terms of preventing rebleeding from gastric varices (RR 0.60, 95 %CI 0.41 to 0.88); however, the authors commented that there was very low quality evidence with uncertainty regarding the derived estimates on all-cause and bleeding-related mortality, failure of intervention, AEs, and control of bleeding. Moreover, in the single included trial that compared cyanoacrylate injection versus alcohol-based sclerotherapy, the investigators also reported very low quality evidence for evaluating 30-day mortality (RR 0.43, 95 %CI 0.09 to 2.04), failure of intervention (RR 0.36, 95 %CI 0.09 to 1.35), prevention of rebleeding (RR 0.85, 95 %CI 0.30 to 2.45), fever as an AE (RR 0.43, 95 %CI 0.22 to 0.80), and control of bleeding (RR 1.79, 95 %CI 1.13 to 2.84).

Two more recent systematic reviews/meta-analyses have reported similar results. Hu et al., after correcting for study heterogeneity, reported that, when gastric varices were treated with cyanoacrylate alone (n = 309), the risk of rebleeding was 15 % (95 %CI 11 % to 18 %) [108]. Chirapongsathorn et al. included seven RCTs (n = 583) comparing endoscopic injection of N-butyl-2-cyanoacrylate glue with any other treatment approach not involving cyanoacrylate (propranolol only, EBL, or sclerotherapy with alcohol or ethanolamine). The investigators reported that cyanoacrylate use was associated with significantly lower all-cause mortality (RR 0.59, 95 %CI 0.36 to 0.98) and rebleeding after hemostasis (RR 0.49, 95 %CI 0.35 to 0.68). The use of endoscopic cyanoacrylate injection was not associated with an increase in serious AEs. The quality of evidence was moderate and was downgraded owing to the small number of events and wide CIs [109].

El Amin et al. performed an RCT where 150 patients with bleeding junctional varices (GOV1) were randomized to receive either EBL or cyanoacrylate injection [110]. Cessation of active variceal bleeding was achieved in 61/75 (81 %) in the EBL group and 68/75 (91 %) in the cyanoacrylate-treated group (*P* = 0.07). The time to variceal obliteration was significantly faster with cyanoacrylate injection therapy. There were no observed differences between the groups in terms of AEs. Although the groups were similar in terms of baseline characteristics, including severity of underlying liver disease, a significantly higher survival rate at 6-month follow-up was observed in the EBL-treated group.

It should be noted that there are potential AEs that may occur with use of cyanoacrylate. These include, but are not limited to, sepsis, distal embolic events (e. g. pulmonary, cerebral), and ulceration at the varix injection site [111].

We identified an additional systematic review/meta-analysis evaluating the efficacy and safety of endoscopic injection of thrombin for GVH [112]. Thrombin converts fibrinogen to fibrin, thereby promoting clot production, leading to hemostasis. Bhurwal et al. included eleven studies (6 retrospective, 2 RCTs, 1 prospective) including 222 patients. Six studies used human thrombin alone, three studies used bovine thrombin alone, and two studies used a combination of thrombin and fibrin [112]. The investigators reported a pooled early gastric variceal rebleeding rate of 9.3 % (95 %CI 4.9 % to 17 %) and a late gastric variceal rebleeding rate of 13.8 % (95 %CI 9 % to 20.4 %). The pooled rescue therapy rate after injecting thrombin in bleeding gastric varices was 10.1 % (95 %CI 6.1 % to 16.3 %). The pooled 6-week gastric variceal-related mortality rate after injecting thrombin in bleeding gastric varices was 7.6 % (95 %CI 4.5 % to 12.5 %). The pooled AE rate after injecting thrombin in bleeding gastric varices was 5.6 % (95 %CI 2.9 % to 10.6 %). Because of these limited and disparate data regarding the role of endoscopic thrombin injection (including both human and bovine types) for GVH, there is currently inadequate evidence to make any formal recommendation regarding its use.

Binmoeller and colleagues first described endoscopic ultrasound (EUS)-guided injection of coils combined with cyanoacrylate for treating GVH in 2011 [113]. They reported a gastric variceal obliteration rate of 96 % in a single treatment session, without signs of cyanoacrylate embolization. Since that initial report, multiple retrospective studies, two RCTs, and systematic reviews/meta-analyses on this topic have been published. Mohan et al., in their meta-analysis evaluating EUS-guided therapy of gastric varices (23 studies; n = 851), reported that the pooled treatment efficacy was 93.7 % (95 %CI 89.5 % to 96.3 %), gastric variceal obliteration 84.4 % (95 %CI 74.8 % to

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90.9%), gastric variceal recurrence 9.1% (95%CI 5.2% to 15.7 %), and the early and late rebleeding rates were 7.0% (95 %CI 4.6% to 10.7%) and 11.6% (95%CI 8.8% to 15.1%), respectively [114]. These rates were comparable with endoscopic glue injection monotherapy (28 studies; n = 3467) used as a historical comparator. Gastric variceal obliteration was significantly better with EUS-guided therapy and, on subgroup analysis, EUS-guided coil/glue combination showed superior outcomes. This study is however significantly limited by the inclusion of retrospective and heterogeneous studies, and the historical comparators used.

McCarty et al., in their systematic review/meta-analysis evaluating combination therapy versus monotherapy for EUS-guided treatment of gastric varices (11 studies; n = 536), reported that, on subgroup analysis, EUS-guided coil embolization plus cyanoacrylate injection resulted in better technical and clinical success compared with cyanoacrylate injection alone (100% vs. 97% and 98% vs. 96%, respectively; both $P < 0.001$) or coil embolization alone (99% vs. 97% and 96% vs. 90%, respectively; both $P < 0.001$) [115]. Coil embolization plus cyanoacrylate also resulted in lower AE rates compared with cyanoacrylate injection alone (10% vs. 21%; $P < 0.001$) and was comparable with coil embolization alone (10% vs. 3%; P = 0.06). AEs may include abdominal pain, fever, pulmonary embolism, and/or procedure-related bleeding. Overall, EUS combination therapy using coil embolization plus cyanoacrylate injection appears to be the preferred strategy for the treatment of gastric varices over EUS-based monotherapy.

5.3.2 Management of failed endoscopic hemostasis and early recurrent bleeding

RECOMMENDATION

ESGE suggests urgent rescue TIPS or BRTO for gastric variceal bleeding when there is a failure of endoscopic hemostasis or early recurrent bleeding.

Weak recommendation, low quality evidence.

There are very limited high level data (e. g. RCTs) comparing TIPS and BRTO for cases where endoscopic hemostasis has failed and/or early recurrent gastric variceal bleeding occurs [116, 117]. In summary, BRTO and TIPS have similar technical success rates and AE rates. TIPS is associated with higher rates of hepatic encephalopathy and BRTO with long-term aggravation of esophageal varices. Patient selection is important; however, given the limited quality of comparative data, specific selection criteria are not currently available.

6 Post-endoscopy management

6.1 Secondary prophylaxis: prevention of recurrent esophageal or gastric variceal hemorrhage

RECOMMENDATION

ESGE recommends that patients who have undergone EBL for acute EVH should be scheduled for follow-up EBLs at 1- to 4-weekly intervals to eradicate esophageal varices (secondary prophylaxis).

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends the use of NSBBs (propranolol or carvedilol) in combination with endoscopic therapy for secondary prophylaxis in EVH in patients with ACLD.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends an individualized approach for secondary prophylaxis of cardiofundal variceal hemorrhage (GOV2, IGV1) based upon patient factors and local expertise owing to the current lack of definitive high level evidence regarding specific eradication therapies for cardiofundal varices (e. g. endoscopic cyanoacrylate injection ± NSBB, EUS-guided injection of coils plus cyanoacrylate, TIPS, or BRTO) and appropriate treatment intervals.

Strong recommendation, low quality evidence.

Current guidelines for treating acute EVH recommend EBL is performed at 1- to 2-weekly intervals over several endoscopy sessions until the varices are eradicated [3, 118, 119]. Others have suggested that an EBL interval of less than 3 weeks may be associated with an increased risk of rebleeding and that a longer interval (> 20 days) may reduce the risk of treatment-related AEs [120]. However, the optimal time interval for EBL sessions remains without consensus owing to the limited evidence [121].

Wang et al. randomly assigned post-acute EVH patients (n = 70) to either monthly or biweekly EBL sessions to achieve esophageal variceal eradication [122]. Patients receiving monthly EBL had similar rebleeding rates (17% vs. 26%; $P = 0.38$) to those receiving biweekly EBL. Both treatment groups had similar rates of esophageal variceal recurrence and mortality. Moreover, the incidence of post-EBL ulcers in the monthly treatment group was significantly lower than that in the biweekly group (11% vs. 57%; $P < 0.001$).

In another RCT involving 90 patients who had all undergone successful initial EBL and started NSBB therapy, Sheibani et al. compared the effectiveness of 1- and 2-weekly intervals for

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EBL in achieving eradication of esophageal varices following acute variceal hemorrhage [123]. Esophageal variceal eradication at 4 weeks was achieved more frequently in the 1-week interval EBL group (37/45 [82 %]) versus the 2-week group (23/45 [51 %]), a difference of 31 % (95 %CI 12 % to 48 %). Eradication occurred more rapidly in the 1-week group (18.1 vs. 30.8 days), a difference of −12.7 days (95 %CI −20.0 to −5.4 days). Rebleeding rates at both 4 weeks and 8 weeks, and mortality rates were similar between the groups. Upper gastrointestinal symptoms (e. g. dysphagia and chest pain) were more frequent in the 1-week interval EBL group (9 % vs. 2 %).

NSBB therapy is the mainstay of portal hypertension treatment. Beta-adrenergic blockade decreases the heart rate and reduces splanchnic vasodilation leading to a decrease in the portal hyperdynamic state [124]. The currently recommended first-line treatment to prevent esophageal variceal rebleeding (secondary prophylaxis) is the combination of endoscopic therapy and NSBB, irrespective of the presence or absence of ascites/refractory ascites [3, 118, 119]. This recommendation is supported by several meta-analyses that compared alternative treatment combinations and found that the reduction in esophageal variceal rebleeding rates was superior with combination therapy compared with monotherapy [125–128]. Moreover, this benefit is greater in patients with more severe liver disease (e. g. Child–Pugh B or C) particularly, in whom combination therapy not only prevents rebleeding, but also increases survival [129].

There is no clear consensus regarding the optimal approach for secondary prophylaxis of gastric variceal bleeding in patients with ACLD. Recurrent GVH is a frequent occurrence (up to 45 % at 3 years) despite endoscopic efforts at gastric variceal eradication [103]. Therefore, effective treatment modalities are an ongoing need. NSBBs are recommended as an adjunctive treatment for gastric varices in patients with concomitant esophageal varices [103]; however, the effectiveness of adding NSBB therapy to endoscopic treatment of gastric varices to decrease recurrent GVH remains unclear. Neither of the two published RCTs evaluating the efficacy of adding propranolol [130] or carvedilol [131] demonstrated a statistically significant benefit on survival or rebleeding.

In addition, a recently published network meta-analysis (nine RCTs with 647 patients who had a history of GVH and follow-up of more than 6 weeks) compared the efficacy of available secondary prophylaxis treatments [132]. BRTO was associated with a lower risk of rebleeding when compared with NSBB therapy alone (RR 0.04, 95 %CI 0.01 to 0.26) and endoscopic injection of cyanoacrylate alone (RR 0.18, 95 %CI 0.04 to 0.77). Moreover, NSBB therapy alone did not demonstrate a benefit in terms of preventing gastric variceal rebleeding compared with most interventions, nor reduce mortality compared with endoscopic injection of cyanoacrylate alone (RR 4.12, 95 %CI 1.50 to 11.36) and endoscopic injection of cyanoacrylate plus NSBB (RR 5.61, 95 %CI 1.91 to 16.43). This study suggested that BRTO may be the best intervention in preventing gastric variceal rebleeding (secondary prophylaxis), whereas an NSBB given as monotherapy cannot be recommended; however, head-to-head direct comparator studies are much needed [132].

6.2 Use of proton pump inhibitor therapy

RECOMMENDATION

ESGE suggests against the routine use of proton pump inhibitors (PPIs) in the post-endoscopic management of acute variceal bleeding and, if initiated before endoscopy, PPIs should be discontinued.

Weak recommendation, low quality evidence.

Proton pump inhibitors (PPIs) are often prescribed prior to upper GI endoscopy in patients with cirrhosis who present with acute UGIH. The rationale for continuing PPIs after proven EGVH is to reduce the risk of rebleeding from post-EBL or post-injection ulceration. The frequency of post-EBL bleeding secondary to ulceration is reported to be between 2.7 % and 5.7 % [133–136] and it appears to be higher following EBL performed in the acute setting, as compared with prophylactic EBL [137]. Shaheen et al., in a small RCT, evaluated the efficacy of PPIs as an adjunct to elective EBL. The investigators suggested that use of adjunctive PPIs following EBL may decrease the risk of post-EBL ulcer bleeding and reduce ulcer size [138].

In GVH, there are two studies suggesting that the administration of PPIs after the injection of N-butyl-2-cyanoacrylate may reduce the risk of rebleeding or delay rebleeding; however, these studies are retrospective, include small numbers of patients, and the duration/dosage of PPI use was variable [139, 140]. Moreover, and importantly, the use of PPIs in cirrhotic patients has been associated with an increased risk of bacterial infection, especially spontaneous bacterial peritonitis and infections caused by multidrug-resistant bacteria [141–144].

6.3 Prevention/treatment of hepatic encephalopathy

RECOMMENDATION

ESGE recommends the rapid removal of blood from the GI tract, preferably using lactulose, to prevent or to treat hepatic encephalopathy in cirrhotic patients with acute variceal hemorrhage.

Strong recommendation, moderate quality evidence.

Hepatic encephalopathy is common in patients with cirrhosis and its prevalence increases during GI bleeding, to as high as 40 %. This is secondary to hyperammonemia in the context of blood protein digestion, liver failure, systemic inflammation, and infection. Hepatic encephalopathy at the time of admission

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during GI bleeding negatively impacts outcome and is independently associated with mortality [50].

Treatment of hepatic encephalopathy with lactulose improves survival in patients with cirrhosis and is recommended for patients with GI bleeding and concomitant hepatic encephalopathy [145,146]. Oral lactulose and/or lactulose enema when the GI bleeding remains uncontrolled is recommended [145,146]. In two RCTs, lactulose, as compared with no lactulose, has been shown to significantly reduce hepatic encephalopathy [147,148]. The reduction in hepatic encephalopathy ranged from 14% to 40% ($P<0.03$) and 3.2% to 16.9% ($P<0.02$), without any observed effect on patient survival. The use of mannitol has also been suggested as an effective therapy to reduce hepatic encephalopathy in patients with GI bleeding [149, 150], reinforcing the beneficial role of the rapid removal of nitrogenous waste products in the prevention of hepatic encephalopathy. Although other ammonium-lowering strategies (e.g. L-ornithine, L-aspartate, and rifaximin) have been suggested to be as effective as lactulose in preventing the development of hepatic encephalopathy in patients with GI bleeding, more studies are needed before these can be recommended [151].

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Competing interests

M.C. Duboc has provided consultancy to Boston Scientific (2017 to 2019), Cook Medical (2019), and AMBU (2021 to 2022); she has received payments from the journal HepatoGastroentérologie et Oncologie digestive. I.M. Gralnek has provided consultancy to and been on the advisory board of Motus GI, has provided consultancy to Boston Scientific, Clexio Biosciences, Medtronic, Neurogastrx, and Symbionix; he has received consultancy and speaker's fees from Vifor Pharma, and speaker's fees from 3-D Matrix; he has received research support from AstraZeneca and Check Cap. J.G. Karstensen has received lecture fees from Norgine (2020 to 2022) and provides consultancy to SNIPR BIOME and AMBU (2020 to present). H. Awadie, M.C. Burgmans. A. Ebigbo, L. Fuccio, J.C. Garcia-Pagan, V. Hernandez-Gea, T. Hucl, I. Jovanovic, I. Mostafa, R. Rosasco, M. Tantau, K. Triantafyllou, and J. Vlachogiannakos declare that they have no conflict of interest.

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