Thieme

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

Authors

Ian M. Gralnek[1,2], Marine Camus Duboc[3], Juan Carlos Garcia-Pagan[4,5,6,7], Lorenzo Fuccio[8], John Gásdal Karstensen[9,10], Tomas Hucl[11], Ivan Jovanovic[12], Halim Awadie[1], Virginia Hernandez-Gea[4,5,6,7], Marcel Tantau[13], Alanna Ebigbo[14], Mostafa Ibrahim[15], Jiannis Vlachogiannakos[16], Marc C. Burgmans[17], Robyn Rosasco[18], Konstantinos Triantafyllou[19]

Institutions

1 Ellen and Pinchas Mamber Institute of Gastroenterology and Hepatology, Emek Medical Center, Afula, Israel
2 Rappaport Faculty of Medicine Technion Israel Institute of Technology, Haifa, Israel
3 Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine (CRSA) & Assistance Publique-Hôpitaux de Paris (AP-HP), Endoscopic Center, Saint Antoine Hospital, Paris, France
4 Barcelona Hepatic Hemodynamic Laboratory, Hospital Clinic, Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver), Barcelona, Spain
5 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
6 Centro de Investigación Biomédica Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain
7 Liver Unit, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain
8 Gastroenterology Unit, Department of Medical and Surgical Sciences, IRCSS-S. Orsola-Malpighi, Hospital, Bologna, Italy
9 Gastroenterology Unit, Copenhagen University Hospital – Amager and Hvidovre, Copenhagen, Denmark
10 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
11 Institute for Clinical and Experimental Medicine, Prague, Czech Republic
12 Euromedik Health Care System, Visegradska General Hospital, Belgrade, Serbia
13 University of Medicine and Pharmacy 'Iuliu Hatieganu' Cluj-Napoca, Romania
14 Department of Gastroenterology, Universitätsklinikum Augsburg, Augsburg, Germany
15 Theodor Bilharz Research Institute, Cairo, Egypt
16 Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece
17 Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
18 Florida State University, Tallahassee, Florida, USA
19 Hepatogastroenterology Unit, Second Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece

published online 29.9.2022

Bibliography
Endoscopy
DOI 10.1055/a-1939-4887
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Ian M. Gralnek, MD, MSHS, Institute of Gastroenterology and Hepatology, Emek Medical Center, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, 18101 Afula, Israel
ian_gr@clalit.org.il

Supplementary material
Supplementary material is available under https://doi.org/10.1055/a-1939-4887

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.

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

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

▶ **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

▶ **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

▶ **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.

▶ **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.

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.

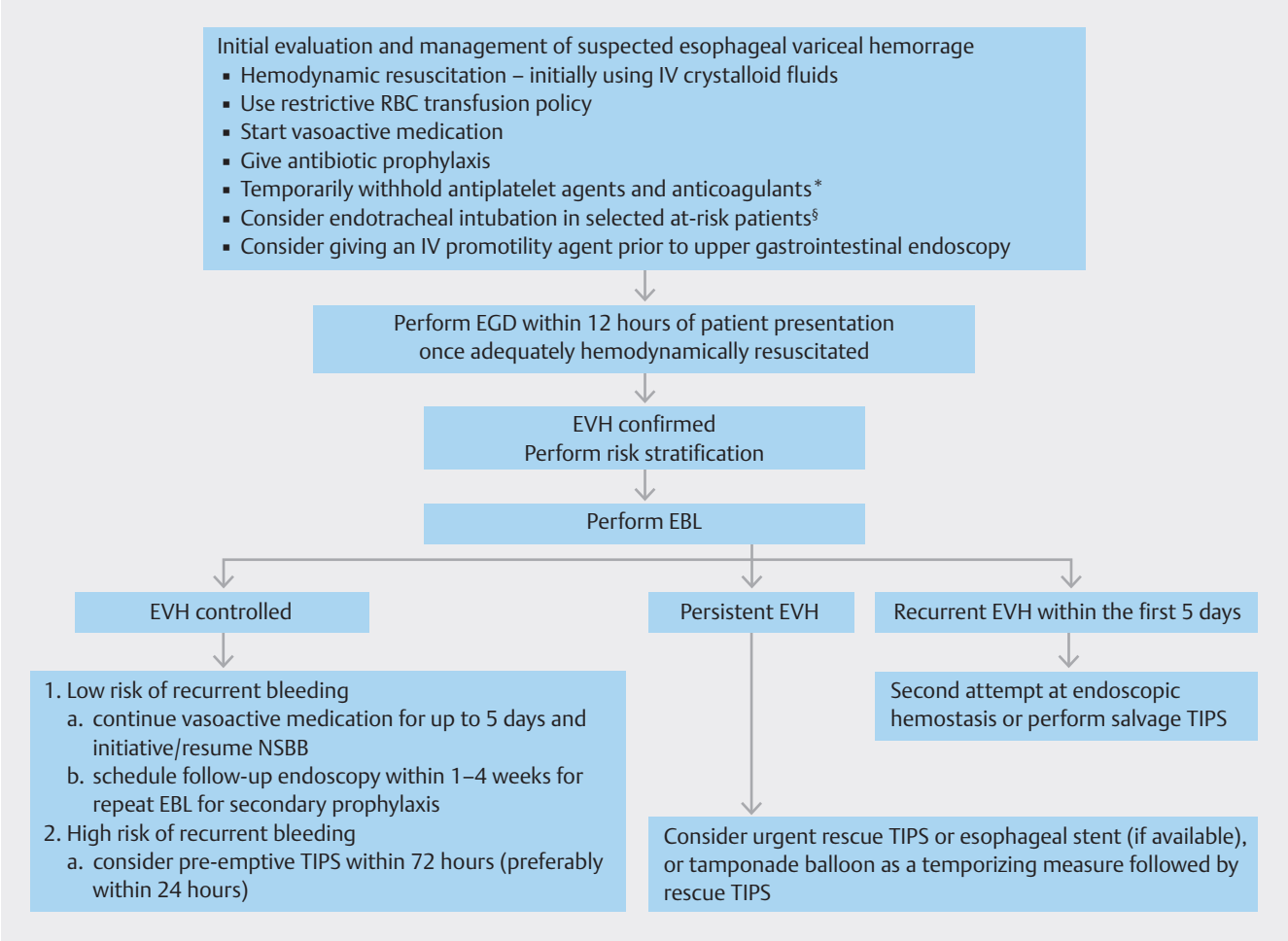
RECOMMENDATION

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

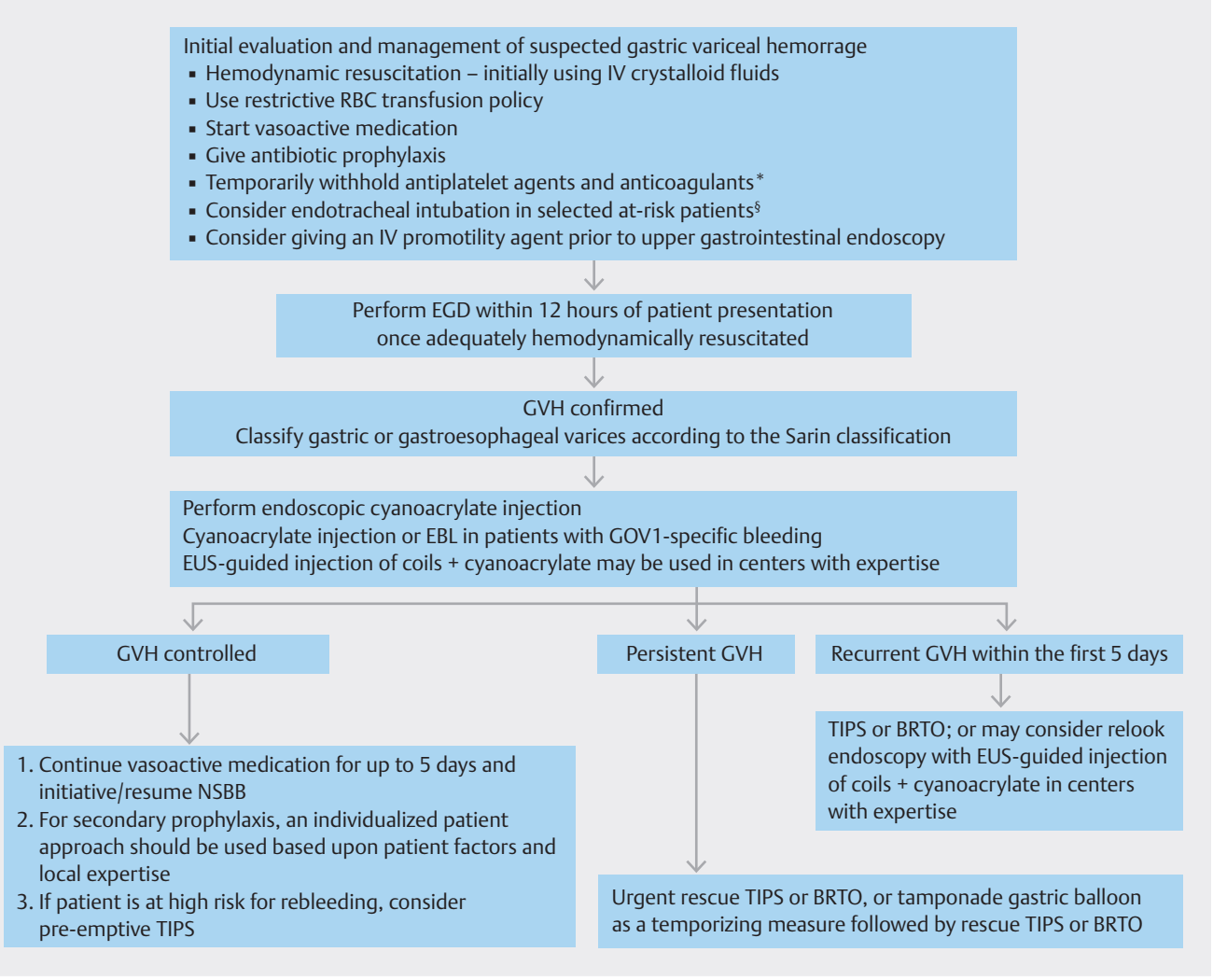
The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multiorgan failure. Early intensive hemodynamic resuscitation of patients with acute UGIH has been shown to significantly decrease mortality (▶ **Fig. 1** and ▶ **Fig. 2**) [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.



▶ **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.

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.

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.

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

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-

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

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

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].

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.

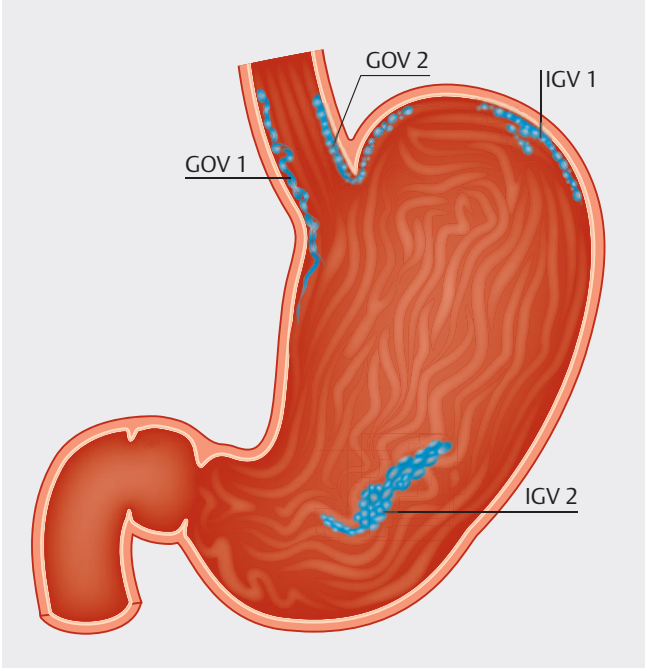
RECOMMENDATION
ESGE recommends endoscopic cyanoacrylate injection or EBL in patients with GOV1-specific bleeding.
Strong recommendations, moderate quality evidence.

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



▶ **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

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

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

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].

Acknowledgments

ESGE wishes to thank the external reviewers, Professors Lars Aabakken and Juan Gonzalez Abraldes, for their critical review and insightful appraisal of this guideline. ESGE also wishes to thank all our Member Societies and Individual Members who provided suggested edits, comments, and queries for this guideline.

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.

References

[1] Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–926

[2] Hassan C, Ponchon T, Bisschops R et al. European Society of Gastrointestinal Endoscopy (ESGE) Publications Policy – Update 2020. Endoscopy 2020; 52: 123–126

[3] de Franchis R. Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743–752

[4] Maurice JB, Brodkin E, Arnold F et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J Hepatol 2016; 65: 899–905

[5] Thabut D, Bureau C, Layese R et al. Validation of Baveno VI criteria for screening and surveillance of esophageal varices in patients with compensated cirrhosis and a sustained response to antiviral therapy. Gastroenterology 2019; 156: 997–1009

[6] Nawalerspanya S, Sripongpun P, Chamroonkul N et al. Validation of original, expanded Baveno VI, and stepwise & platelet-MELD criteria to rule out varices needing treatment in compensated cirrhosis from various etiologies. Ann Hepatol 2020; 19: 209–213

[7] Wang H, Wen B, Chang X et al. Baveno VI criteria and spleen stiffness measurement rule out high-risk varices in virally suppressed HBV-related cirrhosis. J Hepatol 2021; 74: 584–592

[8] Bai W, Abraldes JG. Noninvasive assessment oesophageal varices: impact of the Baveno VI criteria. Curr Opin Gastroenterol 2022; 38: 206–215

[9] Sacher-Huvelin S, Calès P, Bureau C et al. Screening of esophageal varices by esophageal capsule endoscopy: results of a French multicenter prospective study. Endoscopy 2015; 47: 486–492

[10] Colli A, Gana JC, Turner D et al. Capsule endoscopy for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis. Cochrane Database Syst Rev 2014; 2014: CD008760

[11] McCarty TR, Afinogenova Y, Njei B. Use of wireless capsule endoscopy for the diagnosis and grading of esophageal varices in patients with portal hypertension: a systematic review and meta-analysis. J Clin Gastroenterol 2017; 51: 174–182

[12] Sharma M, Singh S, Desai V et al. Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology 2019; 69: 1657–1675

[13] Villanueva C, Sapena V, Lo GH et al. Stratified efficacy of first-line therapy to prevent first variceal bleeding according to previous decompensation of cirrhosis. A competing-risk meta-analyses of individual participant data. J Hepatol 2022; 77: (Suppl. 01): FRI520

[14] Reiberger T, Ulbrich G, Ferlitsch A et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013; 62: 1634–1641

[15] Villanueva C, Torres F, Sarin SK et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol 2022: doi:10.1016/j.jhep.2022.05.021

[16] Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database Syst Rev 2012; 2012: CD004544

[17] Funakoshi N, Duny Y, Valats JC et al. Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding. Ann Hepatol 2012; 11: 369–383

[18] Tian S, Li R, Guo Y et al. Carvedilol vs endoscopic band ligation for the prevention of variceal bleeding: a meta-analysis. Ther Clin Risk Manag 2019; 15: 191–200

[19] Baradarian R, Ramdhaney S, Chapalamadugu R et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol 2004; 99: 619–622

[20] Lu B, Li M-Q, Li J-Q. The use of limited fluid resuscitation and blood pressure-controlling drugs in the treatment of acute upper gastrointestinal hemorrhage concomitant with hemorrhagic shock. Cell Biochem Biophys 2015; 72: 461–463

[21] Kwan I, Bunn F, Chinnock P et al. Timing and volume of fluid administration for patients with bleeding. Cochrane Database Syst Rev 2014; 2014: CD002245

[22] Duan C, Li T, Liu L. Efficacy of limited fluid resuscitation in patients with hemorrhagic shock: a meta-analysis. Int J Clin Exp Med 2015; 8: 11645–11656

[23] Carrick MM, Morrison CA, Tapia NM et al. Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: Early termination of a randomized prospective clinical trial. J Trauma Acute Care Surg 2016; 80: 886–896

[24] Lewis SR, Pritchard MW, Evans DJ et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev 2018; 2018: CD000567

[25] Hammond DA, Lam SW, Rech MA et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. Ann Pharmacother 2020; 54: 5–13

[26] Semler MW, Self WH, Wanderer JP et al. Balanced crystalloids versus saline in critically ill adults. NEJM 2018; 378: 829–839

[27] Mohanty A, Kapuria D, Canakis A et al. Fresh frozen plasma transfusion in acute variceal haemorrhage: Results from a multicentre cohort study. Liver Int 2021; 41: 1901–1908

[28] Kwon JO, MacLaren R. Comparison of fresh-frozen plasma, four-factor prothrombin complex concentrates, and recombinant factor VIIa to facilitate procedures in critically ill patients with coagulopathy from liver disease: a retrospective cohort study. Pharmacotherapy 2016; 36: 1047–1054

[29] Bosch J, Thabut D, Bendtsen F et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology 2004; 127: 1123–1130

[30] Bosch J, Thabut D, Albillos A et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. Hepatology 2008; 47: 1604–1614

[31] Koch DG, Arguedas MR, Fallon MB. Risk of aspiration pneumonia in suspected variceal hemorrhage: the value of prophylactic endotracheal intubation prior to endoscopy. Dig Dis Sci 2007; 52: 2225–2228

[32] Rehman A, Iscimen R, Yilmaz M et al. Prophylactic endotracheal intubation in critically ill patients undergoing endoscopy for upper GI hemorrhage. Gastrointest Endosc 2009; 69: e55–e59

[33] Tang YM, Wang W. Prophylactic endotracheal intubation prior to urgent endoscopy in patients with suspected variceal hemorrhage: an evaluation of outcomes and complications. J Gastroenterol Hepatol Res 2017; 6: 2324–2328

[34] Perisetti A, Kopel J, Shredi A et al. Prophylactic pre-esophagogastroduodenoscopy tracheal intubation in patients with upper gastrointestinal bleeding. Proc Bayl Univ Med Cent 2019; 32: 22–25

[35] Almashhrawi AA, Rahman R, Jersak ST et al. Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis. World J Meta-Anal 2015; 3: 4–10

[36] Alshamsi F, Jaeschke R, Baw B et al. Prophylactic endotracheal intubation in patients with upper gastrointestinal bleeding undergoing endoscopy: a systematic review and meta-analysis. Saudi J Med Juschka Sci 2017; 5: 201–209

[37] Chaudhuri D, Bishay K, Tandon P et al. Prophylactic endotracheal intubation in critically ill patients with upper gastrointestinal bleed: A systematic review and meta-analysis. JGH Open 2020; 4: 22–28

[38] Rout G, Deepak GunjunS, Mahapatra SJ et al. Thromboelastography-guided blood product transfusion in cirrhosis patients with variceal bleeding: a randomized controlled trial. J Clin Gastroenterol 2020; 54: 255–262

[39] Odutayo A, Desborough MJR, Trivella M et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. Lancet Gastroenterol Hepatol 2017; 2: 354–360

[40] Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004; 40: 793–801

[41] Abraldes JG, Villanueva C, Bañares R et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008; 48: 229–236

[42] García-Pagán JC, Caca K, Bureau C et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. NEJM 2010; 362: 2370–2379

[43] Lv Y, Zuo L, Zhu X et al. Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study. Gut 2019; 68: 1297–1310

[44] Fortune BE, Garcia-Tsao G, Ciarleglio M et al. Child-Turcotte-Pugh Class is best at stratifying risk in variceal hemorrhage: analysis of a US multicenter prospective study. J Clin Gastroenterol 2017; 51: 446–453

[45] Nicoară-Farcău O, Han G, Rudler M et al. Effects of early placement of transjugular portosystemic shunts in patients with high-risk acute variceal bleeding: a meta-analysis of individual patient data. Gastroenterology 2021; 160: 193–205

[46] Bambha K, Kim WR, Pedersen R et al. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut 2008; 57: 814–820

[47] Al-Freah MAB, Gera A, Martini S et al. Comparison of scoring systems and outcome of patients admitted to a liver intensive care unit of a tertiary referral centre with severe variceal bleeding. Aliment Pharmacol Ther 2014; 39: 1286–1300

[48] Reverter E, Tandon P, Augustin S et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology 2014; 146: 412–419

[49] Motola-Kuba M, Escobedo-Arzate A, Tellez-Avila F et al. Validation of prognostic scores for clinical outcomes in cirrhotic patients with acute variceal bleeding. Ann Hepatol 2016; 15: 895–901

[50] Rudler M, Bureau C, Carbonell N et al. Recalibrated MELD and hepatic encephalopathy are prognostic factors in cirrhotic patients with acute variceal bleeding. Liver Int 2018; 38: 469–476

[51] Conejo I, Guardascione MA, Tandon P et al. Multicenter external validation of risk stratification criteria for patients with variceal bleeding. Clin Gastroenterol Hepatol 2018; 16: 132–139

[52] Corley DA, Cello JP, Adkisson W et al. Octreotide for acute esophageal variceal bleeding: a meta-analysis. Gastroenterology 2001; 120: 946–954

[53] Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev 2003; 2003: CD002147

[54] Wells M, Chande N, Adams P et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther 2012; 35: 1267–1278

[55] Zhou X, Tripathi D, Song T et al. Terlipressin for the treatment of acute variceal bleeding: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018; 97: e13437

[56] Yan P, Tian X, Li J. Is additional 5-day vasoactive drug therapy necessary for acute variceal bleeding after successful endoscopic hemostasis? A systematic review and meta-analysis Medicine (Baltimore) 2018; 97: e12826

[57] Huaringa-Marcelo J, Huaman MR, Brañez-Condorena A et al. Vasoactive agents for the management of acute variceal bleeding: a systematic review and meta-analysis. J Gastrointest Liver Dis 2021; 30: 110–121

[58] Rengasamy S, Ali SM, Sistla SC et al. Comparison of 2 days versus 5 days of octreotide infusion along with endoscopic therapy in preventing early rebleed from esophageal varices: a randomized clinical study. Eur J Gastroenterol Hepatol 2015; 27: 386–392

[59] Azam Z, Hamid S, Jafri W et al. Short course adjuvant terlipressin in acute variceal bleeding: a randomized double blind dummy controlled trial. J Hepatol 2012; 56: 819–824

[60] Jha SK, Mishra M, Jha A et al. Comparison of continuous versus intermittent infusions of terlipressin for the control of acute variceal bleeding in patients with portal hypertension: An open-label randomized controlled trial. Indian J Gastroenterol 2018; 37: 313–320

[61] Lee S, Saxinger L, Ma M et al. Bacterial infections in acute variceal hemorrhage despite antibiotics-a multicenter study of predictors and clinical impact. United European Gastroenterol J 2017; 5: 1090–1099

[62] Soares-Weiser K, Brezis M, Tur-Kaspa R et al. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. Scand J Gastroenterol 2003; 38: 193–200

[63] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review. Aliment Pharmacol Ther 2011; 34: 509–518

[64] Fernández J, Ruiz del Arbol L, Gómez C et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006; 131: 1049–1056

[65] Lee TH, Huang CT, Lin CC et al. Similar rebleeding rate in 3-day and 7-day intravenous ceftriaxone prophylaxis for patients with acute variceal bleeding. J Formos Med Assoc 2016; 115: 547–552

[66] Chang TS, Tsai YH, Lin YH et al. Limited effects of antibiotic prophylaxis in patients with Child-Pugh class A/B cirrhosis and upper gastrointestinal bleeding. PLoS One 2020; 15: e0229101

[67] Intagliata NM, Argo CK, Stine JG et al. Concepts in coagulation in liver disease: a summary of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost 2018; 118: 1491–1506

[68] Radaelli F, Dentali F, Repici A et al. Management of anticoagulation in patients with acute GI bleeding. Dig Liver Dis 2015; 47: 621–627

[69] Eisenberg MJ, Richard PR, Libersan D et al. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. Circulation 2009; 119: 1634–1642

[70] Veitch AM, Radaelli F, Alikhan R et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. Gut 2021; 70: 1611–1628

[71] Dasa O, Pepine CJ, Pearson TA. Aspirin in primary prevention: what changed? A critical appraisal of current evidence Am J Cardiol 2021; 141: 38–48

[72] Antithrombotic Trialists (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet 2009; 373: 1849–1860

[73] Sung JJY, Lau JYW, Ching JYL et al. Continuation of low dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med 2010; 152: 1–9

[74] Chan FKL, Leung KiE-L, Wong GLH et al. Risks of bleeding recurrence and cardiovascular events with continued aspirin use after lower gastrointestinal hemorrhage. Gastroenterology 2016; 151: 271–277

[75] Cerini F, Gonzalez JM, Torres F et al. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology 2015; 62: 575–583

[76] Barkun AN, Bardou M, Martel M et al. Prokinetics in acute upper GI bleeding: a meta-analysis. Gastrointest Endosc 2010; 72: 1138–1145

[77] Mantides A, Xynos E, Chrysos F et al. The effect of erythromycin in gastric emptying of solids and hypertonic liquids in healthy subjects. Am J Gastroenterol 1993; 88: 198–202

[78] Altraif B, Handoo FA, Aljumah A et al. Effect of erythromycin before endoscopy in patients presenting with variceal bleeding: a prospective, randomized, double-blind, placebo-controlled trial. Gastrointest Endosc 2011; 73: 245–250

[79] Habashi SL, Lambiase LR, Kottoor R. Prokinetics infusion prior to endoscopy for acute upper gastrointestinal bleeding: a randomized, controlled, double-blind & placebo-controlled trial. Am J Gastroenterol 2007; 102: S526

[80] Sussman DA, Deshpande AR, Parra JL et al. Intravenous metoclopramide to increase mucosal visualization during endoscopy in patients with acute upper gastrointestinal bleeding: a randomized, controlled study [abstract]. Gastrointest Endosc 2008; 67: AB247

[81] Jung DH, Huh CW, Kim NJ et al. Optimal endoscopy timing in patients with acute variceal bleeding: A systematic review and meta-analysis. Sci Rep 2020; 10: 4046

[82] Bai Z, Wang R, Cheng G et al. Outcomes of early versus delayed endoscopy in cirrhotic patients with acute variceal bleeding: a systematic review with meta-analysis. Eur J Gastroenterol Hepatol 2021; 33: (Suppl. 01): e868–e876

[83] Huh CW, Kim JS, Jung DH et al. Optimal endoscopy timing according to the severity of underlying liver disease in patients with acute variceal bleeding. Dig Liver Dis 2019; 51: 993–998

[84] Yoo JJ, Chang Y, Cho EJ et al. Timing of upper gastrointestinal endoscopy does not influence short-term outcomes in patients with acute variceal bleeding. World J Gastroenterol 2018; 24: 5025–5033

[85] Gralnek IM, Stanley AJ, Morris AJ et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021. Endoscopy 2021; 53: 300–332

[86] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022; 76: 1151–1184

[87] Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 1995; 123: 280–287

[88] de Quados Onofrio F, Pereira-Lima JC, Valenca FM et al. Efficacy of endoscopic treatments for acute esophageal variceal bleeding in cirrhotic patients: systematic review and meta-analysis. Endosc Int Open 2019; 7: e1503–e1514

[89] Ramirez FC, Colon VJ, Landan D et al. The effects of the number of rubber bands placed at each endoscopic session upon variceal outcomes: a prospective, randomized study. Am J Gastroenterol 2007; 102: 1372–1376

[90] Lee SW, Lee TY, Chang CS. Independent factors associated with recurrent bleeding in cirrhotic patients with esophageal variceal hemorrhage. Dig Dis Sci 2009; 54: 1128–1134

[91] Xu L, Ji F, Xu QW et al. Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation. World J Gastroenterol 2011; 17: 3347–3352

[92] Ibrahim M, El-Mikkawy A, Abdel Hamid M et al. Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial. Gut 2019; 68: 844–853

[93] Lv Y, Yang Z, Liu L et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019; 4: 587–598

[94] Vangeli M, Patch D, Burroughs AK. Salvage tips for uncontrolled variceal bleeding. J Hepatol 2002; 37: 703–704

[95] Maimone S, Saffioti F, Filomia R et al. Predictors of re-bleeding and mortality among patients with refractory variceal bleeding undergoing salvage transjugular intrahepatic portosystemic shunt (TIPS). Dig Dis Sci 2019; 64: 1335–1345

[96] Panés J, Teres J, Bosch J et al. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. Dig Dis Sci 1988; 33: 454–459

[97] Hubmann R, Bodlaj G, Czompo M et al. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. Endoscopy 2006; 38: 896–901

[98] Zehetner J, Shamiyeh A, Wayand W et al. Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. Surg Endosc 2008; 22: 2149–2152

[99] McCarty TR, Njei B. Self-expanding metal stents for acute refractory esophageal variceal bleeding: A systematic review and meta-analysis. Dig Endosc 2016; 28: 539–547

[100] Escorsell À, Pavel O, Cardenas A et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 2016; 63: 1957–1967

[101] Saad WE, Sabri SS. Balloon-occluded retrograde transvenous obliteration (BRTO): technical results and outcomes. Semin Intervent Radiol 2011; 28: 333–338

[102] Kumamoto M, Toyonaga A, Inoue H et al. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroenterol Hepatol 2010; 25: 1129–1135

[103] Pagán JCG, Barrufet M, Cardenas A et al. Management of gastric varices. Clin Gastroenterol Hepatol 2014; 12: 919–928

[104] Sarin SK, Lahoti D, Saxena SP et al. Prevalence, classification, and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992; 16: 1343–1349

[105] Ye X, Huai J, Chen Y. Cyanoacrylate injection compared with band ligation for acute gastric variceal hemorrhage: a meta-analysis of randomized controlled trials and observational studies. Gastroenterol Res Pract 2014; 2014: 806586

[106] Qiao W, Ren Y, Bai Y et al. Cyanoacrylate injection versus band ligation in the endoscopic management of acute gastric variceal bleeding: meta-analysis of randomized, controlled studies based on the PRISMA statement. Medicine (Baltimore) 2015; 94: e1725

[107] Ríos Castellanos E, Seron P, Gisbert JP et al. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. Cochrane Database Syst Rev 2015; 2015: CD010180

[108] Hu Z, Zhang D, Swai J et al. Risk of rebleeding from gastroesophageal varices after initial treatment with cyanoacrylate; a systematic review and pooled analysis. BMC Gastroenterol 2020; 20: 181

[109] Chirapongsathorn S, Manatsathit W, Farrell A et al. Safety and efficacy of endoscopic cyanoacrylate injection in the management of gastric varices: A systematic review and meta-analysis. JGH Open 2021; 5: 1047–1055

[110] El Amin H, Abdel Baky L, Sayed Z et al. A randomized trial of endoscopic variceal ligation versus cyanoacrylate injection for treatment of bleeding junctional varices. Trop Gastroenterol 2010; 31: 279–284

[111] Cheng LF, Wang ZQ, Li CZ et al. Low incidence of complications from endoscopic gastric variceal obturation with butyl cyanoacrylate. Clin Gastroenterol Hepatol 2010; 8: 760–766

[112] Bhurwal A, Makar M, Patel A et al. Safety and efficacy of thrombin for bleeding gastric varices: a systematic review and meta-analysis. Dig Dis Sci 2022; 67: 953–963

[113] Binmoeller KF, Weilert F, Shah JN et al. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). Gastrointest Endosc 2011; 74: 1019–1025

[114] Mohan BP, Chandan S, Khan SR et al. Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis. Endoscopy 2020; 52: 259–267

[115] McCarty TR, Bazarbashi AN, Hathorn KE et al. Combination therapy *versus* monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis. Endosc Ultrasound 2020; 9: 6–15

[116] Paleti S, Nutalapati V, Fathallah J et al. Balloon-occluded retrograde transvenous obliteration (BRTO) versus transjugular intrahepatic portosystemic shunt (TIPS) for treatment of gastric varices because of portal hypertension: a systematic review and meta-analysis. J Clin Gastroenterol 2020; 54: 655–660

[117] Yu Q, Liu C, Raissi D. Balloon-occluded retrograde transvenous obliteration versus transjugular intrahepatic portosystemic shunt for gastric varices: a meta-analysis. J Clin Gastroenterol 2021; 55: 147–158

[118] Tripathi D, Stanley AJ, Hayes PC et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Clinical Services and Standards Committee of the British Society of Gastroenterology. Gut 2015; 64: 1680–1704

[119] Garcia-Tsao G, Abraldes JG, Berzigotti A et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017; 65: 310–335

[120] Harewood GC, Baron TH, Song LM. Factors predicting success of endoscopic variceal ligation for secondary prophylaxis of esophageal variceal bleeding. J Gastroenterol Hepatol 2006; 21: 237–241

[121] Lo GH. The role of endoscopy in secondary prophylaxis of esophageal varices. Clin Liver Dis 2010; 14: 307–323

[122] Wang HM, Lo GH, Chen WC et al. Randomized controlled trial of monthly versus biweekly endoscopic variceal ligation for the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol 2014; 29: 1229–1236

[123] Sheibani S, Khemichian S, Kim JJ et al. Randomized trial of 1-week versus 2-week intervals for endoscopic ligation in the treatment of patients with esophageal variceal bleeding. Hepatology 2016; 64: 549–555

[124] Salerno F, Guevara M, Bernardi M et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int 2010; 30: 937–947

[125] Gonzalez R, Zamora J, Gomez-Camarero J et al. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Ann Intern Med 2008; 149: 109–122

[126] Cheung J, Zeman M, van Zanten SV et al. Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices. Aliment Pharmacol Ther 2009; 30: 577–588

[127] Thiele M, Krag A, Rohde U et al. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. Aliment Pharmacol Ther 2012; 36: 1155–1165

[128] Puente A, Hernández-Gea V, Graupera I et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. Liver Int 2014; 34: 823–833

[129] Albillos A, Zamora J, Martínez J et al. Stratifying risk in the prevention of recurrent variceal hemorrhage: Results of an individual patient meta-analysis. Hepatology 2017; 66: 1219–1231

[130] Hung HH, Chang CJ, Hou MC et al. Efficacy of non-selective β-blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: a randomized controlled trial. J Hepatol 2012; 56: 1025–1032

[131] Chen WC, Hsin IF, Chen PH et al. Addition of carvedilol to gastric variceal obturation does not decrease recurrence of gastric variceal bleeding in patients with cirrhosis. Clin Gastroenterol Hepatol 2019; 17: 2356–2363

[132] Osman KT, Nayfeh T, Abdelfattah AM et al. Secondary prophylaxis of gastric variceal bleeding: a systematic review and network meta-analysis. Liver Transpl 2022; 28: 945–958

[133] Schmitz RJ, Sharma P, Badr AS et al. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy versus band ligation. Am J Gastroenterol 2001; 96: 437–441

[134] Petrasch F, Grothaus J, Mossner J et al. Differences in bleeding behavior after endoscopic band ligation: a retrospective analysis. BMC Gastroenterol 2010; 10: 5

[135] Vanbiervliet G, Giudicelli-Bornard S, Piche T et al. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: A case-control study. Aliment Pharmacol Ther 2010; 32: 225–232

[136] Kang SH, Yim HJ, Kim SY et al. Proton pump inhibitor therapy is associated with reduction of early bleeding risk after prophylactic endoscopic variceal band ligation a retrospective cohort study. Medicine (Baltimore) 2016; 95: 1–9

[137] Sinclair M, Vaughan R, Angus PW et al. Risk factors for band-induced ulcer bleeding after prophylactic and therapeutic endoscopic variceal band ligation. Eur J Gastroenterol Hepatol 2015; 27: 928–932

[138] Shaheen NJ, Stuart E, Schmitz SM et al. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: A randomized, controlled trial. Hepatology 2005; 41: 588–594

[139] Jang WS, Shin HP, Lee JI et al. Proton pump inhibitor administration delays rebleeding after endoscopic gastric variceal obturation. World J Gastroenterol 2014; 20: 17127–17131

[140] Kim KR, Jun CH, Cho KM et al. Can proton pump inhibitors reduce rebleeding following Histoacryl sclerotherapy for gastric variceal hemorrhage? Korean J Intern Med 2015; 30: 593–601

[141] Bajaj JS, Zadvornova Y, Heuman DM et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. Am J Gastroenterol 2009; 104: 1130–1134

[142] Bajaj JS, Ratliff SM, Heuman DM et al. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. Aliment Pharmacol Ther 2012; 36: 866–874

[143] Deshpande A, Pasupuleti V, Thota P. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. J Gastroenterol Hepatol 2013; 28: 235–242

[144] Merli M, Lucidi C, Di G et al. The chronic use of beta-blockers and proton pump inhibitors may affect the rate of bacterial infections in cirrhosis. Liver Int 2015; 35: 362–369

[145] Vilstrup H, Amodio P, Bajaj J et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014; 60: 715–735

[146] de Franchis R, Bosch J, Garcia-Tsao G et al. Baveno VII – renewing consensus in portal hypertension: Report of the Baveno VII Consensus Workshop: personalized care in portal hypertension. J Hepatol 2022; 76: 959–974

[147] Sharma P, Agrawal A, Sharma BC et al. Prophylaxis of hepatic encephalopathy in acute variceal bleed: a randomized controlled trial of lactulose versus no lactulose. J Gastroenterol Hepatol 2011; 26: 996–1003

[148] Wen J, Liu Q, Song J et al. Lactulose is highly potential in prophylaxis of hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding: results of a controlled randomized trial. Digestion 2013; 87: 132–138

[149] Rolachon A, Zarski JP, Lutz JM et al. Is the intestinal lavage with a solution of mannitol effective in the prevention of post-hemorrhagic hepatic encephalopathy in patients with liver cirrhosis? Results of a randomized prospective study Gastroenterol Clin Biol 1994; 18: 1057–1062

[150] Tromm A, Griga T, Greving I et al. Orthograde whole gut irrigation with mannite versus paromomycine + lactulose as prophylaxis of hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding: results of a controlled randomized trial. Hepatogastroenterology 2000; 47: 473–477

[151] Higuera-de-la-Tijera F, Servín-Caamaño A, Salas-Gordillo F et al. Primary prophylaxis to prevent the development of hepatic encephalopathy in cirrhotic patients with acute variceal bleeding. Can J Gastroenterol Hepatol 2018; 2018: 3015891

Supplementary material

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

Appendix 1s KEY QUESTIONS

1. **Primary prevention of EGVH (include in this section primary prevention of both esophageal and gastric variceal hemoirrhage)**
    a. Role of upper endoscopy (including role of EUS and EUS in measuring portal pressure gradients) in screening for esophago-gastric varices in patients with decompensated cirrhosis / portal hypertension?
        i. Who to screen?
        ii. When to screen?
        iii. How often to screen?
        iv. What to document endoscopically?
        v. What endoscopic treatment to be used for primary prophylaxis?
        vi. Role of “early / pre-emptive TIPS” as primary prophylaxis?
    b. How does variceal size, markings (e..g, red wale markings), and / or Child-Pugh score / MELD score influence choice of endoscopic band ligation prophyalxis and/or pharmacologic therapy as prophylaxis (e.g., non specific beta blockers)?

2. **Acute EVGH – Pre-endoscopy management**
    a. Patient assessment
        i. Initial assessment – what initial evaluations are needed? History, physical exammination, lab work, blood cultures?

Supplementary material

ii. How should the patient presenting with signs of acute upper GI bleeding (hematemesis, coffee ground emesis, melena, hematochezia) suspected to be secondary to EGVH be initially hemodynamically resuscitated?

- What type of fluid(s) should initially be used? E.g., crystalloid fluids, plasma-expanders, fresh frozen plasma, platelets, other?

iii. Airway management recommendations (e.g., prophylactic endotracheal intubation)?

iv. Platelet transfusion recommendations?

- Should platelet transfusion be considered in EGVH?
- If yes, what platelet level would trigger platelet transfusion?
- What target platelet level is desired prior to upper endoscopy?

v. Red blood cell transfusion recommendations?

- Restrictive vs liberal red blood cell transfusion policy?
- What hgb level triggers blood transfusion?
- Target hemoglobin post transfusion for otherwise healthy individuals?
- Target hemoglobin post transfusion for individuals with cardiovascular disease?

b. What is the role of patient risk assesssment / risk stratification score(s) to be used in suspected EGVH patoients? MELD? CP Score? GBS?

c. Role of vasoactive pharmacologic agents? What to use? When to initiate? Dosing? Duration of vasoactive treatment? Contraindications?

d. Role of antibiotics? What antibiotic(s) to use? Dosing? When to initiate? How long to use antibiotics?

e. How should we manage the patient using anti-platelet agents (as monotherapy or DAPT) at the time of suspected EVGH?

i. continue without interruption? temporarily stop? If stopping, for how long? When to restart?

Supplementary material

ii. give reversal agents (e.g., platelet transfusions)?

iii. give fresh frozen plasma? Cryoprecipitate? Platelets? Tranxemic acid? Other?

f. How should we manage the patient using anti-coagulants (Vit K antagonists / DOACs) at the time of suspected EVGH?

i. continue without interruption? temporarily stop? If stopping, for how long? When to restart?

ii. give reversal agents (e.g., Vitamin K, DOAC reversal agents)?

iii. give fresh frozen plasma? Cryoprecipitate? Platelets? Tranxemic acid? Other?

g. Is there a role for prokinetic agents (e.g., erythromycin) prior to upper endoscopy in patients with suspected EVGH?

i. When to use?

ii. In whom to use?

iii. When to give prokintec agent prior to upper endoscopy?

iv. What dosing?

v. What are the contraindications to use?

h. Timing of endoscopy in suspected EVGH

i. What should be the timing of endoscopy in patients presenting with suspected EVGH? Within 12 hours of presentation? 24 hours of presentation?

ii. Does INR level at presentation influence timing of upper endoscopy?

3. **Endoscopic management of acute esophageal variceal hemorrhage**

a. Which endoscopic therapy should be used for treating esophageal variceal hemorrhage?

i. Injection sclerotherapy? What agent(s)?

ii. Band ligation?

iii. Topical agents (e.g., TC-325)

Supplementary material

b. Management of failure of endoscopic hemostasis in esophageal varices

   i. Immediate failure of hemostasis (e.g., balloon tamponade, stent, “rescue” TIPS), not able to achieve primary hemostasis (persistent bleeding)?
   ii. Recurrent variceal bleeding (role of repeat endoscopy with repeat endoscopic therapy (including possible role of over-the-scope-clip for rescue therapy in rebleeding), TIPS, BRTO)

4. Endoscopic management of acute gastric variceal hemorrhage

a. Define types of gastric varices (e.g., GOV 1, GOV2, IGV1, IGV2 etc)

b. What hemostasis modaility should be used stratified by type of gastric varix (GOV1, GOV2, IGV1, IGV2)?

c. Which endoscopic therapy should be used for treating gastric variceal hemorrhage?

   i. Injection sclerotherapy? What agents?
   ii. Cyanoacrylate glue?
   iii. Band ligation?
   iv. EUS guided coils alone? EUS guided glue alone? EUS guided coils + glue?
   v. Topical agent (e.g., TC-325)

d. Management of failure of endoscopic hemostasis in gastric varices

   i. Immediate failure of hemostasis (e.g., balloon tamponade, stent, “rescue” TIPS), not able to achieve primary hemostasis (persistent bleeding)?
   ii. Recurrent variceal bleeding (role of repeat endoscopy with repeat endoscopic therapy, TIPS, BRTO)

5. Post-endoscopic management

a. When should follow up endoscopy be scheduled for repeat endoscopic treatment to eradicate varices (secondary prophylaxis)?

   i. For esophageal varices?

Supplementary material

ii. For gastric varices?

b. What are the recommendations for use of anti-secretaory agent (e.g., PPI) post endoscopic hemostasis in variceal bleeding?

c. What are the recommendations for use of beta blockers post endoscopy?

d. Management of hepatic encephalopathy associated with variceal bleeding

e. How to manage the patient with EGVH using anti-platelet and anti-coagulant drugs (anti-thrombotic agents) post endoscopy? When do we restart these medications post endoscopy?

Supplementary material

Appendix 2s: Literature search strategies summary

The following databases were searched in July – September 2021; results were limited to English-language articles published between 01 January 2000 – 31 December 2021:

- Ovid MEDLINE ALL
- Embase (Elsevier)
- Cochrane Library

The search strategies combined search terms for main concepts "esophageal/gastric varices" and "hemorrhage/bleeding" with the following secondary concepts:

- "endoscopy"
- "primary prevention"
- "acute"
- "preoperative"
- "diagnosis"
- "transfusion/fluids administration"
- "vasoactive pharmacologic agents"
- "risk assessment"
- "antibiotics"
- "anti-platelet agents"
- "anti-coagulants"
- "pro-coagulants"
- "pro-kinetic agents"
- "endoscopy timing"
- "upper endoscopy"
- "injection sclerotherapy"
- "band ligation"
- "topical agent/TC-235"
- "TIPS"
- "BRTO"
- "balloon tamponade"
- "SEMS/esophageal stent"
- "repeat endoscopy"
- "OTSC"
- "definitions/terminology"
- "endoscopic cyanoacrylate injection"
- "EUS-guided"
- "coils"
- "follow-up"
- "PPIs"
- "beta blockers"

Concept (AND ↓)	Example Search Terms* (OR ↓)	
Main Concepts		
Esophageal/ Gastric Varices	• esophageal/oesophageal varices/varix	• esophago-gastric/ oesophago-gastric varices/varix

Supplementary material

	• gastric varices/varix • esophgogastric/oesophgogastric varices/varix	• EGVH
Hemorrhage/ Bleeding	• hemorrhage/haemorrhage • bleed/bleeding/bled • rebleed/re-bleed/re-bleeding	• haematemesis/hematemesis • melena/melaena • coffee ground emesis
Endoscopy	• endoscopy • esophagoscopy	• oesophagoscopy • gastroscopy
Secondary Concepts		
Primary Prevention	• prevent/prevention • prophylaxis/prophylactic • thwart/ward off/ deter • pre-emptive/preemptive	• screen/screening • reduce/reduction • diminish/decrease/minimize
Acute	• acute • emergency • critical • intensive care unit//ICU/ITU	• CCU accident and emergency • A&E • shock
Preoperative	• preoperative period • preoperative care • disease management • clinical decision making	• pre-admission • pre-endoscopy • patient evaluation/assessment
Diagnosis	• diagnosis/diagnostic • wait and see • clinical observation	• conservative • expectant
Transfusion/ Fluids Administration	• hemodynamic resuscitation • fluid administration • blood transfusion • hemodialysis • crystalloid fluids	• colloids • plasma-expanders • fresh frozen plasma • platelets

Supplementary material

Vasoactive Pharmacologic Agents	• Sandostatin • octeotide	• vasopressin • Glypressin
Risk Assessment	• risk assessment/stratification • MELD • Child-Pugh • Rockall • Glasgow Blatschford	• ASA • Charlson • AIM65 • CURE
Antibiotics	• antibiotics • anti-infective agents • antibacterial • nitroimidazoles	• tetracyclines • penicillins • fluoroquinolones • cephalosporins
Anti-Platelet Agents	• antiplatelet • antithrombocytic • platelet aggregation inhibitor • cyclooxygenase inhibitor • thienopyridines • phosphodiesterase Inhibitor	• thromboxane A2 antagonist/inhibitor • purinergic P2Y receptor antagonist • thrombopoiesis • megakaryocytes • thrombopoietin receptor
Anti-Coagulants/ Pro-Coagulants	• anti-coagulants • blood coagulation • factor XIII • factor IX • fibrinogen • prothrombin • coagulation factor • factor concentrate	• clotting factor • recombinant factor • plasma-derived concentrate • pro-coagulant • pro-hemostatic • vitamin K antagonist • heparin • factor Xa/factor 10a
Pro-Kinetic Agents	• prokinetics • gastroprokinetics • antiemetics	• metoclopramide • cisapride • cholinesterase inhibitors

Supplementary material

	• benzamides • domperidone • antiemetics	• erythromycin • serotonin antagonists
Endoscopy Timing	• time factors • time-to-treatment • time/timing	• early/earlier/earliest • late/later/latest • 24 hours/one day
Upper Endoscopy	• endoscopy • esophagoduodenoscopy • esophagogastroduodenoscopy	• EGD • esophagogastroduodenoscopy
Injection Sclerotherapy	• sclerotherapy • sclerosing solutions • phenol	• sodium morrhuate • sodium tetradecyl sulfate • polidocanol
Band Ligation	• ligation • band/banding	• rubber • EBL/EVL/EBD
Topical Agent/TC-235	• hemostatics • hemostatic powder/spray/agent • TC-235 • hemospray	• bentonite • topical antihemorrhagic agent
TIPS	• transjugular intrahepatic portosystemic shunt • Dean Warren shunt • H-shunt	• TIPS • PSS
BRTO	• balloon occlusion/tamponade/ catheter/embolization • balloon occluded retrograde transvenous obliteration • BRTO • dual balloon	• lumen tube • Sengstaken-Blakemore • Linton tube • Minnesota tube/Minnesota 4-lumen tube
SEMS/	• stent/stent/stenting • prosthesis	• fully-covered SEMS • uncovered SEMS

Supplementary material

Esophageal Stent	• SEMS/FCSEMS/ UCSEMS	• Danis stent
Repeat Endoscopy	• recur/recurrence/repeat/secondary and endoscopy	
OTSC	• Ovesco • over-the-scope-clip	• OTSC
Definitions/ Terminology	• terminology • GOV1/GOV2/IGV1/IGV2 • Sarin • definition/define/defined/ defining • lexicon	• classify/classification • codification/codify/codified/ codifying • catalog/cataloged/catalogued • category/categorize • type/types/typology
Endoscopic Cyanoacrylate Injection	• cyanoacrylates • adhesives • Bucrylate • Enbucrilate	• n-butyl-2-cyanoacrylate • Histoacryl • Dermabond
EUS-Guided	• endosonography • fine needle biopsy • endoscopic ultrasound/ultrasonography	• endosonography • EUS • FNA
Coils	• therapeutic embolization • coil/coils	• hydrocoil/hydrocoils • Guglielmi coils
Follow-Up	• follow-up • postoperative period/complications/ care/pain/hemorrhage • secondary • routine • post-endoscopy	• longitudinal • survival • mortality • Prognosis • quality of life • treatment outcome
PPIs	• proton pump inhibitor • omeprazole	• esomeprazole sodium • PPI/PPIs
Beta Blockers	• adrenergic beta-antagonists	• Penbutolol

Supplementary material

	• Oxprenolol Sotalol • Propranolol • Nadolol	• Timolol • beta antagonist/blocker/receptor/ adrenergic

*Related terms, variations, spellings, and relevant controlled vocabulary were used in the complete search strategies.

Databases were also searched for specific study designs using the following search terms:

1. Meta-analysis
2. Systematic review
3. Randomized controlled trial
4. Observational/cohort study
5. Practice guideline

Supplementary material

Table 1s Evidence tables

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Colli 2014, Cochrane	To determine the diagnostic accuracy of capsule endoscopy for the diagnosis of esophageal varices (EV) in children or adults with chronic liver disease or portal vein thrombosis,	Studies that evaluated the diagnostic accuracy of capsule endoscopy for the diagnosis of EV using EGD as the reference standard in children or adults of any age, with chronic liver disease or portal vein thrombosis	capsule endoscopy for the diagnosis of EV in children or adults with chronic liver disease or portal vein thrombosis	EGD as the reference standard in children or adults of any age, with chronic liver disease or portal vein thrombosis	To investigate the accuracy of capsule endoscopy as triage or replacement of EGD	Systematic review	936 participants were included; the pooled estimate of sensitivity was 84.8% and of specificity 84.3% in the accuracy of capsule endoscopy for the diagnosis of EV of any size in people with cirrhosis	We cannot support the use of capsule endoscopy as a triage test in adults with cirrhosis, administered before EGD, despite the low incidence of adverse events and participant reports of being better tolerated. We found no data assessing capsule endoscopy in children and in people with portal thrombosis

Supplementary material

Sacher-Huvelin, 2015, Endoscopy	To compare Esophageal video capsule endoscopy (ECE) with esophagogastroduodenoscopy (EGD) for the diagnosis of esophageal varices (EV) in patients with cirrhosis	Patients with cirrhosis and with no known EV	Patients underwent ECE first, followed by EGD (gold standard).	EGD following ECE - The endoscopists who performed EGD were blind to the ECE result	The primary end point was the detection of varices	Prospective trial	The ECE procedure was feasible in 297/300 patients (99 %). The EGD procedure was feasible in all patients ECE identified EV in 121 patients (40 %) .EGD identified EV in 140 patients (47 %). the overall sensitivity, specificity, PPV, and NPV of ECE were 76%, 91%, 88%, and 81%, respectively, and the overall accuracy was 84%.	ECE was well tolerated and safe in patients with liver cirrhosis and suspicion of portal hypertension. The sensitivity of ECE is not currently sufficient to replace EGD as a first exploration in these patients
McCarty, 2017, J Clin Gastroent	To perform a systematic review and structured meta-analysis of all eligible studies to evaluate the efficacy of wireless capsule endoscopy (CE) for screening and diagnosis of esophageal varices (EV) among patients with portal hypertension	Patients with cirrhosis of Child Pugh Class A, B, or C were included as well as patients with portal vein thrombosis	Only studies investigating the use of CE for the screening or surveillance of EV were included	EGD for EV	The primary outcome : the diagnostic accuracy, sensitivity, and specificity of CE in identifying EV in patients with portal hypertension	Metanalysis and systematic review	The diagnostic accuracy of CE in the diagnosis of EV was 90%. The diagnostic pooled sensitivity and specificity were 83% and 85% respectively.	CE is well tolerated and safe in patients with liver cirrhosis and suspicion of portal hypertension. The sensitivity of CE is not

Supplementary material

					Secondary outcomes were the assessment of CE in establishing the presence of medium or large EV and the rates of complications related to CE		The diagnostic accuracy of CE for the grading of medium to large EV was 92%. The pooled sensitivity and specificity were 72% and 91%, respectively, for the grading of EV	currently sufficient to replace EGD as a first exploration in these patients

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Binmoeller, 2011 GIE	Assess the feasibility, safety, and outcomes of transesophageal EUS-guided therapy of GFV with combined coil and CYA injection	Patients with hemorrhage from large GFV, Tertiary care medical center	A standardized approach by using EUS-guided coil and CYA treatment	nill	Hemostasis, rebleeding rate, complications	Retrospective query of a prospectively maintained database	Thirty patients with GFV were treated between March 2009 and January 2011. At index endoscopy, 2 patients had active hemorrhage and 14 had stigmata of recent hemorrhage EUS-guided transesophageal treatment of GFV was successful in all. Mean number of GFV treated was 1.3 per	Transesophageal EUS-guided coil and CYA treatment of GFV is feasible and deserves further study to determine whether this novel approach can improve safety and efficacy over standard endoscopic

Supplementary material

							patient, and the mean volume of 2-octyl-CYA injected was 1.4 mL per varix. Hemostasis of acute bleeding was 100%. Among 24 patients with mean follow-up of 193 days, GFV were obliterated after a single treatment session in 23 (96%). Rebleeding occurred in 4 patients (16.6%), with none attributed to GFV. There were no procedure-related complications and no symptoms or signs of CYA embolization	injection of CYA alone
Romero-Castro, 2013, GIE	To compare CYA and ECA embolization of feeding GV for feasibility, safety, and applicability	30 patients with GV were enrolled in the study.	CYA injection	ECA embolization	to compare both EUS-guided techniques, CYA injection and coil deployment into feeding vessels, for the	Retrospective analysis of a prospectively maintained database Multicenter study, tertiary	11 patients in the coil group and 19 patients in the CYA group. The GV obliteration rate was 94.7% CYA versus 90.9% ECA; mean number of endoscopy sessions was 1.4 _ 0.1 (range 1-3). Adverse events	EUS-guided therapy for GV by using CYA or ECA is effective in localized GV. ECA required fewer endoscopies and tended to have

Supplementary material

					treatment of GV with a focus on feasibility and adverse event rate.	referral centers	occurred in 12 of 30 patients (40%) (CYA, 11/19 [57.9%]; ECA, 1/11 [9.1%]; P! .01); only 3 were symptomatic, and an additional 9 (CYA group) had glue embolism on a CT scan but was asymptomatic. Six patients (20%) died unrelated to the procedures or bleeding	fewer adverse events compared with CYA injection. Larger comparative studies are needed to prove these data

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Mattos, 2019 Annals of Hepatology	To review studies of non-invasive methods to screen for EV in patients with cirrhosis.	-Aspartate aminotransferase-to-platelet ratio index (APRI) -platelet count /spleen diameter ratio (PC\SD) -liver stiffness, spleen stiffness and an association between liver stiffness and platelet count, referred to as the Baveno VI criteria		EGD		Systematic review	-APRI was independently associated to the presence of EV, but its sensitivity to predict them was low (56.7%-71%). -Platelet count, for a cut-off value around 120,000 had a pooled sensitivity of 77% for the prediction of any varices. Spleen length, for a cut-off value around 110 mm had a pooled sensitivity of 85% for the prediction of any varices. PC/SD, for a cut-off value of 909 had a pooled	Despite reasonable performances of some of these methods, especially platelet count/spleen diameter ratio and the association between liver stiffness and platelet count, we understand that the available evidence still has relevant limitations and that physicians should decide on screening cirrhotic patients for esophageal varices with endoscopy or non-invasive methods on a

Supplementary material

							sensitivity of 93% for the prediction of any varices. -liver stiffness measurement under 20 kPa and a platelet count over 150,000/mm3, a situation in which patients could spare endoscopy due to the very low risk of having varices requiring prophylaxis	case-by-case basis.
Maurice, 2016, Journal of Hepatology	To validate (BAVENO VI) that cirrhotic patients with a liver stiffness measurement (LSM) <20 kPa and a platelet count >150,000/ll can avoid screening endoscopy as their	LSM P10 kPa and an EGD within 12 months, with a diagnosis of compensated chronic liver disease	Transient elastography data was collected from two institutions from 2006–2015			retrospective cohort study	310 cases that met the inclusion criteria for the study. The median LSM in was 18.4 kPa. Liver stiffness measurement was significantly higher in patients with HRV than in those without	Our data partly supports the Baveno VI statement that identifying low risk patients who do not require surveillance endoscopy is a realistic goal with the current technologies, which could

Supplementary material

	combination is highly specific for excluding clinically significant varices.						HRV (26.0 kPa vs. 18.4 kPa, p <0.015). In the cases with LSM <20 kPa, 14% had any varices, of which 3% were HRV. Of the cases with LSM 20 kPa, 34% had any varices, of which 7% had HRV. The median platelet count was 147,000. The Baveno VI consensus guidelines combine LSM <20 kPa and platelet count >150,000/ll. In this cohort, 33% met these criteria, of whom 11% had any varices and 2% had HRV. Among the 67% cases that fell outside of the Baveno VI	produce a significant cost saving and beneficially impact on patient experience. However, this data also highlights that a small proportion of cases will be miss-classified and thus be denied proven prophylactic therapies for primary prevention of variceal bleeding

Supplementary material

							criteria, 29% had any varices and 6% had HRV Combining LSM and platelet count using the recommended cut-off values to detect HRV gives a sensitivity 0.87, specificity 0.34, PPV 0.06, NPV 0.98, LR+ 1.31, LR_0.39. The AUROC for the combination of LSM and platelets was 0.746. Using the Baveno VI guideline 2/15 (13%) of HRV were missed	
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**
Gluud 2012, Cochrane	To compare the benefits and harms of banding ligation (EVL) versus non-selective beta-blockers (BB) as	Adult patients with endoscopically verified EV that have never bled were included	banding ligation	comparisons of EVL versus BB	the primary outcome: All-cause mortality	Systematic review of Randomized trials	Nineteen randomised trials on EVL versus BB for primary prevention in EV were	This review found a beneficial effect of EVL on primary prevention of UGIB in patient with EV. The effect on

Supplementary material

	primary prevention in adult patients with endoscopically verified oesophageal varices (EV)	regardless of the underlying liver disease					included. Most trials specified that only patients with large or high-risk EV were included. Bias control was unclear in most trials. In total, 176 of 731 (24%) of the patients randomized to EVL and 177 of 773 (23%) of patients randomized to BB died. EVL reduced UGIB and variceal bleeding compared with BB (RR 0.69; and RR 0.67; respectively	bleeding did not reduce mortality
Schepke, 2004 hepatology	To compare endoscopic variceal banding ligation (VBL) with propranolol (PPL) for primary	Patients with 2 or more EV with a diameter greater than 5 mm; proven liver cirrhosis;	endoscopic variceal banding ligation (VBL) for primary prophylaxis	propranolol (PPL) for primary prophylaxis of variceal bleeding	gastrointestinal bleeding due to portal hypertension and death from any cause	randomized controlled multicenter trial	152 cirrhotic patients with 2 or more EV (diameter>5 mm) without prior bleeding were	VBL and PPL were similarly effective for primary prophylaxis of variceal bleeding. VBL should be offered to patients

Supplementary material

	prophylaxis of variceal bleeding	Child-Pugh score below 12; and age 18 to 75 years.	of variceal bleeding				randomized to VBL (n75) or PPL (n77). The groups were well matched with respect to baseline characteristics, alcoholic etiology 51%, Child-Pugh score 7.2 _ 1.8). The mean follow-up was 34 months. Neither bleeding incidence nor mortality differed significantly between the 2 groups. Variceal bleeding occurred in 25% of the VBL group and in 29% of the PPL group. The actuarial risks of bleeding after 2 years were 20%	who are not candidates for long term PPL treatment.

Supplementary material

							(VBL) and 18% (PPL). Fatal bleeding was observed in 12% (VBL) and 10% (PPL). It was associated with the ligation procedure in 2 patients (2.6%). Overall mortality was 45% (VBL) and 43% (PPL) with the 2-year actuarial risks being 28% (VBL) and 22% (PPL).	
Pérez-Ayuso, 2010, annals of Hepatology	To compare EVL with propranolol (PPL) for primary prophylaxis of variceal bleeding.	Patients with Cirrhosis with No history of hemorrhage from esophageal varices. -High risk varices, defined as large size or medium sized (diameter between 3 and	EVL were performed at 3 weeks intervals until eradication	Pharmacological treatment with Propranolol was started at a dose of 20 mg twice daily.	Primary outcome was variceal bleeding. Secondary outcomes were survival, source of bleeding and serious adverse events.	randomized controlled trial	Over a 9-year period, 75 patients with cirrhosis and high-risk EV (HREV) were recruited and allocated to EVL (n=39) or PPL (n=36). Variceal bleeding occurred in 12% of EVL and in	The present study supports that PPL should be considered the first choice in primary prophylaxis of variceal bleeding offering similar effects and lower severe adverse events compared with EVL

Supplementary material

		5 mm) with red color signs -No current treatment with β-blockers					25% of PPL group (p=0.17). The actuarial risks of bleeding after 2 years were similar in both groups. Overall mortality was 51% in EVL and 33% in PPL group (p=0.17). Patients in the EVL group showed a lower rate of esophageal variceal bleeding (5.1% v/s 25%, p=0.027) and a higher rate of sub-cardial variceal bleeding compared with PPL group (7.7% v/s 0%, p=0.027). Serious adverse events related to EVL occurred in 2 patients,	

Supplementary material

							including 1 death.	
Funakoshi, 2012, annals of Hepatology	To perform an updated meta-analysis comparing β-blockers (BB) with endoscopic variceal banding ligation (EVBL) in the primary prophylaxis of esophageal variceal bleeding	patients with portal hypertension due to proven cirrhosis, and one study included 6 patients with extra-hepatic portal vein obstruction and one patient with non-cirrhotic portal fibrosis	endoscopic variceal banding ligation (EVBL) in the primary prophylaxis of esophageal variceal bleeding	β-blockers (BB) in the primary prophylaxis of esophageal variceal bleeding	Main outcomes were variceal bleeding rates and all-cause mortality, calculated overall and at 6, 12, 18 and 24 months	metanalysis	19 randomized controlled trials were analyzed including a total of 1,483 patients. Overall bleeding rates were significantly lower for the EVBL group No significant difference was found for either bleeding related mortality or for all-cause mortality overall or at 6, 12, 18 or 24 months. BB were associated with more frequent severe adverse events (OR 2.61, 95% CI 1.60-4.40, P < 0.0001)	EVBL appears to be superior to BB in preventing the first variceal bleed, although this finding may be biased as it was not confirmed by high quality trials. No difference was found for mortality. Current evidence is insufficient to recommend EVBL over BB as first-line therapy.

Supplementary material

							whereas fatal adverse events were more frequent with EVBL (OR 0.14, 95% CI 0.02-0.99, P = 0.05).	
Tian, 2019, Therapeutics and Clinical Risk Management	To perform a meta-analysis of randomized controlled trials (RCTs) evaluating the benefits and harms of carvedilol vs EBL for the prevention of variceal bleeding.	prospective RCTs with patients with a confirmed diagnosis of esophageal varices by endoscopy	carvedilol as prophylaxis of variceal bleeding	endoscopic band ligation (EBL) prophylaxis of variceal bleeding	Main outcomes in selected studies (variceal bleeding, all-cause deaths, bleeding-related deaths, and adverse events) were pooled into a meta-analysis	meta-analysis	Seven RCTs were identified in this meta-analysis, including a total of 703 patients. A total of 359 patients were randomized to carvedilol group and 354 were randomized to EBL group. No significant difference in variceal bleeding was observed between carvedilol use and EBL groups (relative ratio [RR] =0.86, 95% CI =0.60–1.23, $I2$=11%), without publication bias. No	There is no significant difference between carvedilol use and EBL intervention for the prophylaxis of variceal bleeding in patient with esophageal varices. Large-scale clinical trials are further needed to make a confirmed conclusion.

Supplementary material

							significant difference was found neither for all-cause deaths (RR =0.82, 95% CI =0.44–1.53, $I2$=66%) nor for bleeding-related deaths (RR =0.85, 95% CI =0.39–1.87, $I2$=42%) in four included studies. Moreover, no reduced trend was observed toward adverse events in carvedilol group compared with that in EBL group	
Binmoeller, 2011 GIE	Assess the feasibility, safety, and outcomes of transesophageal EUS-guided therapy of GFV with combined coil and CYA injection	Patients with hemorrhage from large GFV, Tertiary care medical center	A standardized approach by using EUS-guided coil and CYA treatment	nill	Hemostasis, rebleeding rate, complications	Retrospective query of a prospectively maintained database	Thirty patients with GFV were treated between March 2009 and January 2011. At index endoscopy, 2 patients had active	Transesophageal EUS-guided coil and CYA treatment of GFV is feasible and deserves further study to determine whether this novel approach can improve safety and

Supplementary material

							hemorrhage and 14 had stigmata of recent hemorrhage EUS-guided transesophageal treatment of GFV was successful in all. Mean number of GFV treated was 1.3 per patient, and the mean volume of 2-octyl-CYA injected was 1.4 mL per varix. Hemostasis of acute bleeding was 100%. Among 24 patients with mean follow-up of 193 days, GFV were obliterated after a single treatment session in 23 (96%). Rebleeding occurred in 4 patients	efficacy over standard endoscopic injection of CYA alone

Supplementary material

							(16.6%), with none attributed to GFV. There were no procedure-related complications and no symptoms or signs of CYA embolization	
Romero-Castro, 2013, GIE	To compare CYA and ECA embolization of feeding GV for feasibility, safety, and applicability	30 patients with GV were enrolled in the study.	CYA injection	ECA embolization	to compare both EUS-guided techniques, CYA injection and coil deployment into feeding vessels, for the treatment of GV with a focus on feasibility and adverse event rate.	Retrospective analysis of a prospectively maintained database Multicenter study, tertiary referral centers	11 patients in the coil group and 19 patients in the CYA group. The GV obliteration rate was 94.7% CYA versus 90.9% ECA; mean number of endoscopy sessions was 1.4 _ 0.1 (range 1-3). Adverse events occurred in 12 of 30 patients (40%) (CYA, 11/19 [57.9%]; ECA, 1/11 [9.1%]; P! .01); only 3 were symptomatic,	EUS-guided therapy for GV by using CYA or ECA is effective in localized GV. ECA required fewer endoscopies and tended to have fewer adverse events compared with CYA injection. Larger comparative studies are needed to prove these data

Supplementary material

							and an additional 9 (CYA group) had glue embolism on a CT scan but was asymptomatic. Six patients (20%) died unrelated to the procedures or bleeding	

Supplementary material

Initial assessment – what initial evaluations are needed bleeding in cirrhosis									
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)*** **Or limitations**
Kim et al. 2021	Development a novel bedside risk-scoring model to predict the 6-week mortality in cirrhotic patients undergoing EBL for AVB	cirrhotic patients undergoing EBL for AVB derivation cohort n = 1373 validation cohort n = 200	Bedside risk-scoring model	Child-Turcotte-Pugh (CTP) and the model for end-stage liver disease scores in the validation cohort (n = 200).	Predictive accuracy of the new model for the 6-week mortality in the validation cohort	Cox regression analysis was used to assess the relationship of clinical, biological, and endoscopic variables with the 6-week mortality risk after EBL	5 variables: use of beta-blockers, hepatocellular carcinoma, CTP class C, hypovolemic shock at initial presentation, and history of hepatic encephalopathy The score stratified the 6-week mortality risk in patients as low (3.5%), intermediate (21.1%), and high (53.4%) (P < 0.001). AUROC curve for 6-week mortality showed that this model was a better prognostic indicator than the CTP class alone in the derivation (P < 0.001) and validation (P <0.001) cohorts	A simplified scoring model for prediction of 6-week mortality in high-risk cirrhotic patients, thereby aiding the targeting and individualization of treatment strategies for decreasing the mortality rate No external validation	

Supplementary material

Zullo A et al. 2021	Independent risks factors of mortality and other outcomes in cirrhotics with UGIB	50 centers The study enrolled 706 cirrhotics, including 516 (73%) variceal and 190 (27%) nonvariceal UGIB	Na	between variceal and nonvariceal in cirrhotics	The 6-week mortality rate, need of blood transfusion, intensive care unit (ICU) admission, radiologic or surgical intervention, rebleeding rate, and length of stay in hospital	Prospective, multicenter, cohort study on UGIB cirrhotics univariate and multivariate analysis	78 (11%; 95% CI = 8.7–13.4) deceases, without any difference between variceal (11.0%) and nonvariceal (11.0%) groups Child–Pugh score C (OR:6.99; 95% CI = 2.58–18.95), and development of either hepatorenal syndrome (OR: 16.5;95% CI = 7.02–38.9) or hepatic encephalopathy (OR: 2.38; 95% CI = 1.25–4.5) were independent predictors of mortality. Transfusions and onset of hepatic encephalopathy were signicantly more frequent in variceal, whereas ICU admission rate was higher in nonvariceal bleedings. Overall, antibiotic prophylaxis was eventually administered in only	Data found that the overall mortality rate in cirrhotics with UGIB seems to be reducing and that the value did not differ between variceal and nonvariceal types.	

Supplementary material

							392 (55.5%) patients.		
2021, Lv Y et al 14	To test the hypothesis that risk stratification using CLIF-C ADs would effectively identify a group of patients with Child- Pugh B cirrhosis and AVB at higher risk of mortality or further bleeding who have the potential for benefit from early TIPS	Patients with Child-Pugh B cirrhosis and acute variceal bleeding	Current standard of care	CLIF-C Ads vs active bleeding at endoscopy vs recalibrated MELD vs MELD, MELD-HE, and Child-Pugh	6 weeks and 1-year mortality Composite endpoint of 6-week death or further bleeding	1 - observational study retrospectively analyzed the prospectively collected data of consecutive patients 2-RCT	The concordance index values of CLIF-C ADs for 6-week and 1-year mortality (0.715 and 0.708) were significantly better than those of active bleeding at endoscopy (0.633 [P < 0.001] and 0.556 [P < 0.001]) and other prognostic models patients were categorized as low risk (CLIF-C ADs <48), intermediate risk (CLIF-C ADs 48-56), and high risk (CLIF-C ADs >56), with a 5.6%, 16.8%, and 25.4% risk of 6-week death, respectively. The performance of CLIF-C ADs for predicting a composite endpoint was not satisfactory (AUC= 0.588). A nomogram incorporating components of CLIF-C Ads and albumin, platelet, active bleeding,	In patients with Child-Pugh B cirrhosis and AVB, risk stratification using CLIF-C ADs identifies a subgroup with high risk of death that may derive survival benefit from early TIPS With improved prediction accuracy for 6-week death or further bleeding, the data-driven nomogram may help to stratify patients in randomized trials	

Supplementary material

							and ascites significantly improved the prediction accuracy (AUC=0.725)		
Jiménez-Rosales R et al. 2018	Analyze in-hospital and delayed 6-months mortality, identifying risk factors	patients with upper GI bleeding over 36 months n= 441 patients	Independent risk factors	na	In-hospital and delayed-6 month-mortality	Prospective observational study Multivariate analysis	Overall inpatient mortality: 9.8% Mortality directly related to bleeding: 5.1% Patients who died presented lower systolic blood pressures, platelet recounts, prothrombin times and lower levels of hemoglobin, calcium, albumin, urea, creatinine and total proteins. Cirrhosis and neoplasms determined a higher in-hospital mortality. Albumin levels were protective, whereas creatinine and an active bleeding were risk factors for in-hospital death	Albumin levels were a protective factor for in-hospital	
Camus M et al. 2016	In cirrhotics versus non-cirrhotics presenting	2 university-based medical centers	Independent risk factors	na	Etiology of hemorrhage	Prospective cohort study	Cirrhosis independently predicted an upper gastrointestinal source of bleeding (OR 3.47; 95	Cirrhosis was predictors of an upper GI tract site of	

Supplementary material

	with severe hematochezia, aimed at identifying independent predictors of bleeding from the upper gastrointestinal tract versus small bowel or the colon, and comparing 30-day clinical outcomes	n= 860 consecutive patients with severe hematochezia admitted from 1995 to 2011 160 (18.6 %) cirrhotics					% CI 2.01-5.96) as well as history of hematemesis, melena in the past 30 days, positive nasogastric aspirate, prior upper gastrointestinal bleeding or use of aspirin or non-steroidal anti-inflammatory. The most prevalent diagnoses were esophageal varices (20 %) in cirrhotics	bleeding in patients with hematochezia Emergent upper endoscopy should be strongly considered in such patients	
Tsai MH et al. 2014	Evaluation of adrenal function using short corticotropin stimulation test	Patients with liver cirrhosis and acute gastroesophageal variceal bleeding Ten-bed gastroenterology-specific medical ICU at university teaching	Na	Na	5-day treatment failure and 6-week mortality	Prospective observational study Multivariate analysis	Critical illness-related corticosteroid insufficiency occurred in 29.9% of patients critical illness-related corticosteroid insufficiency had higher rates of treatment failure and 6-week mortality (63.8% vs 10.9%, 42.6% vs 6.4%, respectively; $p < 0.001$). The cumulative rates of survival at 6 weeks were 57.4% and 93.6% for the critical illness-related	Multivariate analysis identified Model for End-Stage Liver Disease score, hypovolemic shock, and bacterial infection at inclusion as independent factors associated with 6-week mortality	

Supplementary material

		hospital in Taiwan 157 episodes of gastroesophageal variceal bleeding in 143 patients with cirrhosis					corticosteroid insufficiency group and normal adrenal function group, respectively ($p < 0.001$) Multivariate analysis identified also Model for End-Stage Liver Disease score, hypovolemic shock, and bacterial infection at inclusion as independent factors associated with 6-week mortality		
Triantos CK et al. 2014	Evaluation of adrenal function using salivary cortisol and free serum cortisol	acute variceal bleeding (AVB) (n=38) and in stable cirrhosis (n=31)	Total serum cortisol, salivary corticol (SC), cortisol-binding globulin, and free serum corticol (FC) (Coolens' formula)		6-week survival	Prospective study Multivariate analysis	Independent associations with 6-week mortality in AVB were FC at least 3.2 µg/dl ($p<0.001$), hepatocellular carcinoma ($p<0.001$), CPC ($p<0.001$), and early rebleeding ($P<0.001$) Among patients with normal cortisol-binding globulin (n=14) and albumin (n=31), the factors were hepatocellular carcinoma ($p=0.003$), CP ($p=0.003$), and FC ($p=0.036$). SC was also found to be an	Higher FC is associated independently with bleeding-related mortality. However, whether high FC solely indicates the severity of illness or whether there is significant adrenal insufficiency cannot be discerned	

Supplementary material

							independent predictor of 6-week mortality (p<0.001). Area under the curve of FC for predicting 6-week mortality was 0.79		
Matei D et al. 2013	To analyze the clinical and laboratory parameters which are predictors of the UGIB etiology, and to develop a score for predicting variceal or non-variceal bleeding	Patients presenting to the emergency department of a tertiary care center with UGIB, throughout a 1-year period 517 patients with UGIB, 29.8% had variceal and 70.2% non-variceal bleeding	Na	Na	Etiology of hemorrhage	Prospective study Multivariate analysis	6 factors were associated with variceal hemorrhage: cirrhosis (OR=10.74, 95% CI: 3.50-32.94, p<0.001), history of variceal hemorrhage (OR=13.11, 95%CI: 3.09-55.57, p<0.001), ascites (OR=4.41, 95% CI: 1.74-11.16, p=0.002), thrombocytopenia (OR=2.77, 95% CI: 1.18-6.50, p=0.01), elevated INR (OR=4.77, 95% CI:1.47-15.42, p=0.009) elevated bilirubin levels (OR=2.43, 95% CI:1.01-5.84, p=0.04)		

Supplementary material

Chen PH et al. 2012	To determe indicators of 6-week re-bleeding and mortality in patients with "active" esophageal variceal bleeding	From July 2005 to December 2009 cirrhotic patients with endoscopy-proven active esophageal variceal bleeding n= 101 patients	Na	Na	6-week re-bleeding and mortality	Multivariate analysis	Overall 6-week re-bleeding rate: 25.7% (n=26) overall 6-week mortality: 31.7% (n=32) MELD score, and portal vein thrombosis were indicators of 6-week re-bleeding Hematemesis upon arrival, MELD score, and hepatocellular carcinoma were indicators of 6-week mortality		
Hearnshaw SA et al 2011	To describe the patient characteristics, diagnoses and clinical outcomes of patients presenting with acute upper gastrointestinal bleeding (AUGIB) in the 2007 UK Audit	208 participating UK hospitals admitting patients with AUGIB All adults (>16 years) presenting in or to UK hospitals with AUGIB	Na	Na		Multi-centre survey	Mortality was highest in those with variceal bleeding (15%) and with malignancy (17%) The majority (1266/1745) of those with a history of alcohol excess were under 60 years of age. The age-adjusted mortality	Mortality is particularly high among inpatients and those bleeding from varices	

Supplementary material

		between 1 May and 30 June 2007 n= 6750 patients					ratio overall for those with such a history was 1.80 (95% CI 1.49 to 2.17) and was highest in those with cirrhosis. For other co-morbidities, grade 3 cardiac failure, respiratory disease, stroke and malignancy were associated with a twofold or higher risk of death		
Bambha K et al. 2008	To determine risk factors for 6-week mortality, and re-bleeding within 5 days in patients with cirrhosis and AVH	256 patients with AVH	Na	Na	Mortality within 6 weeks Re-bleeding within 5 days	Multivariate analysis from a randomised prospective trial	Mortality within 6 weeks: 14% Only MELD score and units of PRBCs transfused in the first 24 h were associated with 6-week mortality univariately (HR 1.11, p < 0.001; HR 1.22, p < 0.001) and bivariately (HR MELD = 1.10, p < 0.001; HR per unit of PRBCs transfused = 1.15, p = 0.005).	Patients with AVH and MELD score > or = 18, requiring > or = 4 units of PRBCs within the first 24 h or with active bleeding at endoscopy are at increased risk of dying within 6 weeks	

Supplementary material

							Re-bleeding within 5 days: 15% MELD score (p = 0.01) and a clot on a varix (p = 0.05) predicted re-bleeding		
Lecleire S et al. 2005	To assess epidemiologic features and predictive factors of mortality of acute upper gastrointestinal	All the UGIB occurring in a geographic area of 3 million people 2,133 UGIB 21.9% in cirrhotic patients (n = 468)	Data from cirrhotic patients were compared with those of noncirrhotic patients bleeding	Na	Mortality during hospitalization	During a 6-month period, a prospective population-based study including	6 independent predictive factors of mortality were observed in both patient groups: prothrombin level<40% inpatient UGIB concomitant dig carcinoma hematemesis recent use of steroid drugs age>60 years Four other predictive factors of mortality were also identified in noncirrhotic patients	Although epidemiologic features, clinical course, management, and prognosis of UGIB were quite different in cirrhotic and noncirrhotic patients, the majority of predictive factors of mortality were the same in both patient groups	

Supplementary material

Patients with upper GI bleeding AND limited fluid resuscitation									
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)*** **Or limitations**
Lu B, et al. 2015	The Use of Limited Fluid Resuscitation and Blood Pressure Controlling Drugs in the Treatment of Acute Upper Gastrointestinal Hemorrhage Concomitant with Hemorrhagic Shock.	n = 51; conventional group = 24 patients vs limited fluid resuscitation group (study group) = 27 patients	limited fluid resuscitation regimen combined with blood pressure-controlling drugs (dopamine) in treating acute upper gastrointestinal hemorrhage concomitant with hemorrhagic shock	conventional group	pre- and 12 h post-infusions, arterial blood samples for blood gas analysis, venous blood samples for routine blood analysis, blood lactate, base excess values, hemoglobin, amount of fluid resuscitation, mortality, complications	**RCT**	complication rates were lower in patients who received limited fluid resuscitation and drug-induced hypertension effective restoration of circulating blood volume and perfusion maintenance of vital organs	Limited fluid resuscitation combined with blood pressure-controlling drugs effective maintains blood perfusion of vital organs, improves whole body perfusion indicators, reduces the volume of fluid resuscitation, and achieves better bleeding control and	single center - Chinese population - small sample size difficult to draw abovementioned conclusion from presented results

Supplementary material

								resuscitation effectiveness	
Duan C, et al. 2015	Efficacy of limited fluid resuscitation in patients with hemorrhagic shock: a meta-analysis.	11 studies and 1482 patients (3 studies upper GI bleeding patients) ; 752 in limited fluid resuscitation group vs. 757 in regular fluid resuscitation group	efficacy of limited fluid resuscitation during active hemorrhage compared with regular fluid resuscitation		mortality, complication	**Meta-analysis**	reduction in mortality with limited fluid resuscitation (RR0.67; 95% CI=0.56-0.81, p<0.00001) reduction in occurrence of postoperative complication with limited fluid resuscitation (MODS: RR 0.37; 95% CI 0.21-0.66, p = 0.0008, ARDS RR = 0,35 (95% CI 0.21-0.6, p<0.0001	Limited fluid resuscitation should be used in active hemorrhage in trauma setting Limit: Only Chinese population in upper GI bleeding series (3/11), not generalization to European population	

Critically ill patients; comparison of crystalloids vs colloids									
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)* Or limitations**
Lewis SR et al. 2018	Colloids versus crystalloids for fluid resuscitation	69 studies : 65 RCTs, 4 quasi-RCTs	comparison of four types of colloid (i.e.	crystalloids	mortality 30day, 90day	**Systematic Review**	little or no difference in all-cause mortality at the end of follow-up, at 90 days, or at 30 days,	**little or no difference** in	

Supplementary material

	in critically ill people	n= 30,020	starches; dextrans; gelatins; and albumin or FFP)				between using colloids (starches; dextrans; or albumin or FFP) or crystalloids for fluid resuscitation in critically ill people	all-cause mortality moderate-certainty evidence of a slight increase in the need for blood transfusion or renal replacement therapy when starches were used for fluid resuscitation moderate-certainty data	
Critically ill patients; comparison of crystalloids vs. saline									
Hammond DA et al. 2020	Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis	fluid resuscitation with balanced crystalloids or 0.9% sodium chloride (saline) 13 studies n = 30 950	crystalloids	0.9% sodium chloride (saline)	28-30-day mortality	**Review and Meta-analysis**	Balanced crystalloids demonstrated lower hospital or 28/30-day mortality (risk ratio [RR] = 0.86; 95% CI = 0.75-0.99; I^2 = 82%) overall odds of major adverse kidney events occurring in the first 30 days were less with balanced crystalloids than saline	Balanced crystalloids should be preferred instead of saline in most critically ill adult patients	critically ill adult patients

Supplementary material

							(OR = 0.78; 95% CI = 0.66-0.91; I^2 = 42%)		
Semler M et al., 2018	Balanced Crystalloids versus Saline in Critically Ill Adults	n= 15 802 adult ICU patients	balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A)	saline 0.9% sodium chloride	major adverse kidney event within 30 days a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction	**RCT**	major adverse kidney event: balanced-crystalloids group: 1139 (14.3%) vs. saline group: 1211 (15.4%) (marginal OR, 0.91; 95% [CI], 0.84 - 0.99; conditional OR, 0.90; 95% CI, 0.82 - 0.99; p=0.04). Among patients with sepsis, 30-day inhospital mortality: 25.2% with balanced crystalloids; 29.4% with saline (adjusted OR, 0.80; 95% CI, 0.67 - 0.97; P=0.02)	balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.	**All ICU patients**
Effect of recombinant Factor VIIa (rFVIIa) on variceal bleeding									
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)* Or limitations**

Supplementary material

Bendtsen et al. 2014	To perform a meta-analysis of the two trials on individual patient data with special focus on high risk patients.	497 patients were eligible for the meta-analysis; 308 (62%) had active variceal bleeding at endoscopy (oozing or spurting) and 283 of these had a Child-Pugh score >8	rFVIIa	Placebo group	Composite five day endpoint: failure to control bleeding, 5-day rebleeding or death.	Meta-analysis ITT	Analysis on the composite endpoint in all patients with bleeding from oesophageal varices did not show any beneficial treatment effect. However, failure rate for the primary composite end-point was significantly lower in treated patients with active bleeding at endoscopy (17%) compared to placebo (26%, p=0.049). This difference was highly significant in patients with Child-Pugh score>8 and active bleeding at endoscopy (rFVIIa 16%, placebo 27%; p = 0.023). No significant treatment effect was found at 42 days. Five thromboembolic events occurred in rFVIIa treated patients compared to none in placebo treated patients	beneficial effect of rFVIIa on the primary composite endpoint of control of acute bleeding, prevention of rebleeding day 1–5 and 5-day mortality in patients with advanced cirrhosis and active bleeding from oesophageal varices at endoscopy. A major drawback of the treatment is a potential increased risk of arterial thrombo-embolic events.	

Supplementary material

Bosch et al., 2007 **Hepatology**	To investigate the efficacy and safety of rFVIIa in a high risk population of patients with cirrhosis, those with severe liver disease (Child-Pugh score _ 8 points) and active variceal bleeding (spurting or oozing at emergency endoscopy)	Acute variceal haemorrhage N=265 (89/88/88)	Two arms of: 1. 600 mcg/kg rFVIIa 2. 300 mcg/kg rFVIIa	Placebo group	treatment failure (modified Baveno II-IV criteria) defined as: failure to control acute bleeding within 24 hours, or failure to prevent clinically significant rebleeding, or death within 5 days of first trial product dosing.	double-blinded, randomized, and conducted across multiple centers (31 hospitals in 12 countries in Europe and Asia), with three parallel arms.	There was no significant effect of treatment with 600 _g/kg rFVIIa compared with placebo on the composite endpoint (odds ratio 0.8, P _ 0.37) and the failure rate was similar at 20% and 23% for rFVIIa and placebo, respectively The failure rate was lower in the 300 _g/kg rFVIIa group (13%); There was no significant difference in 5-day mortality between groups (P _ 0.22)	the current study failed to show a beneficial effect of rFVIIa on the primary composite endpoint of control of acute bleeding, prevention of rebleeding, and reducing 5-day mortality in patients with advanced cirrhosis (Child-Pugh score 9-15) and active variceal hemorrhage.	
Bosch et al, 2004 **gastroenterology**	to evaluate the efficacy and safety of rFVIIa in cirrhotic	Acute variceal haemorrhage	8 doses of either 100 mcg/kg rFVIIa in addition to	placebo	compare the 2 treatment groups with respect to control of acute	RCT	83% of rFVIIa-treated patients and 88% of placebo-treated patients received concomitant	rFVIIa can be used safely in this clinical setting. Although no	

Supplementary material

	patients with acute UGIB	N=242 (212/121)	standard pharmacologic and endoscopic treatment.		bleeding, prevention of rebleeding, and mortality over the 5-day trial period		vasoactive treatment to control bleeding. There was no difference between treatment groups in the proportion of patients who were bleeding actively at first endoscopic procedure no effect was observed on the composite end point or on its components. However, a trend toward a decrease of the failure rate was observed in patients bleeding from varices and treated with rFVIIa (8 of 78 vs. 16 of 80; relative risk reduction, 0.49; P _ 0.12). This trend for a beneficial effect	overall effects were detected, the subgroup of patients with variceal bleeds and with moderate to advanced cirrhosis is likely to benefit from rFVIIa treatment	

Supplementary material

							of rFVIIa was consistent across the components of the composite end point except for mortality		
Effect of recombinant Factor VIIa (rFVIIa) on variceal bleeding									
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)* Or limitations**
Mohanty et al. 2021	To investigate if FFP transfusion affects clinical outcomes in AVH	n= 244 consecutive, eligible patients with AVH 5 centers between 2013 and 2018			Mortality at 42 days and failure to control bleeding at 5 days and length of stay	Retrospective study Multivariate analysis	Patients who received FFP transfusion (n = 100) had higher mean Model for End Stage Liver Disease (MELD) score and more severe variceal bleeding than those who did not received FFP transfusion (n = 144). FFP transfusion was associated with increased odds of mortality at 42 days (odds ratio [OR] 9.41, 95% confidence interval [CI] 3.71-23.90). FFP transfusion was also	The independent association of FFP transfusion with mortality at 42 days persisted when the cohort was restricted to high-risk patients and in patients without active bleeding.	

Supplementary material

							associated with failure to control bleeding at 5 days (OR 3.87, 95% CI 1.28-11.70) and length of stay >7 days (adjusted OR 1.88, 95% CI 1.03-3.42). The independent association of FFP transfusion with mortality at 42 days persisted when the cohort was restricted to high-risk patients and in patients without active bleeding.		

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)* Or limitations
Park et al. 2020	Comparison of sedation and no sedation during emergency EVL (bleeding period) .	1,300 patients were included 430 patients (33.1%) received sedation during EVL 66.9% did not receive sedation during the procedure	Sedation endoscopist- driven sedation propofol and/or midazolam	No sedation	The primary endpoint was treatment failure according to use of sedation during EVL. Treatment failure was defined as failure to control bleeding by EVL, death during EVL, or rebleeding within 5 days after EVL.18,19 The secondary endpoints were procedure time, adverse events, and 30-day mortality after initial EVL	retrospectively collected data 6 centers	The mean procedure time was shorter in the sedation group than in the non-sedation group (12.4 _ 9.5 min vs. 13.8 _ 9.4 min, P = 0.010). The number of band ligations did not differ between the groups (sedation and non-sedation, respectively: 3.3 _ 2.1 and 3.2 _ 2.4, P = 0.362). failure to control bleeding, death during EVL, rebleeding within 5 days did not differ	No difference between sedation and no sedation .	Low Biai selection sedation was selected at the clinicians' discretion Rubber band ligation was performed with single-band ligation devices (Bard

Supplementary material

							between the two groups. Rebleeding within 30 days also did not differ between the groups (10.9% and 12.5%, respectively, P = 0.457). Logistic regression, sedation did not affect treatment failure (odds ratio [95% confidence interval (CI)] = 0.96 [0.60– 1.51]). During EVL, presentation of aspiration, hypoxia, shock, and bradycardia did not differ between the sedation and nonsedation groups (Table 3). Development of HEP also did not depend on sedation status (sedation and non-sedation,		Interventional Products, Tewksbury, MA, USA) with a short transparent cylindrical cap that carries only one band. The single-band ligator requires placement of an overtube (60 French, 20 cm) for repeated intubation to place multiple bands

Supplementary material

							respectively: 7.4% and 7.6%, P > 0.999). Additionally, 30-day mortality in the sedation group was comparable to that of the non-sedation group (8.1% and 9.6%, respectively, P = 0.430). Causes of mortality also did not differ between the groups. In the sedation group, adverse events as well as mortality did not differ among the types of sedatives (Table S1). In the survival analysis, the Kaplan-Meier plot demonstrated no impact of sedation on mortality within 30 days		

Supplementary material

							(Fig. 2a). The Cox proportional hazard model demonstrated that AIMS65 score ≥2 and RBC transfusion within 72 hours were risk factors for treatment failure of EVL (hazard ratio [HR] [95% CI]: AIMS65 ≥ 2, 7.49 [4.57–12.3]; RBC transfusion, 3.86 [1.99–7.46]) (Fig. 2b). Nevertheless, sedation was not associated with 30-day mortality after adjusting for potential confounders (HR [95% CI] = 0.99 [0.66–1.47]).		
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)***

Supplementary material

Chaudhuri D et al. 2019	Examine the clinical outcomes and costs related to prophylactic endotracheal intubation compared to no intubation in UGIB Both variceal and no GI bleeding	Studies including patients older than 16 years undergoing EGD for severe UGIB (defined as patients who needed immediate endoscopy or admission to an ICU), comparing prophylactic intubation (PI) to no PI. 7 studies (all retrospective) n=5662 patients Subgroup analysis for EVGH: 172 patients (3%)	Prophylactic intubation	No prophylactic intubation	Cardiac events (composite outcome of myocardial infarction and cardiac arrest), pneumonia, LOS (in hospital and ICU) and death	Systematic review and meta-analysis of retrospective studies	- PI was associated with Increased mortality (OR 2.59) - hospital LOS was higher in the PI group - PI showed higher rates of pneumonia (OR 6.58) and cardiac events (OR 2.11), and a trend toward increased ICU LOS	Prophylactic intubation in severe UGIB is associated with a greater risk of pneumonia, LOS, death, and cost compared to endoscopy without intubation.	- small number of studies included retrospective nature of the studies

Supplementary material

Perisetti et al. 2019	Descriptive study of outcomes' patients admitted in ICU oth acute UGIB after endotracheal intubation performed within 48 hours before or during EGD for UGIB	Adult (>18 years) patients admitted or transferred to the ICU who had acute UGIB, in whom endotracheal intubation (ETI) was performed within 48 hours before or during EGD for UGIB with an indication of airway protection or shock or respiratory failure n=89 patients EVGH: 43%	endotracheal intubation	No comparison	Pulmonary aspiration, myocardial infarction, pneumonia, acute respiratory distress syndrome, cardiogenic pulmonary edema, sepsis, mortality, hospital days	Single-center retrospective study from 2000 to 2013	ETI group :38% had pulmonary aspiration, 9% myocardial infarction, 9% ARDS, 7% pulmonary edema, the median length of hospital stay was 10 days, and the mortality rate was 22%	Incidence of pulmonary aspiration with pre-EGD tracheal intubation was high (38%).	No comparison Single center Small sample size; the patients who were intubated could have been more critically ill
Alshamsi F, et al 2017	Examine the clinical outcomes related to prophylactic endotracheal intubation compared to no intubation in UGIB	Studies including patients with UGIB requiring emergent EGD, comparing those who underwent prophylactic endotracheal intubation (PEI) and those who did not undergo PEI	Prophylactic intubation	No prophylactic intubation	Aspiration, pneumonia, mortality, hospital length of stay	Systematic review and meta-analysis of retrospective studies	PEI was associated with increased risk of aspiration (OR 3.85; 6 studies), risk of pneumonia (OR 4.17; 5 studies) PEI not affect mortality (8 studies) - PEI increased the hospital		Lack of adjustment for the severity of Clinical situation Low to very low quality evidence from observation

Supplementary material

	Both variceal and no GI bleeding	10 studies n= 6068 patients Subgroup analysis for EVGH : n = 172 patients (2,8%)					length of stay (6 studies) No differences between variceal vs. nonvariceal bleeding		al studies suggests that PEI in the setting of UGIB may be associated with higher rates of respiratory complication and, less likely, with increased mortality
Tang et al. 2017 (abstract)	Retrospective comparison between cohorts was performed	Urgent esophagogastroduodenoscopy (EGD) for suspected variceal hemorrhage were included in the study and categorized into two cohorts, one with prophylactic intubation and one without. n= 110 urgent EGD	Prophylactic intubation	No prophylactic intubation	immediate aspiration, post EGD pneumonia, death, other complications, post EGD intensive care unit (ICU) stay, total ICU stay and total hospital stay	Single-center retrospective comparison	Prophylactic intubation was performed in 65 occurrence. Demographics, clinical background and significant comorbidities similar in both cohorts. Immediate aspiration, post EGD pneumonia, and mortality were similar in both cohorts. Complications other than cardiac and pulmonary related were higher in	prophylactic intubation prior to urgent EGD for variceal hemorrhage (VH) did not improve clinical outcomes.	Only abstract

Supplementary material

		EVGH : 100%					prophylactic intubation group than no intubation group (40% vs 17.78%, P = 0.02). Overall average hospital stay of both cohorts and overall average ICU stay similar. Average ICU stay post EGD was significant longer in prophylactic intubation group than no intubation group (4.7 ± 3.9 days vs 2.6 ± 2.6 days, P = 0.002)		
Hayat 2017	Compare the incidence of cardiopulmonary unplanned events between critically ill patients with brisk UGIB who underwent endotracheal intubation	Patients aged 18 years or older who presented at Cleveland Clinic between 2011 and 2014 with hematemesis and/or patients with melena with evidence of hemodynamic compromise (systolic blood pressure < 90 mm Hg and heart rate > 100 beats/min	Prophylactic endotracheal intubation	No intubation	The primary outcome was a composite of several cardiopulmonary unplanned events (pneumonia, pulmonary edema, acute respiratory distress syndrome, persistent shock/hypotension after the procedure, arrhythmia, myocardial infarction, and cardiac arrest) occurring within 48	Single center retrospective study Propensity score matching	The baseline characteristics, comorbidity scores, and prognostic scores similar between the 2 groups More oesophageal varices in the intubation group Overall cardiopulmonary unplanned event rates were significantly higher in the intubated group compared with the non-	The benefits and risks of intubation should be carefully weighed when considering airway protection before an EGD	

Supplementary material

	versus those who did not	requiring either fluids or vasopressor agents) n= 200 EVGH: 40,6% in the PIE group vs. 27,3% in the no-PIE group (p=0,05)			hours of the endoscopic procedure		intubated group (20% vs 6%, p <0.008), which remained significant (p<0.012) after adjusting for the presence of esophageal varices LOHS, in-hospital mortality (10%) and rates of repeat therapeutic intervention required to control the bleed were similar	in this group of patients	
Park 2016	compared adverse events related to propofol based sedation during emergency endoscopy between patients with non-variceal and variceal bleeding	Clinical records of patients who underwent emergency endoscopy for UGIB under sedation were reviewed. 703 endoscopies, EVGH : 164 exclusion : patients with unstable vital signs	Sedation Endoscopists and nurses administering propofol-based Sedation Propofol +/- midazolam	None	Adverse events, including shock, hypoxia, and paradoxical reaction, were compared between the nonvariceal and variceal bleeding groups. + analyzed the relationship between the	Retrospective study Korean study between January 2012 and April 2015	Shock was more common in patients with variceal bleeding compared to those with non-variceal bleeding (12.2 vs. 3.5 %, P\ 0.001). All patients except one recovered from shock after normal saline hydration, and emergency endoscopy could be finished without interruption in most		Low

Supplementary material

		despite adequate hydration, red blood cell transfusion, or vasopressor infusion, or who were graded as American Society of Anesthesiologist (ASA) physical status V, underwent emergency endoscopy without sedation			procedure time and administered dose of propofol using scatter plots because these two variables are potential risk factors for sedation-related adverse events. In order to identify dose-dependent impacts of propofol and procedure time on the occurrence of adverse events, scatter plots were displayed according to the adverse events. a paradoxical reaction was defined as the occurrence of at least one of the following: (1) irrational		cases. The incidence of hypoxia and paradoxical reaction did not differ based on the source of bleeding (non-variceal bleeding vs. variceal bleeding: hypoxia, 3.5 vs. 1.8 %, p= 0.275; paradoxical reaction interfering with the procedure, 4.1 vs. 5.5 %, p= 0.442). Procedure time was longer in the variceal bleeding group than in the non-variceal bleeding group (22.7 ± 9.3 vs. 17.2 ± 11.4 min, p< 0.001). A much larger dose of propofol was required in the non-variceal bleeding group than in the variceal group when patients		

Supplementary material

					talking or increased talkativeness such as mumbling to oneself, (2) restlessness or loss of cooperation such as resisting the insertion of the endoscope or trying to bite the scope, (3) excessive movement requiring repositioning such as jerking or swinging movements of the arms and legs or trying to draw out the scope or mouthpiece, and (4) hostile action such as trying to strike the endoscopists or attending nurses		were sedated with propofol alone (167.4 ± 115.2 vs. 115.2 ± 71.8 l g/kg/min, p= 0.001).		

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Kawanishi, 2016	Identify risk factors for aspiration pneumonia after endoscopic hemostasis	504 eligible patients with upper GI bleeding that was treated by endoscopic hemostasis between January 2004 and January 2015	na	na	Aspiration pneumoniae	Retrospective study	Hemostasis was successful in 496 (98 %) of the 504 patients (male, 381 (76 %); mean age, 65.2 ± 13.3 years) who underwent endoscopic hemostasis during the study period. Aspiration pneumonia developed in 24 (4.8 %) of 504 patients after endoscopic hemostasis. Endotracheal intubation was required for three of them, and one died of the complication. Multivariate analysis revealed that age [75 years (odds ratio (OR) 4.4; 95 % confidence interval	Considered intubation for long procedure, comorbidies (history of renal insuffiency or stroke) and elderly patients	Low

Supplementary material

							(CI) 1.5–13.6; p = 0.0073), procedural duration 30 min (OR 5.6; 95 % CI 1.9–18.2; p = 0.0023), hemodialysis (OR 3.6; 95 % CI 1.2–11; p = 0.024), and a history of stroke (OR 3.8; 95 % CI 1–14; p = 0.041) were independent risk factors for developing aspiration pneumonia.		
Author, publication year	**Study Objective**	**Participants/ Setting**	**Intervention**	**Comparisons**	**Outcome**	**Study Type**	**Results**	**Conclusion**	**Quality assessment (for RCTS)***
Almashhrawi et al. 2015	Evaluate usefulness of prophylactically intubating upper gastrointestinal bleeding (UGIB) patients	Studies examining the impact of prophylactic endotracheal intubation (PEI) on UGIB outcomes 4 studies	prophylactic endotracheal intubation	No prophylactic endotracheal intubation	Pneumonia within 48 h, mortality, aspiration	Meta-analysis of retrospective studies	- PEI associated with increased risk of pneumonia (OR 3.13; 3 studies) - PEI was not associated with higher mortality or aspiration, but sensitivity analyses demonstrated statistically significant worse outcomes in those	Pneumonia within 48 h is more likely in UGIB patients who received prophylacti c endotrac	Small number of included studies; all studies were observational; significant

Supplementary material

		n=367 patients both NVUGH et EVGH but no subgroup analysis					undergoing prophylactic intubation	heal intubation prior to endoscopy	heterogeneity was identified in 2 of the 3 outcomes (mortality and aspiration)
Rehman et al 2009	Evaluate the practice and outcome of elective prophylactic endotracheal intubation prior to endoscopy for UGI hemorrhage in the ICU	ICU patients who underwent endoscopy for UGI hemorrhage n= 307 patients EVGH : 43% in the PIE group vs. 35% in the no-PIE group	Elective Intubation	No intubation	Cardiopulmonary complications, ICU and hospital length of stay and mortality	Single center retrospective study Propensity matched case-control study	53 out of 307 patients underwent elective prophylactic intubation prior to UGI endoscopy Probability of intubation depended on APACHE III score (OR 1.4, 95%, CI 1.2 to 1.6), age (OR 0.97, 95%CI 0.95 to 0.09), presence of hematemesis (OR 1.9, 95%CI 0.8 to 5.1), prior lung disease (OR 2.1, 95%CI 0.8 to 4.9) and number of transfusions (OR 1.1 95%CI 1.0 to 1.1 per unit).	No difference	Single center Retrospective More EVGH in the PIE than in the no-PIE group Non-intubated matched controls were identified for all but 4 patients

Supplementary material

							Cumulative incidence of cardiopulmonary complications (53% vs 45%, p=0.414), ICU (median 2.2 days vs. 1.8 days, p=0.138) and hospital length of stay (6.9 vs. 5.9, p=0.785), and hospital mortality (14% vs. 20%, p=0.366) were similar.		with active massive hematemesis who were excluded from matched analysis.
Koch et al. 2007	Comparison of incidence of pulmonary infiltration after endoscopic procedure for acute VH	All endoscopic procedures for acute VH from January 1995 to December 2002 only patients with the absence of hepatic encephalopathy greater than stage II and normal chest x-ray at admission were included n= 62 patients EVGH : 100%	Elective Intubation n=42	No intubation n=20	The use of prophylactic intubation, postprocedure chest x-ray, and mortality	Single center comparative retrospective study	1) Elective intubation = 42 patients Pulmonary infiltrates: 17% Overall mortality 21% 2) no intubation = 20 patients Pulmonary infiltrates: 0% Overall mortality 5% Mortality: ns Aspiration p<0,01	patients with suspected variceal bleeding, elective intubation is associated with a risk of aspiration pneumonia	Low retrospective no comparison Exclusion of patients (encephalopathy >grade II) More patients in

Supplementary material

							LOS: ns More sclerotherapy in no intubation group (p<0,006)		the PIE group

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Rout, 2020 **J Clin Gastroenterol**	to assess the use of TEG to guide the need and the amount of blood product transfusion in cirrhotic patients with coagulopathy (platelet count <50,000/mm3 and/or INR >1.8) presenting with acute variceal bleeding and its impact on rebleeding and mortality	Acute variceal haemorrhage N=60	In the TEG group, patients received FFP at a dose of 5 mL/ kg of ideal body weight when R time was >15 minutes. Patients were transfused platelets when the MA was <30mm (3 units of platelets over 30 to 60min).	conventional transfusion group, patients received FFP 5mL/kg of when the INR was >1.8 and received 3 units of platelet transfusion when the platelet count was <50,000/mm3	The primary outcome measure was the difference in the amount of FFP and/or platelets transfused before endoscopy between the 2 groups to correct coagulopathy. Secondary outcome measures were rebleeding at day 5 and 42 and mortality at 6 weeks	open-label, randomized controlled trial	TEG parameters, R time, and MA values were similar between the 2 groups. Of the total 60 patients recruited, 34 (56.7%) patients had a platelet count <50,000/mm3 in isolation; INR >1.8 was seen in 15 (25.0%), and both abnormal parameters were seen in 11 (18.3%) patients Four patients in the TEG	use of TEG-guided blood product transfusion strategy reduced blood product transfusions and rebleeding in cirrhotic patients with acute variceal bleeding and coagulopathy.	

Supplementary material

							group (13.3%) required blood product transfusions (either FFP or platelet transfusion), as compared with all 30 (100%) patients in the conventional transfusion group. The total volume of FFP transfused in the TEG group was less, as compared with the conventional transfusion group (1345.0mL vs. 4605.0mL).		

Supplementary material

							Platelets were transfused in 3 (10.0%) patients in the TEG group, as compared with 21 (70.0%) patients in the conventional transfusion group (P<0.001). Three (10.0%) patients in the TEG group and 5 (16.7%) patients in the conventional transfusion group received both FFP and platelet transfusion(P= 0.706). There was no difference between the 2 groups with		

Supplementary material

							regard to the number of packed red blood cell transfusions. The control of bleeding at the initial endoscopy was achieved in all patients in the TEG group and in 29/30 (96.7%) patients in the conventional transfusion group		

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion Limitations
Odutayo, A.et al. 2017	Comparison of restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding	4 published and 1 unpublished randomised controlled trial 1965 participants 919 restrictive transfusion strategy and 1064 liberal transfusion strategy	Restrictive transfusion strategy	Liberal transfusion strategy	Mortality Rebleeding Ischaemic events Mean RBC transfusion	Systematic review and meta-analysis	Number of RBC units transfused lower in the restrictive transfusion group (mean difference -1·73 units, 95% CI -2·36 to -1·11, p<0·0001). Restrictive transfusion associated with lower risk of all-cause mortality (RR 0·65, 95% CI 0·44-0·97, p=0·03) and rebleeding overall (0·58, 0·40-0·84, p=0·004) No difference in risk of ischaemic events Comparison treatment effects between patient subgroups, including patients with liver cirrhosis, patients with non-variceal upper gastrointestinal bleeding, and patients with ischaemic heart disease at baseline (No statistically significant differences in the subgroups)	Restrictive strategy is safe in all subgroups of patients

Supplementary material

Jairath V, et al. 2015	Comparison of restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER)	patients aged 18 years or older with new presentations of acute upper gastrointestinal bleeding, irrespective of comorbidity, except for exsanguinating haemorrhage 936 patients across six hospitals (403 patients in three hospitals with a restrictive policy and 533 patients in three hospitals with a liberal policy)	RBC transfusion Restrictive: 80 g/L 11% cirrhotics	RBC transfusion liberal: 100 g/L 17% cirrhotics	Feasibility (primary), mortality, rebleeding, acute myocardial infarction, stroke, transfusion reactions, acute kidney injury, bacterial infection, red blood cell FU : 28 days	RCT pragmatic, open-label, cluster randomised feasibility trial	Fewer patients received RBCs on the restrictive policy than on the liberal policy (restrictive policy 133 [33%] vs liberal policy 247 [46%]; difference –12% [95% CI –35 to 11]; p=0.23), with fewer RBC units transfused (mean 1.2 [SD 2.1] vs 1.9 [2.8]; difference –0.7 [–1.6 to 0.3]; p=0.12), although these differences were not significant. No significant difference in clinical outcomes	Restrictive strategy is safe
Abid, 2014	to establish the usefulness of Adjusted Blood Requirement Index (ABRI) in	Cirrhotic pts with Variceal bleeding who received PRBC N=137	transfusion of PRBC if HB< 8 g/dl The number of blood units transfus	Baveno IV-based criteria	ABRI 0.75 or more at any time point defines failure to control bleeding	Prospective	The median ABRI score was 0.43, with an interquartile range of 0.56. The number of patients with ABRI 0.75 or more was 34 (24.8%), indicating a failure to control variceal bleeding according to the Baveno IV criteria	This study showed a very poor correlation between ABRI and other Baveno IV-based criteria for failure to control bleeding. We conclude that

Supplementary material

	determining the failure to control variceal bleeding		ed, change in hemoglobin values, and ABRI were calculated after each unit of blood transfusion till 120 h				Failure to control acute variceal bleeding occurred in 52 (37.9%) patients	ABRI is not a useful additional tool to define failure to control bleeding after variceal hemorrhage in cirrhotic patients
Villanueva C, 2013, NEJM	To compare the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy	Acute UGIB N= 444/445	- restrictive strategy (transfusion when the HB < 7g/dl) - Randomization was stratified according to the	liberal strategy (transfusion when the HB < 9g/dl) 31% cirrhotic	-**Primary**- rate of death from any cause within the first 45 days. -**Secondary** – rate of further bleeding and in-hospital complications	RCT	(All) Mortality at 45 days was significantly lower in the restrictive-strategy group than in the liberal strategy group: 5% (23 patients) as compared with 9% (41 patients) (P = 0.02). Among all patients with cirrhosis, the risk of death was slightly lower in the restrictive-strategy group than in the liberal strategy group. In the subgroup of patients with cirrhosis and Child–Pugh class A or B disease, the risk of death was significantly lower among patients	(General statement or all cause UGIB): restrictive transfusion strategy, as compared with a liberal transfusion strategy, improved the outcomes among patients with acute upper

Supplementary material

			presence or absence of liver cirrhosis 31% cirrhotic				in the restrictive-strategy group than among those in the liberal-strategy group, whereas in the subgroup of patients with cirrhosis and Child–Pugh class C disease, the risk was similar in the two groups The rate of further bleeding was significantly lower in the restrictive-strategy group than in the liberal-strategy group: 10% (45 patients), as compared with 16% (71 patients) (P = 0.01) In the subgroup of patients with cirrhosis, the risk of further bleeding was lower with the restrictive transfusion strategy than with the liberal transfusion strategy among patients with Child–Pugh class A or B disease and was similar in the two groups among patients with Child–Pugh class C disease. Among patients with bleeding from esophageal varices, the rate of further bleeding was lower in the restrictive strategy group than in the liberal-strategy group (11% vs. 22%, P = 0.05).	gastrointestinal bleeding.

Supplementary material

Colomo A, 2009 AASLD abstract	to assess the relationship between the strategy of transfusion and hemodynamic changes in cirrhotic patients with acute variceal bleeding	patients with cirrhosis and acute variceal bleeding N = 147 = 74/73	-restrictive-strategy HB<7g/dl	-liberal-strategy HB<9g/dl	a hemodynamic study was performed within the first 48 hours and repeated 2 to 4 days later	Abstract only - RCT	Both therapeutic failure and 42-d survival without failure were significantly worse in the liberal-strategy group. liberal-strategy group showed in the second hemodynamic study a significant increase in Hb (10 to 12 g/l), P=0.05), HVPG (from 20.6 to 21.3) mmHg, p=0.03), mean arterial pressure (P=0.06) and systemic vascular resistance (from 799 to 915 dyn.s.cm5, P<0.01), and a significant decrease in cardiac index (from 4.5 to 4.1 l/min/m2, P=0.04) No significant hemodynamic changes were observed in the restrictive-strategy group. MELD at admission, HVPG, Group of Transfusion and bacterial infection at admission were independent predictors of 42-days survival without failure in the multivariate analysis	a liberal-strategy of transfusion significantly increased HVPG, while a restrictive strategy did not. HVPG was an independent predictor of survival without rebleeding.

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
2004, Monescillo et al 1	To assess the accuracy of HVPG cutoff value to predict treatment failure and survival, to test whether decreasing portal hypertension by early TIPS placement in patients with high HVPG could reduce treatment failure and improve survival	Cirrhotic patients with acute variceal bleeding	HVPG measured within 24 h of admission. Patients with HVPG>20 mmHg (high risk group), were randomised into those receiving TIPS within 24 of admission and those receiving current standard of care	Current standard of care vs early placement of TIPS	Failure to control bleeding Early rebleeding (from initial bleeding to 5 d later) 6-week mortality	RCT	Early TIPS placement reduced treatment failure (125, P = .003), in-hospital and 1-year mortality (1 1% and 31%, respectively P < .05)	increased portal pressure estimated by early HVPG measurement is a main determinant of treatment failure and survival in variceal bleeding, and early TIPS placement reduces treatment failure and mortality in high risk patients defined by hemodynamic criteria	Good quality
2008, Abraldes JG et al	To evaluate the performance of early HVPG	Cirrhotic patients with acute variceal bleeding	HVPG measured in hemodynami	HVPG vs Clinical variables	5-day treatment failure (composi	Retrospective, 4 centres in Spain	HVPG >=20 mmHg had a Se 83% (90% CI: 65–93), Sp 48% (90% CI: 39–56), PPV 22% (90% CI: 14–31), NPV	HVPG has independent prognostic value in patients with acute	MELD did not have the same performanc

Supplementary material

2	measurement as a predictor of treatment failure To evaluate whether clinical variables may be of similar predictive accuracy as the measurement of HVPG		cally stable conditions a median of 30 h after admission while off vasoactive drug-therapy for at least 30 min		te of uncontrolled bleeding, early rebleeding or death within 5 days) bleeding related mortality		94% (90% CI: 89–100), +LR of 1.59 (90% CI: 1.26–2.01) and -LR 0.35 (90% CI: 0.15–0.85) to predict 5-day failure Multivariate analysis identified 3 variables independently associated with 5-day failure: HVPG 20, systolic blood pressure at admission <100 mmHg and non-alcoholic cause of cirrhosis (c statistics 0.79) Clinical variables: CTP class,, systolic blood pressure <100 mmHg and etiology were independent predictors of 5-day failure (c statistic: 0.81, 90% CI: 0.72–0.90)	variceal bleeding treated with the current standard of care similar predictive accuracy can be achieved using only simple clinical variables combination of Child class, etiology and systolic blood pressure on admission might help identifying patients at low and high risk of failure	e, low no events limits
2008, Bambha 3	To determine risk factors for 6-week mortality, and re- bleeding within 5 days in patients	Cirrhotic patients with acute variceal bleeding	Patients were treated with standard of care	Clinical and endoscopic variables	6-week mortality 5-day mortality and risk of	Retrospective analysis from apProspective collectio	High MELD >=18 vs low MELD <18 revealed no significant difference in 5-day post-AVB survival (p=0.2)	MELD is a significant and strong predictor of short-term mortality at 5 days and 6 weeks after an AVB.	

Supplementary material

	with cirrhosis and AVH				variceal re-bleeding	n of an internati onal, randomis ed, double-blinded, placebo-controlle d clinical trial	High MELD >=18 vs low MELD <18 revealed a significant increase in 6-week mortality post-AVB (p,0.001); c-statistic 0.76 (95% CI 0.65 to 0.88) MELD and volume of blood transfused in the first 24 h predicted mortality at 6 weeks: c-statistic 0.80 (95% CI 0.70 to 0.90). MELD score was significantly associated with the risk of re-bleeding (HR=1.05 (95% CI 1.01 to 1.08), p=0.01) at 5days compared with patients with MELD <18)without endoscopic evidence of active bleeding, those patients with either a high MELD (>18) alone), or both high MELD (>18) and endoscopic evidence of active bleeding (HR=9.9 (95% CI 3.0 to 32.5), p,0.001) had a significantly	patients with a high MELD score (>18) are at increased risk of death within 6 weeks after an acute variceal bleeding episode and are also at increased risk of re-bleeding within the first 5 days. Additionally, the severity of the variceal bleeding episode, as indicated by the volume of blood transfusion required within the first 24 h, contributes additional prognostic value to the MELD score at 6 weeks.	

Supplementary material

							increased risk of death at 6 weeks Bivariable analysis demonstrated that both MELD and the presence of clot on a varix were predictive of re-bleeding within 5 days (HR for MELD=1.04 (95% CI 1.002 to 1.07), p=0.04; HR for clot on a varix=2.43 (95% CI 1.07 to 5.49), p=0.03).		
2010, Garcia-Pagan 4	To determine wether early treatment with TIPS, with the use of a stent covered with extended polytetrafluoroethylene (e-PTFE), can improve outcomes in patients with cirrhosis and variceal bleeding who are at high risk for treatment	High risk patients with cirrhosis (Child C<14, Child B plus active bleeding)	Randomization within 24h after admission One arm patients treated with current standard of care and the other arm patients treated with early TIPS that was placed within 72h from	Early TIPS placement vs standard of care	6 weeks survival, 1 year survival Failure to control bleeding /early rebleeding, new/worsening ascites, hepatic encephalopathy	RCT	The 1-year actuarial probability of remaining free of composite end point (failure to control bleeding/rebleeding) was 50% in the pharmacotherapy–EBL group versus 97% in the early-TIPS group (P<0.001) The 1-year actuarial survival was 61% in the pharmacotherapy–EBL group versus 86% in the early- TIPS group (P<0.001). The 1-year actuarial probability of HE was 28%	Patients with Child–Pugh class C disease or class B disease with active bleeding who were admitted for acute variceal bleeding, the early use of TIPS with an e-PTFE–covered stent was associated with significant reductions in the failure to control bleeding, in rebleeding, and in mortality, with no increase in the risk of hepatic encephalopathy	Good quality

Supplementary material

	failure and death		diagnostic endoscopy				in the early-TIPS group as compared with 40% in the pharmacotherapy–EBL group (an absolute difference of 12 percentage points; 95% CI, −18 to 40; P = 0.13) The 1-year actuarial probability of new or worsning ascites was 33% in the pharmacotherapy–EBL group and 13% in the early-TIPS group — an absolute difference of 20 percentage points (95% CI, −8 to 47; P = 0.11).		
2014, Al Freah et al 5	To identify the outcome of patients with AVB admitted to ICU To identify factors associated with mortality	Cirrhotic patients with uncontrolled bleeding requiring ICU		Comparison between different clinical scors CTP, MELD, SOFA, MSOFA, MNFO	6 week mortality Long term mortality Re-bleeding	Retrospective	MELD was a better predictor for hospital mortality than CTP (AUROC 0.84 vs 0.75) MELD score performed as well as APACHE II, SOFA and NFO (P < 0.001) in predicting HM (AUROC = 0.84, 0.81, 0.79 and 0.82, respectively P > 0.05 for pair wise comparisons).	MELD performance in predicting short term mortality was better than other liver prognostic models and comparable to ICU prognostic models Blood lactate also a predictive for mortality	More advanced disease

Supplementary material

							Patients with day-1 lactate >= 2 mmol/L had increased HM (P < 0.001).		
2014, Reverter E, et al 6	To improve risk prediction in AVB To validate a new MELD calibration in 2 external series of patients with AVB	Patients with cirrhosis and ABV	Standard of care treatment,	CHILD MELD D'Amico model	6-weeks mortality	Retrospective analysis of a prospective collected data	MELD model showed the best overall performance for predicting 6-Week Mortality MELD<=11-low risk patients MELD>19 high risk patients Variables reflecting the severity of bleeding, including a systolic arterial pressure less than 100 mm Hg within the first 3 hours from admission and active bleeding at endoscopy, did not significantly add to the predictive value of the MELD- based model (P=.25 and P = .55, respectively)	MELD offered an objective and accurate prognostic prediction with variables available early after admission. MELD could be more efficient than the current criteria for selecting high- risk patients who might benefit from more aggressive treatments	
2016, Motola-Kuba et al 7	To compare the scores for the MELD, MELD-Sodium, Child–Pugh, GBS, Rockall, and AIMS65	Cirrhotic patients with variceal bleeding	Standard of care- Endoscopy performed within 48 h	MELD vs Child-Pugh vs GBS vs Rockall vs AIMS65	Overall mortality Rebleeding during hospitalization	Retrospective, multicenter	MELD had the highest AUROC for predicting inhospital mortality (0.828; 95% CI 0.748-0.909; Hosmer-Lemeshow test P = 0.543),	The AIMS65 is particularly accurate for predicting in-hospital mortality in patients with cirrhosis	Exclusion of hcc and infection Outcomes not clear

Supplementary material

	systems to predict in-hospital mortality To compare the accuracy of these scoring systems for predicting rebleeding						and AIMS65 (0.817; 95% CI 0.724-0.909; Hosmer-Lemeshow test P = 0.851). The best cutoff values for predicting in-hospital mortality were MELD 13 (Se 95.2%, Sp 53.2%), and AIMS65 >= 1 point (Se 85.7%, 57%). The GBS has higher AUROC for predicting in-hospital rebleeding (0.756; 95% CI 0.640-0.827; Hosmer-Lemeshow test P = 0.218)	and acute variceal bleeding	Ai grija
2017, Fortune B et al 8	To determine predictors associated with 6-week mortality and 5-day treatment failure To compare the ability of CTP, MELD and recalibrated MELD scores in	Cirrhosis with acute variceal bleeding	Standard of care Endoscpy performed within 12h of presentation Exclusion of balloon tamponade treat, CTP>13, HCC difuse		6 weeks mortality 5 days treatment failure	Prospective, open-label RCT study	Only CTP (P=0.01) and MELD (P=0.004) remained as independent significant predictors of 6-week mortality Although the AUROC for MELD score (AUROC: 0.79; 95% confidence interval, 0.68-0.90) was greater than for the CTP score (AUROC: 0.75; 95% confidence interval, 0.63-0.87), the difference was	Child-Pugh score has the best overall performance in the prediction of 6-week mortality and is best at stratifying risk	high

Supplementary material

	predicting 6-week mortality						not statistically significant (P=0.27) Only CTP (P=0.03) and MELD (P=0.02) remained as independent significant predictors of 5-day treatment failure Agreement between observed and predicted risk of 6-week mortality was best for the CTP score (P=0.45, ie, there was no significant disagreement between observed and predicted), intermediate for the MELD score (P=0.02, ie, a significant disagreement between observed and predicted)		
2018, Conejo I et al 9	To evaluate the external validity of criteria for risk stratification in AVB (early-TIPS criteria, ChildC-C1, MELD19)	Cirrhosis with acute variceal bleeding	Standard of care	Early-TIPS high risk criteria vs Child-C1 and MELD >=19 criteria	6 weeks mortality	Retrospective analysis of prospectively collection of data Observational	active bleeding at initial endoscopy did not confer additional risk to Child-Pugh B patients (11.7% (9/77, 95 CI 4.5-18.9) vs. 11.7% (16/137, 95 CI 6.3-17.1, p=1.0). Child C with creatinine < 1 mg/d – high risk (21.5%,	active bleeding at endoscopy does not seem to add relevant prognostic information in Child-Pugh B patients. The patients can be conveniently stratified as low/intermediate/hig	

Supplementary material

	To evaluate the risk in Child-Pugh B patients with or without active bleeding					multicenter Prospective and retrospective collection of data	20/93, 95CI 13.2-29.9).fig 2 MELD ≥ 19 identified patients at high- risk under standard therapy. Below that threshold, using a MELD11 threshold allows the generation of three categories of risk similar to Child-Pugh class	h risk using either Child-Pugh classes or equivalent MELD categories	
2019, Lv Y 10	To assess the effects of early TIPS (compared with standard treatment) on the mortality, failure to control acute bleeding or rebleeding, new or worsening ascites and overt hepatic encephalopathy (OHE) among patients with cirrhosis and AVB who were stratified by	Cirrhosis with acute variceal bleeding	Early TIPS vs standard of care	MELD vs early TIPS criteria vs Child-Pugh C-C1 criteria	6 weeks mortality 1 year mortality Failure to control bleeding /rebleeding New/worsening ascites Hepatic Encephalopathy	Retrospective , multicenter observational	Survival: MELD<=11 no benefit (6 W, 1 Y)(p=0.393;p=0.362) MELD>=19 p-TIPS benefit (p=0.01; p=0.008) MELD 12-18 benefir 6W but not 1 Y (p=0.004;p=0.239) CP-C class benefit at 6 W(p=0.002) and 1Y(P=0.021) CP-B class-benefit at 6 W(P=0.002), but not at 1 Y(p=0.160) Benefit in CP-B with active bleeding (P=0.012) but not	The study supports the early use of TIPS in MELD ≥19 or Child-Pugh C patients who have a high risk of death with standard treatment but benefit the most from early TIPS. However, TIPS may not be necessary in MELD ≤11 or Child-Pugh A patients considering their low risk of death with standard treatment Although early TIPS may be a valuable option for MELD 12–18 or Child-Pugh B	

Supplementary material

	current available risk stratification systems						in CP-B without active bleeding(p=0.214) C-C1-criteria- benefit in the high-risk group (p=0.046)	patients, further studies are needed.	
2019 Rudler M et al 11	To identify the factors associated with 6-week mortality, focusing on the prognostic value of active bleeding at the time of endoscopy; To assess whether the recalibrated MELD based score accurately predicted 6-week mortality	Cirrhosis with acute variceal bleeding		Early TIPS criteria vs MELD recalibrated criteria	6 weeks mortality	Prospective observational multicenter	CP-B cirrhosis, independent factors associated with 6-week mortality: the presence of HE at the time of inclusion (OR 6.5, CI95% 2.7-15.5, P=.001), HCC(OR 7.4, CI95% 2.9-19,P=.001) and an ongoing infection at the time of inclusion (OR 3.5,CI95%1.01-12.5,P=.04). Active bleeding at the time of endoscopy was not an independent factor associated with 6-week mortality in the univariate analysis (HR = 1.034, 95% CI [0.201-5.331], P = .97). For prediction of 6 week mortality: c- index was 0.777 for the Child- Pugh	MELD- based score accurately predicted mortality HE is a factor of bad prognosis. Active bleeding at the time of endoscopy had no prognostic value, but hetero-geneity was high among the centres	

Supplementary material

							score, compared to 0.804 for the MELD score		
2020, Trebicka, J et al 12	To evaluate the prevalence of ACLF at admission in patients with AVB; To evaluate the influence of ACLF at admission on AVB outcomes (rebleeding and mortality); The impact of pTIPS on mortality of patients with ACLF and AVB.	Cirrhosis with acute variceal bleeding	Standard of care p-TIPS placement in high-risk patients		6 weeks and 1 year mortality rebleeding	Retrospective analysis of a prospective collection of data observational	Patients with ACLF had a higher rate of rebleeding compared to patients without ACLF (42-day: 19.1% vs. 10.1%, p<0.001; 1-year: 22.9% vs. 17.7%, p= 0.024). The risk of rebleeding increased in line with ACLF grade patients with ACLF had higher mortality than patients without ACLF (42-day: 47.1% vs. 10.0%; p<0.001, 1-year: 55.0% vs. 23.1%, p<0.001), The mortality increased in line with severity of ACLF pTIPS placement was independently associated with a lower 42-day rebleeding rate (HR 0.128; 95% CI 0.017–0.937; p= 0.043) in patients with ACLF	study confirms that ACLF is frequent in patients with AVB, that ACLF is an independent predictor of rebleeding and mortality, and that pTIPS could improve survival in patients with ACLF and AVB	

Supplementary material

							treatment with pTIPS in these patients reduced the risk of rebleeding due to ACLF Mortality was significantly lower in the pTIPS compared to the non-pTIPS group of patients with ACLF (42-day: 13.6% vs. 51.0%, p= 0.002; 1-year: 22.7% vs. 56.5%, p= 0.002). Treatment with pTIPS reduced 42-day (multivariate sHR 0.22; 95% CI 0.07–0.74; p= 0.014) and 1-year (multivariate sHR 0.33; 95% CI 0.12–0.92; p= 0.034) mortality after adjustment for confounders		
2021, Nicoara-Farcau O et al 13	To evaluate the efficacy of p-TIPS versus standard-of-care treatment	High risk patients with cirrhosis and acute variceal bleeding	Standard of care vs p-TIPS	Child Pugh C <13 p vs Child-Pugh B with active bleeding	6 week and 1 year survival	Individual patient data meta analysis	Survival benefit for p-TIPS over Drugs + Endo (HR=0.443, CI 95%: [0.323-0.607], p<0.001). This effect was observed in both Child B+AB (HR=0.524, CI 95%: [0.307–0.896], p=0.018)	p-TIPS placement in high risk patients (defined as CP-B+ AB > 7 points and CP- C <14 points) significantly improves	

Supplementary material

							and in CP-C patients (HR=0.374, CI 95%: [0.253-0.553], p<0.001) improved survival in CP-B+AB high risk category (CP-B+AB with a score of 8 and 9 points; Log rank p=0.0006; but not in patients with CP-B+AB of 7 points (CP-B+AB low risk group) (Log Rank p=0.68)	survival in comparison with standard of care	
2021, Lv Y et al 14	To test the hypothesis that risk stratification using CLIF-C ADs would effectively identify a group of patients with Child- Pugh B cirrhosis and AVB at higher risk of mortality or further bleeding who have the potential for	Patients with Child-Pugh B cirrhosis and acute variceal bleeding	Current standard of care	CLIF-C Ads vs active bleeding at endoscopy vs recalibrated MELD vs MELD, MELD-HE, and Child-Pugh	6 weeks and 1 year mortality composite endpoint of 6-week death or further bleeding	1 - observational study retrospectively analyzed the prospectively collected data of consecutive patients 2-RCT	The concordance index values of CLIF-C ADs for 6-week and 1-year mortality (0.715 and 0.708) were significantly better than those of active bleeding at endoscopy (0.633 [P < 0.001] and 0.556 [P < 0.001]) and other prognostic models patients were categorized as low risk (CLIF-C ADs <48), intermediate risk (CLIF-C ADs 48-56), and high risk (CLIF-C ADs >56), with a 5.6%, 16.8%, and 25.4% risk of 6-week death, respectively.	In patients with Child-Pugh B cirrhosis and AVB, risk stratification using CLIF-C ADs identifies a subgroup with high risk of death that may derive survival benefit from early TIPS With improved prediction accuracy for 6-week death or further bleeding, the data-driven nomogram may help to stratify patients in randomized trials	

Supplementary material

	benefit from early TIPS						The performance of CLIF-C ADs for predicting a composite endpoint was not satisfactory (AUC= 0.588). A nomogram incorporating components of CLIF-C Ads and albumin, platelet, active bleeding, and ascites significantly improved the prediction accuracy (AUC=0.725).		
Kim et al. 2021	Development a novel bedside risk-scoring model to predict the 6-week mortality in cirrhotic patients undergoing EBL for AVB	cirrhotic patients undergoing EBL for AVB derivation cohort n = 1373 validation cohort n = 200	Bedside risk-scoring model	Child-Turcotte-Pugh (CTP) and the model for end-stage liver disease scores in the validation cohort (n = 200).	predictive accuracy of the new model for the 6-week mortality in the validation cohort	Cox regression analysis was used to assess the relationship of clinical, biological, and endoscopic variables with the 6-week mortality risk after EBL	5 variables: use of beta-blockers, hepatocellular carcinoma, CTP class C, hypovolemic shock at initial presentation, and history of hepatic encephalopathy The score stratified the 6-week mortality risk in patients as low (3.5%), intermediate (21.1%), and high (53.4%) (P < 0.001). AUROC curve for 6-week mortality showed that this model was a better prognostic indicator than the CTP class alone in the derivation (P < 0.001) and	A simplified scoring model for prediction of 6-week mortality in high-risk cirrhotic patients, thereby aiding the targeting and individualization of treatment strategies for decreasing the mortality rate	No external validation

Supplementary material

							validation (P <0.001) cohorts		

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Huaringa-Marcelo 2021	To assess the efficacy and safety of terlipressin and vasopressin (T-V) versus octreotide and sandostatine (O-S) for the management of acute variceal bleeding	2,431 patients with acute variceal hemorrhage	Administration of T-V or O-S for acute variceal hemorrhage after endoscopic therapy	T-V or O-S	Main outcomes: Mortality and adverse events; Secondary outcomes: bleeding control, rebleeding, blood transfusion, hospital stay	Systematic review and metanalysis of 21 RCT's	Mortality, bleeding control rebleeding rate, blood transfusion, hospital stay were similar between T-V and O-S groups. Adverse events, significantly higher in the T-V compared to the O-S group	T-V and O-S with similar efficacy but higher adverse events for T-V than with O-S	Low to moderate
Zhou 2018	To examine the efficacy and safety of terlipressin for AVB in liver cirrhosis.	3344 patients	Terlipressin	No vasoactive drug Sandostatine and octreotide treatment Vasopressin treatment	Control of bleeding within 48 hours; in-hospital mortality; complications	Systematic review and metanalysis of 30 RCT's	Compared with no vasoactive drug, terlipressin significantly improved the control of bleeding within 48 hours (OR = 2.94, P = .0008) and decreased the in-hospital mortality (OR = 0.31, P = .008). Compared with somatostatin, terlipressin had a significantly higher risk of complications (OR = 2.44, P = .04).	Terlipressin is superior to no vasoactive treatment in control of variceal bleeding and in-hospital mortality Terlipressin has a higher complication rate compared	Low to moderate

Supplementary material

							Compared with octreotide, terlipressin had a significantly inferior control of bleeding within 24 hours (OR = 0.37, P = .007). Compared with vasopressin, terlipressin had a significantly lower risk of complications (OR = 0.15, P = .02).	with sandostatine Octreotide is superior to terlipressin in bleeding control within 24 hours Terlipressin has a lower risk of complications compared with vasopressin	
Yan 2018	To evaluate the efficacy and optimal duration of adjuvant vasoactive drugs	1074 patients after hemorrhage control by endoscopic therapy	Administration of a vasoactive drug after endoscopic therapy	No administration of a vasoactive drug 3-5 days vs. shorter duration	The primary outcomes were re-bleeding in 5 days after endoscopic therapy, 5 and 42-day mortality rate, and adverse effects.	Systematic review and metanalysis of 11 RCT's	The risk of re-bleeding after adjuvant vasoactive drugs therapy was significantly lower (RR 0.48, 95% CI 0.27–0.83, P=.07, I 2=62%): Marginal reduction of 5-day mortality No significant reduction of 42-day mortality; No difference between 3-5 day course and shorter duration.	After successful endoscopic therapy, vasoactive drugs significantly reduce the risk of re-bleeding within 5 days after hermorrhage; A 3- 5 day-course of treatment is not superior to a shorter duration	Moderate

Supplementary material

Jha 2018	To compare the efficacy of continuous infusion vs. intermittent boluses of terlipressin to control acute variceal bleeding (AVB)	86 patients with acute variceal bleeding	Continuous infusion vs. bolus infusion for 5 days following variceal ligation	4 mg for 24 hrs vs 1 mg every 6 hours	Rebleeding or death within 5 days	Prospective RCT, single-center	Lower rate of treatment failure (4.7%) for continuous administration as compared to bolus administration (20.7%) (p = 0.02); no difference in mortality	Continuous infusion of terlipressin may be more effective than intermittent infusion to prevent treatment failure in patients with variceal bleeding	Low to moderate
Rengasamy 2015	To evaluate the effect of combination therapy (octreotide and endoscopy), the exact duration of octreotide infusion, its cost-effectiveness, and the outcome in terms of rebleed and mortality.	Patients with acute variceal bleeding who underwent endoscopic therapy (n=62/58)	continuous octreotide infusion	2 days vs. 5 days of continuous octreotide infusion (50 µg/kg).	Early rebleeding (within 42 days of index bleed according to Baveno IV consensus guidelines), transfusion requirement, and mortality	RCT	Rebleeding 4.8% vs. 8.6% (P>0.05). Survival rates within 6 weeks were comparable (P>0.05).	Two days of octreotide infusion following endoscopic therapy is sufficient and as efficacious as 5 days of infusion	Low to moderate
Azam 2012	To assess whether terlipressin can be administered for a shorter period of time	130 patients	24-hour Terlipressin treatment after successful	24-hour vs. 72-hour	30-day rebleeding rate;	RCT	No difference between both groups	24-h course of terlipressin is as effective as a 72-h course when used as an adjunctive	Moderate

Supplementary material

			band ligation		30-mortality rate			therapy to successful EVBL	
Wells M et al. 2012	To determine whether the administration of vasoactive medications to adult patients with acute variceal bleeding reduces the risk of mortality	3111 patients with acute variceal bleeds	Comparison of intravenously administered vasoactive agents to placebo or routine medical management alone		Mortality Hemostasis Transfusion Requirements Hospital stay	Metanalysis of 30 RCT's	Significantly lower risk of 7-day mortality (RR 0.74; 95% CI 0.57–0.95; P = 0.02; I2 = 0%; moderate quality of evidence), significant improvement in haemostasis (RR 1.21, 95% CI 1.13–1.30; P < 0.001; I2 = 28%; very low quality of evidence), lower transfusion requirements (pooled mean difference −0.70 units of blood transfused, 95% CI −1.01 to −0.38; P < 0.001; I2 = 82%; moderate quality of evidence), shorter duration of hospitalisation (pooled mean difference −0.71 days; 95% CI −1.23 to −0.19; P = 0.007; I2 = 0%; low quality of evidence).	The use of vasoactive agents was associated with a significantly lower risk of acute all-cause mortality and transfusion requirements, and improved control of bleeding and shorter hospital stay. Studies comparing different vasoactive agents did not show a difference in efficacy, although the quality of	Low to moderate

Supplementary material

							Comparisons of terlipressin with somatostatin, terlipressin with vasopressin, octreotide with terlipressin and octreotide with somatostatin failed to demonstrate a significant difference for any of the outcome measures examined	evidence was very low.	
Ioannou GN, et al. 2003	To determine if treatment with terlipressin improves outcome in acute oesophageal variceal haemorrhage and is safe.	1609 patients.	Terlipressin vs. a. Placebo. b. Balloon tamponade. c. Endoscopic treatment (ligation or sclerotherapy). d. The other vasoactive drugs (somatostatin, octreotide, or vasopressin).		The primary outcome measure was mortality.	metanalysis of 20 RCT's	terlipressin was associated with a statistically significant reduction in all cause mortality compared to placebo (relative risk 0.66, 95% confidence interval 0.49 to 0.88).	On the basis of a 34% relative risk reduction in mortality, terlipressin should be considered to be effective in the treatment of acute variceal hemorrhage.	Low to moderate

Supplementary material

Bruha 2002	To compare the effectiveness of two-day administration of Terlipressin 0.2 mg i.v after 4-hour intervals, with the effectiveness of 5-day administration of 1 mg i.v. after 4-hour intervals	N 45/41 patients with acute variceal hemorrhage	1 mg Terlipressin every 4 hours	0.2 mg vs 1 mg Terlipressin	Bleeding control Transfusion necessity Adverse events	RCT, multi center	No difference in bleeding control; significantly less transfusion in higher dose group	Lower dose Terlipressin equally effective in bleeding control	Low
Corley DA, et al. 2001	to evaluate the safety and efficacy of octreotide for esophageal variceal hemorrhage.		Octreotide vs placebo Octreotide vs vaso/terlipressin		Primary outcome: mortality	Metaanalysis of 13 RCTs	Overall mortality at the end of follow-up was not decreased significantly by octreotide compared with alternative pharmacologic or mechanical interventions (i.e., sclerotherapy, band ligation, or balloon tamponade) (RR, 0.89; 95% confidence interval [CI], 0.7–1.14; Octreotide improved control of esophageal variceal hemorrhage compared with all alternative therapies combined (relative risk [RR],	No difference in mortality. Results favor octreotide over vasopressin/terlipressin in the control of esophageal variceal	Low to moderate

Supplementary material

							0.63; 95% confidence interval [CI],		

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results
Lee 2017	to evaluate the characteristics and clinical impact of ‘‘early’’ infections (developing within 14 days) of AVH in a real-world setting	multicenter retrospective data from a cohort of 371 adult patients with cirrhosis and AVH all of whom had received antibiotic prophylaxis	Antibiotic therapy	No Therapy	Breakthrough infections	Retrospective multicenter cohort study	14% of patients develop infection within 14 days despite antibiotic prophylaxis, with respiratory infections accounting for more than 50% of infections, and with a high proportion of culture-positive infections due to organisms resistant to the recommended FQ and Ceph3 antibiotics. Intubation and outpatient antibiotic prophylaxis are important risk factors for early infections with the presence of

Supplementary material

							ascites trending to significance. In addition to the MELD score, early infections contribute independently to six-week mortality
Lee 2016	To investigate the duration of antibiotic prophylaxis for cirrhotic patients with acute esophageal variceal bleeding.	38 patients in Group I and 33 patients in Group II	Ceftriaxone 500 mg i.v. every 12 hours	3 days vs 7 days	Primary: rebleeding rate within 14 days survival rate within 28 days amount of transfusion during admission	Prospective RCT	rebleeding within 14 days (8% vs. 9%, p > 0.99) transfusion amount (2.71 ± 2.84 units vs. 3.18 ± 4.07, p = 0.839) survival rate in 28 days (100 vs. 97%, p Z 0.465)
Agarwal 2015	To assess the role of antibiotic prophylaxis in the prevention of rebleeding in acute variceal hemorrhage.	30 patients in the prophylaxis group and 26 patients in the on-demand group	Administration of ofloxacine for 7 days after endoscopic therapy	Administration of ofloxacine only when infection was evident	rebleeding and infection during the hospital stay.	RCT	incidence of infection was 5/30 (16.7%) in the prophylaxis group and 7/26 (26.9%) in the on-demand group (P = 0.52) The incidence of early rebleeding in the prophylaxis

Supplementary material

							vs. the on-demand group was 3 vs. 5 (P = 0.69), and the incidence of late rebleeding was 6 vs. 8 (P = 0.48).
Chavez-Tapia 2011	To assess the benefits and harms of antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding by performing a systematic review of randomised trials	Twelve trials (1241 patients)	antibiotic prophylaxis	Prophylaxis vs. placebo or no prophylaxis	Overall mortality; mortality from bacterial infections; bacterial infections; rebleeding rate; hospital stay	Systematic review of randomized trials	reduced overall mortality (RR 0.79, 95% CI 0.63–0.98), reduced mortality from bacterial infections (RR 0.43, 95% CI 0.19–0.97), reduced bacterial infections (RR 0.35, 95% CI 0.26–0.47), reduced rebleeding (RR 0.53, 95% CI 0.38–0.74) and days of hospitalisation (MD)1.91, 95% CI)3.80–0.02)
Soares-Weiser 2003	to evaluate the efficacy of antibiotic prophylaxis in inpatients with cirrhosis	13 RCT	Antibiotic prophylaxis	Antibiotic prophylaxis vs placebo or no prophylaxis	Mortality Prevention of bacterial infections	Meta-analysis and systematic	significant beneficial effect on mortality (RR: 0.70; 95% CI: 0.56, 0.89) and

Supplementary material

						review of RCTs	prevention of bacterial infections (RR: 0.39; 95% CI: 0.32, 0.48) w
Fernandez 2006	to compare oral norfloxacin vs intravenous ceftriaxone in the prophylaxis of bacterial infection in cirrhotic patients with gastrointestinal bleeding	111 patients (n=57/54)	oral norfloxacin (400 mg twice daily; n 57) or intravenous ceftriaxone (1 g/day; n 54) for 7 days	Norfloxacin vs ceftriaxone	prevention of bacterial infections within 10 days after inclusion	RCT	infections, spontaneous bacteremia and spontaneous bacterial peritonitis were significantly higher in patients receiving norfloxacin (33% vs 11%, P .003; 26% vs 11%, P .03; and 12% vs 2%, P .03, respectively)
Higuera-de-la-Tijera 2018	to compare if primary prophylaxis with lactulose or L-ornithine L-aspartate or rifaximin, in cirrhotic patients with variceal bleeding, is better than placebo for avoiding the development of hepatic encephalopathy	87 patients	rifaximin (Flonorm) administered at a standard dose of 400 mg orally every 8 hours	Lactulose vs L-ornithine L-aspartate vs Placebo	development of hepatic encephalopathy	RCT	Placebo vs. rifaximin (54.5% versus 23.8%; OR = 0.3, 95% CI 0.07-0.9; P = 0.04)

Supplementary material

Hou 2004	To evaluate the efficacy of antibiotic prophylaxis in preventing rebleeding in patients with acute variceal hemorrhage	N= 59/61	Antibiotic prophylaxis with Ofloxacine	Ofloxacin 200 mg i.v. q12h for 2 days followed by oral ofloxacin 200 mg q12h for 5 days) or receive antibiotics only when infection became evident (on-demand group).	Rebleeding rate Bacteria Infections Blood transfusions	RCT	The probability of rebleeding was higher in patients without prophylactic antibiotics (P = .0029)
Conejo 2013 (AASLD Abstract)	To investigate the effect of iv ceftriaxone compared to oral norfloxacine in patients after endoscopic treatment of acute variceal bleeding	N= 108 norfloxacine /107 ceftriaxone	Ceftriaxon for 7 days vs norfloxacine oral for 7 days	Ceftriaxon for 7 days vs norfloxacine oral	Bacterial infections	Retrospective	significantly less infections for ceftriaxone (15.5% vs. 5.5%, p=0.029)
Te-Sheng Chang 2020	To evaluate the need for antibiotic prophylaxis in patients with low Child-Pugh scores (Child A/B)	913 patients (N=840/73)	Antibiotic prophylaxis	Prophylaxis vs. no prophylaxis or on demand	Bacterial infection; Rebleeding; Mortality	Retrospective study	In patients with Child A/B cirrhosis, antibiotic prophylaxis did not reduce the risks of 14-day bacterial infection (relative risk [RR]: 0.932, 95% CI:

Supplementary material

							0.300–2.891, P = 0.902), 14-day rebleeding (RR: 0.791, 95% CI: 0.287–2.181, P = 0.650), or 42-day mortality (RR: 2.710, 95% CI: 0.769–9.524, P = 0.121)
Martínez 2021	To examine the incidence of, and risk factors for, bacterial infections during hospitalization in patients with AVB on antibiotic prophylaxis	1,656 patients	third-generation cephalosporins (76.2%) and quinolones (19.0%)			post hoc analysis of the database of an international, multicenter, observational study	19.3%, 95% CI 16.6%–20.6%) of the 1,656 patients with antibiotic prophylaxis developed bacterial infection; Bacterial infection emerged as a predictor of mortality in the univariate (hazard ratio [HR] 1.7; 95% CI 1.3–2.3) but not in the multivariate analysis Independent

Supplementary material

							factors related to 6-week mortality in the multivariate analysis were age (HR 1.1; 95% CI 1.1–1.2), Child-Pugh B (HR 2.2; 95% CI 1.1–4.4), Child-Pugh C (HR 7.6; 95% CI 3.8–15.1), active bleeding on endoscopy (HR 1.5; 95% CI 1.2–2.0), and shock on admission (HR 2.1; 95% CI 1.6–2.7) ; Forty-six and thirty-six out of the 78 isolates were resistant to TGC (59.0%), and to quinolones (46.2%), respectively.
Wu 2013	This study aimed to compare the outcome of intravenous cefazolin and ceftriaxone as prophylactic antibiotics among cirrhotic patients at different clinical	713 patients with acute variceal bleeding and after	i.v. Cefazoline vs Ceftriaxone	i.v. Cefazoline vs Ceftriaxone	Prevention of infection, time of rebleeding, and death	Prospective cohort study	No difference among Child's A patients (93.1% vs. 90.9%, p = 0.641

Supplementary material

	stages, and to identify the associated risk factors.	endoscopic procedures					A trend of significance in favor of ceftriaxone prophylaxis (77.8% vs. 87.5%, p = 0.072) was seen among Child's B and C patients More rebleeding cases were observed in patients who received cefazolin than in those who received ceftriaxone among Child's B and C patients (66.7% vs. 25.0%, p = 0.011) but not in Child's A patients (32% vs. 40.9%, p = 0.376)

Supplementary material

Author, publication year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Alexandrino *et al.*, 2019[1]	Compare results of very early and early endoscopy (12-24 h) in patients with upper GI bleeding demonstrating low-risk versus high-risk features and nonvariceal versus variceal bleeding	n=25 variceal bleeding patients who underwent urgent endoscopy n=17/25 very early endoscopy n=8/25 early endoscopy	Very early endoscopy (12 hours or less)	Early (12-24 h) endoscopy	Primary: Inpatient death Inpatient rebleeding Surgical intervention ICU admission Secondary: Endoscopic intervention Need for blood transfusion Mean time of hospital stay (days) Primary composite outcome: death, bleeding recurrence, and need for surgery or ICU admission during hospital stay	Retrospective study	Inpatient death 8% Inpatient rebleeding 24% Surgical intervention 0% ICU admission 12% Endoscopic intervention 84% Blood transfusion 88% Mean time of hospital stay (days) 9+/-5.4 Analysis of endoscopy timing on composite outcome: OR (95% CI) 0.188 (0.014-2.468) with p=0.231	Timing of endoscopy was not an important predictor in patients with variceal bleeding

Supplementary material

Abdulrahman *et al.,* 2013[2]	Patients with suspected GI bleeding from Nov 2007 to Jan 2013	n=79/1766 variceal bleeding patients	Endoscopy within 15 hours	Endoscopy not within 15 hours	Mortality Correlation between time to endoscopy (TTE) and full rockall score, pre-endoscopy Rockall Score, Glasgow Blatchford score	Prospective study	Mortality similar in patients who receive endoscopy within 15 hr (8/62) compared to those who did not (1/17) p=0.675 Inverse correlation between TTE and full rockall score p<0.001 and pre-endoscopy rockall score p<0.001 GBS p=0.011 Mortality significantly inc. only with patients	Time to endoscopy didn't affect mortality in patients with variceal bleeding but it is influenced by patients condition. Patient's with more severe disease or bleeding receive endoscopy sooner.

Supplementary material

							with Child Pugh Class C	
Chen *et al.*, 2012[3]	Patients with active EVB proven by endoscopy	n=101 cirrhotic patient with active EVB n=73 with hematemesis vs. non-hematemesis group	Early endoscopy (12 hr or less)	Delayed endoscopy (> 12 h)	6 week rebleeding Mortality	Cohort study	Hematemsis group: Re-bleeding rate lower in early endoscopy patients (18.9%) vs. delayed endoscopy (38.9%) p=0.994 No difference in rebleeding rate in non-hematemesis group Mortality lower in hematemesis group who underwent early endoscopy (27%) than delayed endoscopy (52.8%) p=0.031	Early endoscopy 12 hr or less is associated with better outcome in hematemesis patients

Supplementary material

Cheung *et al.*, 2009[4]	**Hemodynamically stable** AVB patients	n=210 patients with stable AVB n=191 of esophageal varices of variceal bleeding	Urgency times: 4 hrs or less 8 hrs or less 12 hrs or less	More than 4 hours More than 8 hours More than 12 hours	Primary outcome: mortality Other outcomes: - Stigmata at endoscopy - Hemostasis - Blood transfusions - Rebleeding - Renal function - Hospitalization length - Infection - TIPS - Balloon tamponade use	Retrospective study	Number of bands used for ligation was sig. higher in patients receiving endoscopy within 4 hours as compared to those receiving endoscopy after (p=0.03). No sig. difference in the variceal bleeding outcomes by different endoscopy urgency No sig. association btw time to endoscopy and mortality (p=0.91)	For hemodynamically stable variceal bleeding patients, time to endoscopy doesn't not appear to be associated with mortality

Supplementary material

Cho *et al.*, 2018[5]	Patients with esophageal variceal bleeding	n=173 endoscopy within 12 hours n=101 endoscopy after 12 hours	Endoscopy within 12 hours of admission	Endoscopy after 12 hours of admission	- 6 week mortality after variceal bleeding - Hospital admission duration - In-hospital mortality - Re-bleeding rates - Liver transplantation	Retrospective study	6-wk mortality rate was 22.5% in urgent endoscopy group and 29.7% in non-urgent endoscopy group (p=0.266) Median hospital admission duration similar but significant differences in mean rank score (non-urgent group were more right skewed) No different in the in-hospital mortality rate btw the group Re-bleeding within 6 wks was 10.4% in urgent group and 12.9% in non-urgent group (p=0.558)	No significant differences in short-term outcomes between the groups

Supplementary material

Hanafy, 2021[6]	Patients presenting with acute UGIB	n=200 (100 in each group)	Endoscopy within 6 hours	Control group prepared for 24 hours	- Death - ICU stay - Survival correlation with markers	-	Death occurred in control group despite stabilization 10% p=0/000 and longer ICU stay vs 4% death in urgent endoscopy D-dimer, serum lactate, pro-calcitonin, GBS were associated with reduced survival if endoscopy was delayed (OR 2.1) Cutoff values: Serum lactate: 3.6 mmol/l D dimer: 350 Procalcitonin 3.8 ng/ml GBS: 14	Decision for urgent endoscopy was guided by markers such as serum lactate, procalcitonin, D dimer and GBS.

Supplementary material

Hsu *et al.*, 2009[7]	Cirrhotic patients with acute variceal hemorrhage	N=311 cirrhotic patients with acute variceal hemorrhage	Endoscopy before 15 h of admission	Delayed endoscopy – after 15 h of admission	- In-hospital mortality - Failure of first endoscopy (rescue hemostatic procedure after index EGD including another session of endoscopy, TIPS, esophageal balloon tamponade)	- Retrospective study	- In-hospital mortality was 25 patients (8.04%) - Delayed endoscopy was significantly associated with mortality (aOR=3.67) - Differences in the severity indexes (MELD score, Child-Pugh score, vital signs, prognostic score and infection were found btw groups	Delayed endoscopy is associated with inc. risk of in-hospital morality. Other risk factors for mortality include higher MELD score, hematemesis and failure of the first endoscopy.

Supplementary material

Jung *et al.*, 2019[8]	Patients with acute variceal bleeding	Five studies with n=843 urgent endoscopy patients and n=453 non-urgent endoscopy patients	Urgent endoscopy (12 h or less)	Non-urgent endoscopy (> 12 h)	- Mortality - Rebleeding rates - Successful hemostasis - Need for salvage therapy - Length of hospital stay - Number of blood transfusions	- Systematic review and meta-analysis *all studies included are retrospective studies	Pooled analysis showed overall mortality was similar between urgent and non-urgent groups (OR 0.72, p = 0.36). Rebleeding rates was similar between the groups (OR 1.21, p=0.41) Other outcomes were also similar. *High heterogeneity between the studies	No differences in the severity indexes were found between both groups. No significant difference in overall mortality rate btw the groups. Rebleeding was similar between the groups. <u>Endoscopy timing does not affect the mortality or rebleeding rate of patients with AVB.</u>

Supplementary material

Yoo *et al.* 2018[9]	Patients with acute esophageal variceal bleeding	n=172 urgent endoscopy n=101 non-urgent endoscopy	Urgent endoscopy (12 h or less)	Non-urgent endoscopy (> 12 h)	- 6 week mortality - Length of hospital stay	- Retrospective study	6 week mortality was 22.5% in the urgent endoscopy group and 129.7% in the non-urgent endoscopy group (p=0.266) Length of hospital stay was statistically different between groups (p=0.033) No significant different in the in-hospital mortality rate between the two groups (8.1% vs. 7.9%, p=0.960) Multivariate analysis: timing of endoscopy was not associated with 6 wk mortality	In cirrhotic patients with acute variceal bleeding, the timing of endoscopy may be independent of short-term mortality

Supplementary material

Huh *et al.*, 2019[10]	Cirrhotic patients with acute variceal bleeding	n=317 urgent endoscopy n=94 non-urgent endoscopy	Urgent endoscopy (12 h or less)	Non-urgent endoscopy (> 12 h)	- Primary outcome (composite of 6 week rebleeding and mortality) - Successful endoscopic hemostasis - Need for salvage therapy (balloon tamponade, additional endoscopic therapy, TIPS, - length of hospital sta - blood transfusion - number of endoscopies performed during	- Retrospective study	Patients who underwent urgent endoscopy (34.4%) had a significantly higher composite outcome than patients who underwent non-urgent endoscopy(19.1%) (p=0.005) Need for salvager therapy was 14.8% vs. 8.5% p=0.114. Number of transfusions per patient (4.4 vs. 3.1, p=0.004) Number of endoscopies performed during hospitalization (1.6 vs. 1.2, p<0.001).	Urgent endoscopy was significantly associated with poorer outcome in low-risk patients and endoscopy timing was not associated with outcome in the high-risk patients. Worsened prognosis include severity of liver disease (MELD or child-pugh score), shock at the time of hospital admission, infection and hepatocellular carcinoma

Supplementary material

					hospitalization Primary composite outcome was 6-week rebleeding and mortality		Length of hospital stay was not different between the groups. Significant predictors of composite outcome included time to endoscopy, older age, infection, low systolic blood pressure, higher MELD score, and observation without endoscopic therapy. MELD score of 17 was the optimal cut off value for predicting the composite outcome.	

Supplementary material

Laursen *et al.*, 2019**[12] Only abstract published	Patients with variceal bleeding	n-1,373 patients	Endoscopy within 24 hours from time of admission	Endoscopy after 24 hours from time of admission	- 42 day mortality	- Multi-center prospective study	Endoscopy within 24 hr of admission was associated with lower mortality in patients with Child-Pugh A or B cirrhosis (OR= 0.38, p=.020). and patients with SBP < 90 mmHg (OR = 0.053, p-0.11).	Performance of endoscopy within 24 hours is associated with reduced 42-day mortality in patients with Child-Pugh A or B cirrhosis and in those with SBP < 90 mmHg.
Mousa *et al.*, 2021[13]	Patients with acute esophageal variceal hemorrhage	n-297 n=180 within 12 h of admission n=117 within 12-24 h of admission	Endoscopy within 12 h of admission	Endoscopy within 12-24 h of admission	- eGFR - Arterial ammonia - Post-endoscopy hospital stay	- Prospective obser	- Endoscopy within 12 h produced greater fall in ammonia (p<0.001), an improved encephalopathy grade (p=0.048) and shorter hospital stay - Renal function significantly improved in both groups	Endoscopic management of AVB within 12 h of admission is superior to endoscopic management at 12-24 h of admission regarding reduction of hospital stay, ammonia levels, correction of hepatic encephalopathy, re-bleeding and mortality rate.

Supplementary material

						vation al study	compared to pre-treatment levels but not between groups. - No significant difference btw groups as regard blood transfusion or infection - Reduction of arterial ammonia levels was more significant in early endoscopic treated group	

Supplementary material

Samani *et al.*, 2019[14] Only abstract published	Patients with upper gastrointestinal variceal hemorrhage	n=53	Timing of endoscopy: acute (0-12 h)	Early endoscopy (12-24 h) and delayed endoscopy (>24 h)	- 30 day mortality	- Retrospective study	- Mortality rates in acute endoscopy group was 5.6% , 19% in early endoscpy and 21.4% in delayed endoscopy. No association between different groups and 30 day mortality (acute vs. early p-0.3849, acute vs delay p-0.3777)	Mortality rate was lowest in the acute endoscopy group but there was no significant association between timing of endoscopy and 30 day mortality
Sousa *et al.*, 2018[15] Abstract	Patients presenting in the emergency department for variceal bleeding	n=60 patients Very urgent endoscopy in 55% of patients	Very Urgent endoscopy with 6 hours	Endoscopy after 6 hours	- Bleeding recurrence rate - Mortality at 6 weeks - Mortality at 1 year Secondary outcomes:	- Retrospective study	Bleeding recurrence rate was 25% Mortality at 6 weeks was 10% Mortality at 1 year was 44%	No statistically significant relationship between the 3 outcomes and endoscopy timings. None of secondary outcomes were related to endoscopy timing.

Supplementary material

					- Endoscopic hemostasis - Need for blood transfusion - Admission to ICU			
Bai *et al.,* 2021[16]	Cirrhotic patients with AVB	Nine studies with n=2824 patients	Early endoscopy (<12 h)	Delayed endoscopy (> 12 h)	- Overall mortality - In-hospital mortality - 6 week mortality - Overall rebleeding - In-hospital rebleeding - 6 week rebleeding - Length of stay - Endoscopic hemostasis	- Systematic review with meta-analysis	Overall mortality was significantly lower in early endoscopy group than delayed endoscopy group (OR=0.56, P=0.03) Non-significant different in in-hospital mortality, 6-week mortality, overall rebleeding, in-hospital rebleeding, six-week rebleeding, length of stay, endoscopic hemostasis, need for salvage therapy	Early endoscopy may improve the survival of cirrhotic patients with AVB but has no remarkable benefit on the prevention of rebleeding

Supplementary material

					- Need for salvage therapy - Units of transfusion -		and units of transfusion	
Tapper *et al.*, 2018[17]	Patients with acute variceal hemorrhage	n=239 *n=198 who survived index admission	Endoscopy within 12 h	Endoscopy not within 12 h	- 6 week mortality - Treatment failure (as defined by Baveno recommendations)	- Retrospective cohort study	Endoscopy within 12 h group vs. endoscopy not within 12 h group: - *6 wk mortality 6.3% vs. 7.5% (p=0.73) - Length of stay median 3.3-8.6 days vs. 3.6-8.6 days (p=0.81) - *30 day readmission 19% vs.	No association between adherence to timely endoscopy (within 12 hours) and 6 week mortality

Supplementary material

							27.5% (p=0.28) - Treatment failure 20.8% vs. 20.8% (p=1.00)	
Zhang *et al.*, 2020[18] Abstract	Cirrhotic patients with acute variceal bleeding	n=2388 patients in urgent endoscopy group n=950 in urgent endoscopy group	Urgent endoscopy (< 6 h after admission)	Early endoscopy (> 6 h after admission)	- Incidence of 5-day rebleeding after endoscopy management	-	5-day rebleeding was 3.77% in urgent endoscopy group vs. 2.95% in early endoscopy group (p=0.25) Among the patients with re-bleeding the difference was non-significant (p=0.19)	Timing of endoscopy <6 h or > 6 h may not be associated with the incidence of rebleeding within 5 days among cirrhotic patients with AVB

Supplementary material

Paper (copy paste from covidence)	Authors	Design	Patient group	no of patients	Main outcome measure	Key results	Conclusion	Limitations
Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients	SK Sarin, D Lahoti, SP Saxena, NS Murthy, UK Makwana	Prospective cohort	Portal hypertensive patients	568 of which 114 had gastric varices	Incidence of gastric varices and destribution according to Sarin classification	GOV1 represented 74.6% of gastric varices, GOV2 15.8%, IGV1 7.9%, IGV2 19.2%)	The classification estimates the incidence of gastric varices. Bleeding associated with IGV varices is more severe and has lower rates of treatment success	no control group, no other clafficination, non-interventional

Supplementary material

Randomized controlled trial of scleroligation versus band ligation alone for eradication of gastroesophageal varices.	Mansour, Loai; El-Kalla, Ferial; El-Bassat, Hanan; Abd-Elsalam, Sherief; El-Bedewy, Mohamed; Kobtan, Abdelrahman; Badawi, Rehab; Elhendawy, Mohamed	RCT	Cirrotic patients with bleeding from GO1 og GOV2	120	Unclear, but sessions to complete variceal obliteration obliteration	Scleroligation group required less sessions 3.4 vs 2.2	Scleroligation appears to achieve a faster rate of eradication, with fewer treatment sessions and total number of bands deployed to achieve variceal obliteration than band ligation and is comparable in cost, adverse event rate, and recurrence rate	No power estimated og clear primary endpoint. Only GOV1 and GOV2

Supplementary material

Factors influencing clinical outcomes of HistoacrylÂ® glue injection-treated gastric variceal hemorrhage	Prachayakul, V.; Aswakul, P.; Chantarojanasiri, T.; Leelakusolvong, S.	Retrospective cohort	Active gastric variceal bleeding	90	Factors influencing clinical outcomes of Histoacryl® glue injection	No differences in relation to GOV/IGV type	Patients with compromised liver, including ascites, have a higher risk of re-bleeding.	Retrospective, no-control group

Supplementary material

Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension.	Rios Castellanos, Eddy; Seron, Pamela; Gisbert, Javier P; Bonfill Cosp, Xavier	Meta-analysis	Bleeding gastric varices in patients with portal hypertensio n	366	Preventing re-bleeding from gastric varices	There was low quality evidence forthe prevention ofre-bleeding (RR 0.60; 95% CI 0.41 to 0.88).	This review suggests that endoscopic sclerothera py using cyanoacryl ate may be more effective than endoscopic band ligation in terms of preventing re-bleeding from gastric varices. Band ligation could still be a viable treatment, particularly in GOV1 type varices	Large risk of bias. Uncertain about our estimates on all-cause and bleeding-related mortality, failure of interventio n, adverse events, and control of bleeding

Supplementary material

Analysis of prognostic factors in patients with gastric varices after endoscopic treatment.	Wakatsuki, Takeru; Obara, Katsutoshi; Irisawa, Atsushi; Sakamoto, Hiroaki; Kuwana, Toshimitu; Takiguchi, Fujio; Saito, Ayako; Shishido, Hideo; Hikichi, Takuto; Oyama, Hitoshi; Shibukawa, Goro; Takagi, Tadayuki; Yamamoto, Go; Imamura, Hidemichi; Takahashi, Yuta; Sato, Ai; Sato, Masaki; Kasukawa, Reiji; Ohira, Hiromasa	Retrospective cohort	Active gastric variceal bleeding	115	Factors influencing clinical outcomes of Histoacryl® / sclerosant treatment	No relation to varix type	Grade B or C in Child–Pugh classification, emergency or elective situation, and association with hepatocellular carcinoma are negative prognostic factors after endoscopic treatment.	Retrospective, no-control group, dos not apply Sarin

Supplementary material

Primary prophylaxis of gastric variceal bleed comparing cyanoacrylate injection and beta-blockers	Mishra, S.R.; Sharma, B.; Kumar, A.; Sarin, S.K.	RCT	Primary prophylaxis of gastric variceal bleeding. Only GOV1 and IGV2	89	3 study arms, NSBB, no tratment, histoacryl	Primary end-points were bleeding from gastric varix or death.	Primary prophylaxis is recommended in patients with large and high risk gastric varices to reduce the risk of first bleeding and mortality	primary prophylaxis. Only GOV1 and IGV2

Supplementary material

Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial.	Mishra, Smruti Ranjan; Chander Sharma, Barjesh; Kumar, Ashish; Sarin, Shiv Kumar	RCT	Patients with gastro-oesophageal varices type 2 (GOV2) with eradicated oesophageal varices or isolated gastric varices type 1 (IGV1) who had bled from gastric varices	67	Primary end points were gastric variceal rebleeding or death	The probability of gastric variceal rebleeding rate in the cyanoacrylate group was significantly lower than in the b-blocker group (15% vs 55%, p¼0.004) and the mortality rate was lower (3% vs 25%, p¼0.026) during a median follow-up of 26 month	Cyanoacrylate injection is more effective than b-blocker treatment for the prevention of gastric variceal rebleeding and improving survival.	Only GOV2 and IGV1

Supplementary material

Safety and efficacy of endoscopic cyanoacrylate injection in the management of gastric varices: A systematic review and meta-analysis	Chirapongsathorn, S.; Manatsathit, W.; Farrell, A.; Suksamai, A.	Meta-analysis	Patients treated for gastric varices	583	effect of endoscopic cyanoacrylate injection in the management of gastric varices.	meta-analysis demonstrated that overall cyanoacrylate injection resulted in lowered mortality rate compared with other treatment modalities for GV. Furthermore, cyanoacrylate also resulted in significantly lowered rate of bleeding after hemostasis compared with both propranolol, ethanolamine oleate injection, and band ligation. A	The use of endoscopic cyanoacrylate injection therapy for gastric varices may be associated with lower all-cause mortality and better hemostasis compared with other therapies.	Our study was unable to adequately compare cyanoacrylate with other sclerosing agents due to the lack of data for meaningful analysis.

Supplementary material

Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis.	Mohan, Babu P; Chandan, Saurabh; Khan, Shahab R; Kassab, Lena L; Trakroo, Sushruth; Ponnada, Suresh; Asokkumar, Ravishankar; Adler, Douglas G		Patients treated for gastric varices	851	Primary goals were to estimate the pooled rates of treatment efficacy, obliteration and recurrence of gastric varices, early and late rebleeding, and adverse events with EUS-guided therapy in gastric varices	The pooled treatment efficacy was 93.7 % (95 % confidence interval [CI] 89.5 – 96.3, I 2 = 53.7), gastric varices obliteration was 84.4 % (95 %CI 74.8 – 90.9, I 2 = 77), gastric varices recurrence was 9.1 % (95 %CI 5.2 – 15.7, I 2 = 32), early rebleeding was 7.0 % (95 %CI 4.6 – 10.7, I 2 = 0), and late rebleeding was 11.6 % (95 %CI 8.8 – 15.1, I 2 = 22). The rates were comparable to END-glue	EUS-guided therapy demonstrated clinical efficacy for treatment of gastric varices in terms of obliteration, recurrence, and long-term rebleeding, and may be superior to END-glue.	NON-RCT included. Endoscopic group extracted from other studies

Supplementary material

						therapy (28 studies, 3467 patients) except for obliteration, which was significantly better with EUS-guided therapy		

Supplementary material

Cyanoacrylate Injection Versus Band Ligation in the Endoscopic Management of Acute Gastric Variceal Bleeding: Meta-Analysis of Randomized, Controlled Studies Based on the PRISMA Statement.	Qiao, Weiguang; Ren, Yutang; Bai, Yang; Liu, Side; Zhang, Qiang; Zhi, Fachao	Meta-analysis	Active gastric variceal bleeding	194	active bleeding control, blood transfusion, rebleeding, recurrence of varices, complications, and survival of glue vs band	Active bleeding control was achieved in 46 of 49 (93.9%) patients in the cyanoacrylate injection group, compared with 35 of 44 (79.5%) in the band ligation group (P¼ 0.032), for a pooled odds ratio of 4.44 (95% confidence interval, 1.14–17.30). Rebleeding rate was comparable in type 2 gastroesophageal varices (GOV2) between the 2 interventions	Compared with band ligation, injection cyanocrylate have an advantage in the control of acute gastric variceal bleeding, also with lower recurrence rate and rebleeding (except GOV2).	Only 3 RCTs

Supplementary material

						(35.7% vs 34.8%, P¼ 0.895), but cyanoacrylate injection seemed superior for reducing rebleeding rate in type 1 gastroesophageal varices (GOV1, 26.1% vs 47.7%, P ¼ 0.035) and type 1 isolated gastric varices (IGV1, 17.6% vs 85.7%, P ¼ 0.015). Cyanoacrylate injection was also superior in controlling recurrence of gastric varices to band ligation (36.0% vs		

Supplementary material

						66.0%, P¼ 0.002).		

Supplementary material

Cyanoacrylate glue versus band ligation for acute gastric variceal hemorrhage - A randomized controlled trial at services hospital, Lahore	Hassan, I.; Siddique, A.; Azhar, M.I.	RCT	e treatment of bleeding gastric varices (GVH).	60	Glue vs band. initial hemostasis which was defined as cessation of bleeding for more than 72 hours	Initial hemostasis was achieved in 24 patients in group I (80%) and all 30 patients in group II (100%).The difference was statistically significant (p value =0.03).	Cyanoacrylate glue injection is superior to EVL for achieving hemostasis and preventing recurrence of gastric variceal rebleeding but has no advantage over GVL for mortality and complications	NO classification of varix (Sarin), no prestudy publication of protocol

Supplementary material

A retrospective comparative study of histoacryl injection and banding ligation in the treatment of acute type 1 gastric variceal hemorrhage.	Lo, Gin-Ho; Lin, Chih-Wen; Perng, Daw-Shyong; Chang, Chi-Yang; Lee, Ching-Tai; Hsu, Chuan-Yuan; Wang, Huay-Min; Lin, Hui-Chen	Retrospective cohort	acute hemorrhage from GOV1	162	hemostasis, rebleeding, complications and mortality within 42 days	Hemostasis of active bleeding was achieved in 49 of 55 patients (89%) in the Glue group and 24 of 28 patients (85%) in the EVL group (p = 0.70).	Banding ligation was similar to glue injection in achieving successful hemostasis of acute bleeding from GOV1. However, a higher incidence of posttreatment ulcer bleeding and mortality may be associated with banding ligation.	retrospective, selection bias

Supplementary material

A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices.	Lo, G H; Lai, K H; Cheng, J S; Chen, M H; Chiang, H T	RCT	Cirrhotic patients with a history of gastric variceal bleeding	60	acute hemostatic rate of GVO	87% in glue and 45% in band ligation (P 5 .03). Rebleeding from gastric varices occurred in 9 patients (31%) in the GVO group and 14 patients (54%) in the GVL group. M	In conclusion, endoscopic obturation using cyanoacrylate proved more effective and safer than band ligation in the management of bleeding gastric varices	45% in EVLn is really low. The study was terminated.

Supplementary material

A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation.	Tan, Pen-Chung; Hou, Ming-Chih; Lin, Han-Chieh; Liu, Tsu-Te; Lee, Fa-Yauh; Chang, Full-Young; Lee, Shou-Dong	RCT	Liver patients with cirrhosis with or without concomitant hepatocellular carcinoma (HCC) and patients presenting with acute GVH were randomized into two treatment groups	97	Hemostasis and rebleeding	Both treatments were equally successful in controlling active bleeding (14/15 vs. 14/15, P 1.000). More of the patients who underwent GVL had GV rebleeding (GVL vs. GVO, 21/48 vs. 11/49; P .044)	The efficacy of GVL to control active GVH appears not different to GVO. However, the GV rebleeding rate was lower in those treated with GVO than in GVL.	Might be underpowered, no prestudy publication of protocol

Supplementary material

A randomized trial of endoscopic variceal ligation versus cyanoacrylate injection for treatment of bleeding junctional varices.	El Amin, H; Abdel Baky, L; Sayed, Z; Abdel Mohsen, E; Eid, K; Fouad, Y; El Khayat, H	RCT	bleeding junctional varices were included in the study. Only GOV1	150	Hemostasis and rebleeding	Control of active variceal bleeding was achieved in 61 patients (81%) in EVL and in 68 patients (91%) in glue with no significant difference (p =0.07). Re-bleeding was seen in 12 patients (16%) in EVL and 5 patients in glue (6%)	In summary, esophageal variceal ligation of bleeding junctional varices may be as effective as cyanoacrylate injection along with an advantage of lower complication rate in control of bleeding junctional varices. Although the re-bleeding rate was more in EVL group than cyanoacrylate group it was	Only GOV1

Supplementary material

							easily managed.	
Paper (copy paste from covidence)	Authors - Year of publication	Design	Patient group	no of patients	Main outcome measure	Key results		

Supplementary material

Safety and Efficacy of Thrombin for Bleeding Gastric Varices: A Systematic Review and Meta-Analysis	A Bhurwal, M Makar, A Patel, H Mutneja, A Goel, M Bartel, H Shahid, M Gjeorgjievski, Vinod Rustgi, Avik Sarkar - 2021	Systematic review and meta-analysis	Patients with GV bleeding. Human Thrombin was injected in 6 studies, bovine thrombin in 3 studies and a combination of thrombin and fibrin in 2 studies.	11 studies were included in the analysis with a total of 222 patients. Two randomized clinical trials, one prospective study and 8 retrospective studies.	Pooled early and late rebleeding rate, pooled gastric variceal related mortality rate, pooled rescue therapy rate, and pooled adverse event rate with the use of thrombin in bleeding gastric varices.	Pooled early rebleeding rate of 9.3% (95% CI 4.9–17) and late rebleeding rate 13.8% (95% CI 9–20.4). Pooled rescue therapy rate was 10.1% (95% CI 6.1–16.3). The pooled 6-week gastric variceal-related mortality rate was 7.6% (95% CI 4.5–12.5). A total of 4 adverse events in 222 patients with pooled adverse event rate

Supplementary material

						of 5.6% (95% CI 2.9–10.6).
A prospective, randomized trial of thrombin versus cyanoacrylate injection in the control of acute gastric variceal hemorrhage	GH Lo, CW Lin, CM Tai, DS Perng, IL Chen, JH Yeh, HC Lin - 2020	RCT	Acute GV Bleeding	68 patients were randomized to thrombin injection (33 patients) or glue injection (35 patients)	The primary end point was injection-induced gastric ulcers. Secondary end points were acute hemostasis, rebleeding, and	Treatment failure at 5 days in 2 patients (6.1 %) in the thrombin group and 2 patients (5.7 %) in the glue group (P > 0.99). Gastric ulcers

Supplementary material

					mortality within 42 days.	occurred in none of the thrombin group and 11/30 (36.7%) of the glue group (P < 0.001, 95% confidence interval [CI] 8%– 27 %). Complications occurred in 4 (12.1%) and 18 (51.4%) patients in the thrombin and glue groups, respectively (P < 0.001, 95 %CI 22%– 45 %). One patient in each group died.

Supplementary material

A Randomized Controlled Trial of Cyanoacrylate Versus Alcohol Injection in Patients With Isolated Fundic Varices	SK. Sarin, AK. Jain, M Jain and R Gupta - 2002	RCT	Patients with portal hypertension and isolated GVs (17 had a history of bleeding)	37 patients with isolated GVs (17 had a history of bleeding). 17 randomized to alcohol injection and 20 to cyanoacrylate glue injection.	Variceal obliteration, rebleeding, or death was the endpoint of the study	Cyanoacrylate glue injection could achieve arrest of acute GV bleeding more often than alcohol (89% vs 62%). The glue was significantly more effective in achieving variceal obliteration than alcohol (100% vs 44%, p< 0.05). Six patients died from uncontrolled GV bleeding, four being in the

Supplementary material

						alcohol group.
Sclerotherapy for gastric fundal variceal bleeding: Is complete obliteration possible without cyanoacrylate?	K Kojima, H Imazu, M Matsumura, Y Honda, N Umemoto, H Moriyasu, T Orihashi, M Uejima, C Morioka, Y Komeda, M Uemura, H Yoshiji, H Fukui - 2005	Retrospective	Bleeding gastric fundal varices	30 Patients underwent endoscopic injection sclerotherapy using 5% ethanolamine oleate under fluoroscopic guidance	Efficacy of the EIS method using 5% ethanolamine oleate under fluoroscopic guidance for bleeding gastric fundal varices	Complete hemostasis was achieved in 28/30 patients (93.3%). The cumulative rebleeding rate after 1, 3 and 5 years was 13%, 19% and 19%, respectively. The 1-, 3-, and 5-year cumulative mortality rates were 31%, 54% and 59%,

Supplementary material

						respectively. There was no complication related to sclerotherapy procedure.
Cyanoacrylate Injection Versus Band Ligation in the Endoscopic Management of Acute Gastric Variceal Bleeding	W Qiao, Y Ren, Y Bai, S Liu, Q Zhang, and F Zhi - 2015	Meta-Analysis of RCTs	Patients with bleding GVs who received treatment with cyanoacrylate or band ligation	3 RCTs included in the analysis (194 patients)	The main outcomes in the meta-analysis were active bleeding control, blood transfusion, rebleeding, recurrence of varices, complications, and survival.	Active bleeding control was achieved in 46 of 49 (93.9%) patients in the cyanoacrylate group, compared with 35 of 44 (79.5%) in the band ligation group (P=0.032). Rebleeding rate was comparable GOV2 between

Supplementary material

						the 2 interventions (35.7% vs 34.8%, P=0.895), but cyanoacrylate seemed superior for reducing rebleeding rate in GOV1 (26.1% vs 47.7%, P=0.035) and IGV1 (17.6%vs 85.7%, P=0.015). Cyanoacrylate was also superior in controlling recurrence of gastric varices to band ligation (36.0% vs 66.0%,

Supplementary material

						P=0.002). There was no difference in complications or mortality between the 2 interventions.
Endoscopic Management of Acute Gastric Variceal Bleeding	X Ye, J Huai, and Y Chen - 2014	Meta-analysis	Patients with GVs who received treatment with cyanoacrylate or band ligation	7 studies included in the analysis (648 patients). Four randomized clinical trials, 1 prospective study and 2 retrospective studies. Two studies (157 patients)	Incorporate the most recent data from clinical trials and provide a precise estimation of the clinical benefits and risks of	GVO was associated with increased likelihood of hemostasis of active bleeding (odds ratio [OR] = 2.32; 95% confidence interval [CI]

Supplementary material

				included all types of gastric varices according to Sarin classification, 3 studies (396 patients) included only patients with GOV1, and 2 studies (85 patients) included patients with GOV1 and GOV2.	GVO and GVL for the treatment of GVH.	= 1.19–4.51) and a longer gastric variceal rebleeding-free period (hazard ratio = 0.37; 95% CI = 0.24–0.56). No significant differences were observed between GVL and GVO for mortality, likelihood of variceal obliteration, number of treatment sessions required for complete variceal eradication or

Supplementary material

						complications.
Cyanoacrylate Glue versus Band Ligation for Acute Gastric Variceal Hemorrhage - A randomized controlled trial at Services Hospital, Lahore	I Hassan, A Siddique, MI Azhar - 2018	RCT	Patients with bleding GVs who received treatment with cyanoacrylate or band ligation	60 Patients were randomized to either EVL of gastric varices (group l: 30 patients) or cyanoacrylate injection (group ll: 30 patients). Endoscopic sessions were continued till obliteration of the varices.	The primary endpoint was initial hemostasis which was defined as cessation of bleeding for more than 72 hours	Control of active bleeding was achieved in 20 patients (80%) in group I and all the patients (100%) in group II, (p=0.03). Re-bleeding was seen in 4 patients (13.3%) in group I and

Supplementary material

						1 patient in group II (3.3%). Gastric varix obliteration was achieved after one session in 33.3% of patients in group I and 60% of patients in group II, however after 2 sessions it was achieved in 66.7% in group I and 96.7% in group II. Fever, chest pain and dysphagia were observed more frequently

Supplementary material

						in group II than in group I.

Supplementary material

Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial	M Ibrahim,A El-Mikkawy, MA Hamid, H Abdalla, A Lemmers, I Mostafa, J Devière - 2019	RCT	Cirrhotic patients with AVB were randomised to either immediate endoscopy with haemostatic powder application within 2 hours of admission, followed by early elective endoscopy within 12–24 hours of admission (study group) or to early elective endoscopy only (control group)	86 patients were randomly assigned to either the pharmacotherapy–endotherapy group (43 patients) or the powder group (43 patients).	Primary outcome was endoscopic haemostasis at the elective endoscopy.	5/43 in the study group required rescue endoscopy for failure of controlling spurting bleeding (n=4) or for early bleeding recurrence (n=1). In the control group, 13/43 patients required rescue endoscopic haemostasis for failure of clinical haemostasis (12%vs30%, p=0.034). In the remaining patients, early

Supplementary material

						elective endoscopic haemostasis was achieved in all 38 patients in the study group, while all remaining 30 patients in the control group had fresh gastric blood or (10%) spurting bleeding at early elective endoscopy with successful haemostasis in all of them. Six-week survival was significantly

Supplementary material

						improved in the study group (7%vs30%, p=0.006).

Supplementary material

Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension	ER Castellanos, P Seron, JP Gisbert, XB Cosp - 2015	Cochrane meta-analysis	RCTs from inception to September 2014 comparing cyanoacrylate versus other endoscopic methods (sclerotherapy using alcohol-based compounds or endoscopy band ligation) for acute gastric variceal bleeding in people with portal hypertension.	6 RCTs with 3 different comparisons: 1 trial compared two different doses of CYA in 91 adults, bleeding actively from all types of gastric varices; 1 trial compared CYA versus alcohol-based compounds in 37 adults with active or acute bleeding from isolated gastric varices only; and four trials compared CYA versus endoscopic band ligation in 365 adults, with active or acute bleeding	Main outcomes in the included trials were bleeding-related mortality, failure of intervention, re-bleeding, adverse events, and control of bleeding.	CYA vs Alcohol injection (Sarin et al. 2002) see above, CYA 0.5ml vs. 1.0ml (Hou et al. 2009) see below, CYA vs EBL: Bleeding-related mortality 44/185 (23.7%) with CYA vs 50/181 (27.6%) with EBL; RR 0.83; 95% CI 0.52 to 1.31), failure of intervention (RR 1.13; 95% CI 0.23 to 5.69), complications (RR 2.81; 95% CI 0.69

Supplementary material

				from all types of gastric varices.		to 11.49), and control of bleeding (RR 1.07; 95% CI 0.90 to 1.27). There was low quality evidence for the prevention of re-bleeding (RR 0.60; 95% CI 0.41 to 0.88).
A randomized trial of endoscopic cyanoacrylate injection for acute gastric variceal bleeding: 0.5 mL versus 1.0 mL	MC Hou, HC Lin, HS Lee,WC Liao, FY Lee, SD Lee - 2009	RCT	Acute bleeding gastric varices in people with portal hypertension. Compare an injection containing 0.5 mL of CYA (group A) with an injection	44 patients in group A and 47 patients in group B	Occurrence of rebleeding	Rebleeding rate was 29.8% (14/47) in group B compared with 38.6% (17/44) in group A (P Z .504; 95% CI, -10.592 to 28.280). More patients in group B

Supplementary material

			containing 1.0 mL of CYA (group B)			than in group A had post-injection fever (O37.5 C) (23/47 vs 12/44, P Z .059). Treatment failure, complications, 30-day mortality, and survival did not differ between the 2 groups.
Cyanoacrylate for treatment of acute variceal bleeding: A systematic review. [ABSTRACT]	A Inaganti, S Duvuru, S Komanapalli, S Swetha, P Roy - 2012	Systematic review	Effectiveness and safety of CYA for therapy of acute GVB in adult patients. All studies with sample size of 25	19 studies (1.217 patients). 7 studies were prospective and 12 were retrospective.	Effectiveness and safety of CYA injection for treatment of acute gastric variceal bleed	Immediate control of bleeding was achieved in 82-100% of patients. Rebleeding occurred in 10-30% of patients. Treatment

Supplementary material

			patients or greater were included. Outcomes of the procedure (immediate control of bleeding, rate of rebleeding, failure of endoscopic therapy) and complications were extracted.			failure occurred in 6-25% of cases. Eradication of the varices was achieved in 36-80%. Mean number of sessions to achieve eradication ranged from 1.3-2.7 sessions. Complications occurred in 4-35% of patients.

Supplementary material

Should Cyanoacrylate Glue Be the Treatment of Choice for Gastric Varices? A Systematic Review and Meta-analysis. [ABSTRACT]	MA Khan, F Kamal, B Ali, KF Haq, CW Howden, M Kahaleh, S Nair, SK Satapathy - 2016	Systematic Review and Meta-analysis	Studies from inception to June 1, 2016 comparing cyanoacrylate glue injections with other modalities for treatment of GV.	14 studies (8 RCTs and 6 observational studies) with 1156 patients	Risk ratios (RR) were calculated for mortality, re-bleeding, initial hemostasis and adverse events (AE) comparing cyanoacrylate with other modalities.	Pooled RR (95% CI) for initial hemostasis 0.43 (0.25, 0.74) and for mortality 0.74 (0.57, 0.96). RRs for mortality in subgroup analyses were: EO injection 0.39 (0.13, 1.16), banding 0.77 (0.59, 0.99), alcohol injection 0.34 (0.08, 1.53), TIPS 0.82 (0.54, 1.26), BRTO 2.17 (0.71, 6.66), BB 0.26 (0.07, 0.88).

Supplementary material

						Pooled RR for re-bleeding was 0.77 (0.52, 1.16). RR for re-bleeding in subgroup analyses were: EO injection 0.34 (0.13, 0.89), banding 0.51 (0.36, 0.73), alcohol injection 0.85 (0.30, 2.45), TIPS 1.32 (0.76, 2.30), BRTO 4.64 (1.24, 17.33), BB 0.21 (0.07, 0.65). Pooled RR for AEs was 0.89 (0.56, 1.41).

Supplementary material

Risk of rebleeding from gastroesophageal varices after initial treatment with cyanoacrylate; a systematic review and pooled analysis	Z Hu, D Zhang, J Swai, T Liu and S Liu - 2020	Systematic review and pooled analysis	PubMed, EMBASE, SCOPUS, and the Cochrane library were searched for studies that reported the risk of rebleeding during the follow-up period after treatment of gastric or esophageal varices with either cyanoacrylate alone or in combination with other treatments.	25 studies including a total of 2590 patients with gastric variceal bleeding	Assess the pooled risk of gastric and esophageal varices rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments	When gastric varices are treated with cyanoacrylate alone, the risk of rebleeding during the follow-up period is 0.15 (Confidence Interval: 0.11–0.18). When combined with lipiodol, polidocanol or sclerotherapy the rebleeding risks are 0.13 (CI:0.03–0.22), 0.10(CI:0.02–0.19), and 0.10(CI:

Supplementary material

						0.05–0.18), respectively. When combined with percutaneous transhepatic variceal embolization, EUS-guided coils, or ethanolamine, the rebleeding risk are 0.10(CI:0.03–0.17), 0.07(CI:0.03–0.11) and 0.08(CI:0.02–0.14), respectively.

Supplementary material

Safety and efficacy of endoscopic cyanoacrylate injection in the management of gastric varices: A systematic review and meta-analysis	S Chirapongsathorn,W Manatsathit,A Farrell and A Suksamai - 2021	Systematic Review and Meta-analysis	Search of MEDLINE, Embase, Web of Science, Scopus databases, and Cochrane Database of Systematic Reviews through November 2020	7 RCTs (6 for secondary prophylaxis and 1 for primary prophylaxis) in which 126 deaths were reported among 583 patients with gastric varices.	Evaluate the effect of endoscopic cyanoacrylate injection in the management of gastric varices	Cyanoacrylate use was associated with significantly lower all-cause mortality (RR, 0.59; 95% CI, 0.36–0.98; I2 = 41%) and rebleeding rate after hemostasis (RR, 0.49; 95% CI, 0.35–0.68, I2 = 0%) compared with any other treatment approach. The use of cyanoacrylate was not associated with an increase in

Supplementary material

						serious adverse events.
Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis	BP Mohan, S Chandan, SR Khan, LL Kassab, S Trakroo, S Ponnada, R Asokkumar, DG Adler - 2020	Systematic Review and Meta-analysis	A comprehensive search of several databases (inception to June 2019) to identify studies evaluating EUS in the treatment of gastric varices	23 studies (851 patients) were included in the final analysis of EUS-guided therapy (12 cohorts treated with EUS-coil/glue, 9 cohorts treated with EUS-glue therapy, 3 cohorts with EUS-coil placement and 1 each treated with EUS-thrombin,	Pooled rates of treatment efficacy, obliteration and recurrence of gastric varices, early and late rebleeding, and adverse events with EUS-guided therapy in gastric varices.	The pooled treatment efficacy was 93.7%, gastric varices obliteration was 84.4%, gastric varices recurrence was 9.1%, early rebleeding was 7.0%, and late rebleeding was 11.6%. The rates were

Supplementary material

				EUS-coil/thrombin, and EUS-coil/gelatin sponge. For the comparator group (END-glue injection therapy), a total of 28 studies (3467 patients) were included.		comparable to END-glue therapy except for obliteration, which was significantly better with EUS-guided therapy. On subgroup analysis, EUS-coil/glue combination showed superior outcomes.

Supplementary material

Combination therapy versus monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis	TR McCarty, AN Bazarbashi, KE Hathorn, CC Thompson, M Ryou - 2020	Systematic Review and Meta-analysis	Individualized search strategies were developed for PubMed, EMBASE, and Cochrane Library databases, from inception through November 2018 in accordance with the PRISMA guidelines	11 studies (536 patients) were included in this meta-analysis. Two randomized controlled trials, one prospective study, and eight retrospective articles were included.	Evaluate the comparative effectiveness of EUS-guided interventions for the treatment of GV	Overall technical success, clinical success, and adverse events for EUS treatments was 100%, 97% and 14%, respectively. On subgroup analysis, EUS-guided CYA + coil embolization resulted in a better technical and clinical success compared to CYA alone (100% vs. 97%; P < 0.001 and 98% vs. 96%; P <

Supplementary material

						0.001) and coil embolization alone (99% vs. 97%; P < 0.001 and 96% vs. 90%; P < 0.001). CYA + coil embolization also resulted in lower adverse event rates compared to CYA alone (10% vs. 21%; P < 0.001), and comparable rates to coil embolization alone (10% vs. 3%; P = 0.057).

Supplementary material

Endoscopic ultrasonography-guided deployment of embolization coils and cyanoacrylate injection in gastric varices versus coiling alone: a randomized trial	C Robles-Medranda, R Oleas, M Valero, M Puga-Tejada, J Baquerizo-Burgos, J Ospina, H Pitanga-Lukashok - 2020	RCT	Cirrhotic patients with endoscopic evidence of GOV II or IGV I in accordance with the Sarin classification and active bleeding, a history of previous bleeding secondary to gastric varices (secondary prophylaxis), or eligible for primary prophylaxis in accordance with the Baveno VI consensus	60 participants who were randomly allocated to EUS-guided coil embolization and cyanoacrylate injection (n = 30) or EUS-guided coil embolization alone (n = 30).	The primary end points were the technical and clinical success rates of both procedures. The secondary end points were the reappearance of gastric varices during follow-up, along with rebleeding, the need for reintervention, and complication and survival rates	The technical success rate was 100% in both groups. Median survival time was 16.4 months with coils and cyanoacrylate versus 14.2 months with coils alone (P = 0.90). Rebleeding occurred in 3.3% of patients treated with combined treatment and 20% of those treated with coils alone

Supplementary material

						(P = 0.04). With combined treatment, 83.3% of patients were free from reinterventi on versus 60% with coils alone.
Safety and efficacy of EUS-guided coil and glue injection for the primary prophylaxis of gastric variceal hemorrhage	A Kouanda, K Binmoeller, C Hamerski, A Nett, J Bernabe, J Shah, Y Bhat, R Watson - 2021	Single-center observatio nal study	Adult patients with high-risk gastric varices (GV; size >10 mm or cherry red spot) without prior bleeding	80 patients without prior bleeding underwent EUS-guided coil and cyanoacrylate (CYA) injection (EUS-CCI) for the primary prophylaxis of GVB.	The primary outcome was post-treatment GVB	Technical success was achieved in 100%, 96.7% had EUS confirmatio n of GV obliteration, and 67.7% were obliterated with 1 treatment session. Post-treatment GVB

Supplementary material

						occurred in 2 patients (2.5%) and adverse events in 4 (4.9%).

Paper (copy paste from covidence)	Authors	Design	Indication	Comparison	no of patients	Main outcome measure	Conclusion	Limitations GRADE score
#209 - Park 2015 Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) for Treatment of Gastric Varices: Review and Meta-Analysis.	Park, Jonathan K; Saab, Sammy; Kee, Stephen T; Busuttil, Ronald W; Kim, Hyun J; Durazo, Francsico; Cho, Sung-Ki; Lee,	Meta-analysis	At least ten patients with acute bleeding or at-risk gastric varices treated with BRTO	None, BRTO	1016; 24 uncontrolled studies (23 retrospective, one prospective)	immediate technical success, clinical success, and complications	At institutions with the capability and expertise to perform BRTO, the current best evidence suggests that BRTO should be considered as therapy for patients	No comparative group

Supplementary material

	Edward Wolfgang						with bleeding or at-risk gastric varices.	
#25 - Alqadi 2021 Transjugular Intrahepatic Portosystemic Shunt Creation for Treatment of Gastric Varices: Systematic Literature Review and Meta-Analysis of Clinical Outcomes.	Alqadi, Murad M; Chadha, Sakshum; Patel, Shovik S; Chen, Yi-Fan; Gaba, Ron C	Meta-analysis	exclusive treatment of GVs (i.e., no EVs or ectopic varices included in the study cohort)	None, TIPS	209 (5); All investigations were retrospective observational cohort studies. Four of 5 (80%) were single center and 1/5 (20%) was a two-institution study	Outcomes included GV rebleeding rate, overall rebleeding rate, GV occlusion rate, hepatic encephalopathy (HE) incidence, and adverse event (AE) rate	GV rebleed after TIPS is high: Forest plot showed the overall rebleeding rate for each study (Fig. 2B) and a pooled event rate of 21% (95% CI: 15%, 27%) across studies.	No comparative group

Supplementary material

#181 - Wang 2016 Balloon-occluded retrograde transvenous obliteration versus transjugular intrahepatic portosystemic shunt for treatment of gastric varices due to portal hypertension: A meta-analysis. Journal of gastroenterology and hepatology / 2016;31(4):727-33	Wang, Yun-Bing; Zhang, Jian-Ying; Gong, Jian-Ping; Zhang, Fan; Zhao, Yong	Meta-analysis	people who had a diagnosis of gastric and esophagus varices due to portal hypertension, were at high risk of bleeding or were undergoing bleeding	TIPS vs BRTO	5 studies; one RCT and four cohort studies; RCT of 15 pts (7 vs 8)!	The primary markers that need to be evaluated contained technical success rate, hemostasis rate, incidence rate of postoperative rebleeding, incidence rate of hepatic encephalopathy, and postoperative procedure-related complica-tion.	Meta-analysis showed that BRTO and TIPS had no difference in aspects of technical success rate (OR, 0.19; 95% confidence interval [CI], 0.03–1.08; P=0.06), hemostasis rate (OR, 3.41; 95% CI, 0.33–35.40; P=0.30), and incidence rate of postoperative procedure-related complication (OR, 1.98; 95% CI, 0.44–8.84; P=0.37). However, BRTO had a	No RCTs (1 RCT with 15 pts: 14 randomized to BRTO vs TIPS). Cohort studies with risk of selection bias, use of bare stents.

Supplementary material

							lower incidence rate of post-operative rebleeding (OR, 0.27; 95% CI, 0.09–0.81; P = 0.02) and a lower incidence rate of postoperative encephalopathy (OR, 0.05; 95% CI, 0.02–0.13; P < 0.00001)	
#27 - Yu 2021 Balloon-occluded Retrograde Transvenous Obliteration Versus Transjugular Intrahepatic Portosystemic Shunt for Gastric Varices: A Meta-Analysis. Journal of clinical gastroenterology / 2021;55(2):147-158	Yu, Qian; Liu, Chenyu; Raissi, Driss	Meta-analysis	Patient developed GV due to portal hypertension.	TIPS vs BRTO	435 (5); Except for 1 randomized clinical trial study, 4 studies were retrospective cohorts	The goal was to compare the efficacy of BRTO and TIPS in preventing variceal rebleeding and the risk of adverse events such as ascites and hepatic	BRTO and TIPS have similar technical success rates (91.4% vs. 89.7%, P=0.995) and immediate bleeding control rates (97.7% vs. 95.9%,	No RCTs (1 RCT with 15 pts: 14 randomized to BRTO vs TIPS). Cohort studies with risk of selection bias, use

Supplementary material

						encephalopathy	P=0.836). However, compared with TIPS, BRTO has lower likelihood of future cumulative rebleeding (10.6% vs. 18.7%, P = 0.027) and hepatic ence-phalopathy (0.00% vs. 23.1%, P < 0.001) but is more likely to aggravate ascites (22.4% vs. 4.3%, P = 0.009). For cirrhotic patients with GV, our meta-analysis suggests that BRTO is a superior intervention	of bare stents.

Supplementary material

							in preventing future cumulative variceal bleeding compared with TIPS. However, operators should also be cognizant about procedure selection in different patient profiles. TIPS was effective in reducing ascites and might be helpful in managing hydrothorax and hepatorenal syndrome. BRTO should be considered	

Supplementary material

							when HE is a concern.	
#33 - Paleti 2020 Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) Versus Transjugular Intrahepatic Portosystemic Shunt (TIPS) for Treatment of Gastric Varices Because of Portal Hypertension: A Systematic Review and Meta-Analysis. Journal of clinical gastroenterology / 2020;54(7):655-660	Paleti, Swathi; Nutalapati, Venkat; Fathallah, Jihan; Jeepalyam, Sravan; Rustagi, Tarun	Meta-analysis	GV	TIPS vs BRTO	676 (7); Six cohort studies ans same small RCT (n=15)	technical success, hemostasis rate, postprocedural complications, rebleeding rate, incidence of hepatic encephalopathy, and mortality rate at 1 year	There was no difference in pooled technical success rate (OR, 0.87; 95% CI, 0.28-2.73; P=0.81), hemostasis rate (OR, 2.74; 95% CI, 0.61-12.26; P=0.19), and postoperative procedure-related complications (OR, 1.95; 95%	No RCTs (1 RCT with 15 pts: 14 randomized to BRTO vs TIPS). Cohort studies with risk of selection bias, use of bare stents.

Supplementary material

							CI, 0.44-8.72; P=0.38). However, treatment with BRTO was associated with lower rates of postoperative rebleeding (OR, 0.30; 95% CI, 0.18- 0.48; P < 0.00001), postoperative encephalopathy (OR, 0.06; 95% CI, 0.02-0.15; P < 0.00001), and mortality at 1 year (OR, 0.43; 95% CI, 0.21-0.87; P = 0.02).	

Supplementary material

#48 - Wang 2020 Comparison of the Effects of TIPS versus BRTO on Bleeding Gastric Varices: A Meta-Analysis. Canadian journal of gastroenterology & hepatology / 2020;2020(101623613):5143013	Wang, Zi Wen; Liu, Jin Chao; Zhao, Fang; Zhang, Wen Guang; Duan, Xu Hua; Chen, Peng Fei; Yang, Si Fu; Li, Hong Wei; Chen, Fu Wen; Shi, Hong Sheng; Ren, Jian Zhuang	Meta-analysis	patients with a clear diagnosis of GVs due to portal hypertension	TIPS vs BRTO	Nine studies; one RCT (n=15) and eight cohort studies	overall survival (OS) rate, imminent haemostasis rate, rebleeding rate, technical success rate, procedure complication rate (hepatic encephalopathy and aggravated ascites), and Child-Pugh score	There was a significant difference between TIPS and BRTO in the OS rate (RR, 0.81 (95% CI, 0.66 to 0.98); P = 0.03) and rebleeding rate (RR, 2.61 (95% CI, 1.75 to 3.90); P < 0.00001). TIPS had a higher incidence rate of hepatic encephalopathy (RR, 16.11 (95% CI, 7.13 to 36.37); P < 0.00001). There was no significant difference between TIPS and	No RCTs (1 RCT with 15 pts: 14 randomized to BRTO vs TIPS). Cohort studies with risk of selection bias, use of bare stents.

Supplementary material

							BRTO in the immediate haemostasis rate (RR, 0.99 (95% CI, 0.89 to 1.10); P = 0.84), technical success rate (RR, 1.06 (95% CI, 0.98 to 1.16); P = 0.16), aggravated ascites rate (RR, 0.60 (95% CI, 0.33 to 1.09); P = 0.10), or Child-Pugh change (MD, 0.22 (95% CI, −0.21 to 0.65); P = 0.31)	

Supplementary material

#210 - Qi 2015 Transjugular Intrahepatic Portosystemic Shunt for Acute Variceal Bleeding: A Meta-analysis. Journal of clinical gastroenterology / 2015;49(6):495-505	Qi, Xingshun; Jia, Jia; Bai, Ming; Guo, Xiaozhong; Su, Chunping; Garcia-Pagan, Juan C; Han, Guohong; Fan, Daiming	Meta-analysis	cirrhotic patients presenting with acute variceal bleeding	TIPS vs medical/endoscopic	6 studies; 3 RCTs and 3 non-randomized	The primary outcomes evaluated in our meta-analysis were the rates of treatment failure, rebleeding, overall survival, bleeding-related death, and posttreatment hepatic encephalo-pathy.	TIPS was superior to medical/ endoscopic therapy in decreasing the incidence of treatment failure (OR = 0.22; 95% CI, 0.11-0.44), improving overall survival (HR = 0.55; 95% CI, 0.38-0.812), and decreasing the incidence of bleeding-related death (OR = 0.19; 95% CI, 0.06-0.59). Although TIPS did not significantly decrease the incidence of rebleeding (OR = 0.27; 95% CI, 0.06-1.29), it became significantly greater in the subgroup meta-analyses of randomized studies (OR=0.09; 95% CI, 0.03-0.32) than in those of nonrandomized studies (OR = 0.76; 95% CI, 0.40-1.45; subgroup difference, P = 0.003), and in the subgroup meta-analyses of studies including high-risk patients (OR = 0.06; 95% CI, 0.01-0.23) than in those including low-risk patients (OR = 0.83; 95%

Supplementary material

							CI, 0.44-1.56; subgroup differ- ence, P = 0.0007). In addition, TIPS did not significantly increase the incidence of posttreatment hepatic encephalopathy (OR = 1.37; 95% CI, 0.63-2.99).
#138 - Kobayakawa 2017 Short-Term Safety and Efficacy of Balloon-Occluded Retrograde Transvenous Obliteration Using Ethanolamine Oleate: Results of a Prospective, Multicenter, Single-Arm Trial. Journal of vascular and interventional radiology : JVIR / 2017;28(8):1108-1115.e27	Kobayakawa, Masao; Kokubu, Shigehiro; Hirota, Shozo; Koizumi, Jun; Nishida, Norifumi; Yasumoto, Taku; Mochida, Satoshi; Hidaka, Hisashi; Tanaka, Noriko; Tajima, Tsuyoshi	Prospective, 8-site prospective single-arm clinical trial	Patients who had endoscopically confirmed GVs with a gastrorenal shunt were eligible for the study	None, BRTO	45	The primary endpoint was the complete regression rate of GVs on day 90 as judged by the central adjudication com- mittee (CAC) based on the results of the endoscopic ex- amination	In summary, our prescribed BRTO procedure with a limited dose of 5% EO could eliminate ruptured GVs and high-risk GVs

Supplementary material

#194 - Gwon 2015Vascular Plug-Assisted Retrograde Transvenous Obliteration for the Treatment of Gastric Varices and Hepatic Encephalopathy: A Prospective Multicenter Study. Journal of vascular and interventional radiology : JVIR / 2015;26(11):1589-95	Gwon, Dong Il; Kim, Young Hwan; Ko, Gi-Young; Kim, Jong Woo; Ko, Heung Kyu; Kim, Jin Hyoung; Shin, Ji Hoon; Yoon, Hyun-Ki; Sung, Kyu-Bo	Prospective, multicenter	GVs or HE with a portosystemic shunt	None, PARTO	73	Primary study endpoints were assessment of technical success, procedure-related complications, and clinical success. Secondary study endpoints were assessment of follow-up clinical results including change of liver function, worsening of EVs, and incidence of ascites.	In conclusion, the present results of PARTO indicate that it can be rapidly performed with high technical success and durable clinical efficacy for the treatment of GVs and HE in the presence of a portosystemic shunt. Therefore, PARTO might be considered a first-line treatment in appropriate patients.

Supplementary material

#3 - Luo 2021Endoscopic Cyanoacrylate Injection vs BRTO for Prevention of Gastric Variceal Bleeding: A Randomized Controlled Trial. Hepatology (Baltimore, Md.) / 2021;(gbz, 8302946)	Luo, Xuefeng; Xiang, Tong; Wu, Junchao; Wang, Xiaoze; Zhu, Yongjun; Xi, Xiaotan; Yan, Yuling; Yang, Jinlin; Garcia-Pagan, Juan Carlos; Yang, Li	RCT	patients aged 18-75 years with cirrhosis who were (1) admitted to our institution because of acute bleeding from fun- dal GVs (stratum I) or (2) transferred to our hospital after recovering from a previous acute GV bleeding within 4 weeks (stratum II) were considered for inclu- sion	BRTO vs endoscopic cyanoacrylate	64	The primary outcome of this study was gastric var- iceal rebleeding and all-cause rebleeding. Secondary outcomes included all-cause death, side effects of treatments, and worsening of EVs. All patients were followed until death, liver transplantati on (LT), or lost to follow-up.	BRTO is markedly more effective than endo- scopic cyanoacrylate injection to prevent gastric var- iceal rebleeding and all-cause rebleeding, with similar frequencies of complications and mortalities. BRTO is safe, clinically effective, and cost-effective for second- ary prophylaxis of GVs, when technically applicable. The worsening of EVs secondary to BRTO cannot be ignored, so better endoscopy follow-up strategies should be investigated.

Supplementary material

#183 - Holster 2016 Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + beta-blocker for prevention of variceal rebleeding. Hepatology (Baltimore, Md.) / 2016;63(2):581-9	Holster, I Lisanne; Tjwa, Eric T T L; Moelker, Adriaan; Wils, Alexandra; Hansen, Bettina E; Vermeijden, J Reinoud; Scholten, Pieter; van Hoek, Bart; Nicolai, Jan J; Kuipers, Ernst J; Pattynama, Peter M T; van Buuren, Henk R	RCT	a first or second episode of gastric and/or esophageal variceal bleeding, after hemody- namic stabilization upon endoscopic, vasoactive, and antibiotic treatment	long-term endoscopic variceal ligation (EVL) or glue injection 1 b-blocker treatment was compared with TIPS placement	72	The primary outcome of the study was clinically significant variceal rebleeding. This was defined as recurrent melena or hematemesis resulting in either hospital admission, blood transfusion, drop in hemoglobin of at least 3 g/L, or death within 6 weeks after rebleeding.	During a median follow-up of 23 months, 10 (29%) of 35 patients in the endoscopy1b-blocker group, as compared to 0 of 37 (0%) patients in the TIPS group, developed variceal rebleeding (P50.001). Mortality (TIPS 32% vs. endoscopy 26%; P50.418) and treatment failure (TIPS 38% vs. endoscopy 34%; P50.685) did not differ between groups. Early hepatic encephalopathy (within 1 year) was signifi- cantly more frequent in the TIPS group (35% vs. 14%; P50.035), but during long- term follow-up this difference diminished (38% vs. 23%; P50.121. In unselected patients with cirrhosis, who underwent successful endoscopic hemostasis for variceal bleeding, covered TIPS was superior to EVL 1 b-blocker for reduction of vari- ceal rebleeding, but

Supplementary material

							did not improve survival. TIPS was associated with higher rates of early hepatic encephalopathy.	
#199 - Orloff 2015 Randomized trials of endoscopic therapy and transjugular intrahepatic portosystemic shunt versus portacaval shunt for emergency and elective treatment of bleeding gastric varices in cirrhosis. Surgery / 2015;157(6):1028-45	Orloff, Marshall J; Hye, Robert J; Wheeler, Henry O; Isenberg, Jon I; Haynes, Kevin S; Vaida, Florin; Girard, Barbara; Orloff, Karen J	RCT	Bleeding gastric varices and cirrhosis	Initially, ET was compared with PCS. In the second part of our RCT, emergency TIPS was compared with emergency PCS (EPCS)	588	Outcomes were survival, control of bleeding, portal-systemic encephalopathy (PSE), quality of life, and direct costs of care	Permanent control of BGV was achieved in 97–100% of patients treated by emergency or elective PCS, compared with 27–29% by ET. TIPS was even less effective, achieving long-term control of BGV in only 6%. Survival rates after PCS were greater at	Succes rate os endoscopic treatment and TIPS is very low (permanent control in 27-29% and 6%). Bare stents were used. Study period was 1977 to 1997: outdated sudy.

Supplementary material

							all time intervals and in all Child classes (P < .001). Repeated episodes of PSE occurred in 50% of TIPS patients, 16–17% treated by ET, and 8–11% treated by PCS. Shunt stenosis or occlusion occurred in 67% of TIPS patients, in contrast with 0–2% of PCS patients.	

Supplementary material

#386 - Lo 2007 A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. Endoscopy / 2007;39(8):679-85	Lo, G-H; Liang, H-L; Chen, W-C; Chen, M-H; Lai, K-H; Hsu, P-I; Lin, C-K; Chan, H-H; Pan, H-B	RCT	Cirrhotic patients with acute bleeding from gastric varices were consid− ered for inclusion	After initial control, eligible patients were randomly allocated to two groups: TIPS (n = 35) and obturation using cyanoacrylate (n = 37)	72	The primary end point was gastric variceal rebleeding. Second− ary end points included complication s, blood transfusion re− quirements, or death.	TIPS was more effective than endoscopic obturation in decreasing rebleeding from gas− tric varices and reducing blood requirements, with similar fre− quencies of complications and mortalities. TIPS could be the treatment of choice for prevention of gastric variceal rebleeding
Monescillo 2004. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology. 2004 Oct;40(4):793-801.	Monescill o A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, Marrero JM, Buceta E, Sánchez J, Castellot A, Peñate M, Cruz A, Peña E	RCT	GEV bleeding <24h	TIPS vs no-TIPS in high risk pts	116	Efficacy (treatment failure), safety	HVPG main determinant treatment failure and OS; early TIPS reduces treatment failure and mortality in high risk pts

Supplementary material

García-Pagán 2010 Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010 Jun 24;362(25):2370-9.	García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, Nevens F, Vinel JP, Mössner J, Bosch J;	RCT	Cirrhosis and acute variceal bleeding	vasoactive drugs plus endoscopic therapy to treatment with a polytetrafluoroethylene-covered stent	63	The primary end point of the study was a compos- ite outcome of failure to control acute bleeding or failure to prevent clinically significant variceal re-bleeding within 1 year after enrollment.	In conclusion, in patients with Child–Pugh class C disease or class B disease with active bleed- ing who were admitted for acute variceal bleeding, the early use of TIPS with an e-PTFE–covered stent was associated with significant reductions in the failure to control bleeding, in rebleeding, and in mortality, with no increase in the risk of hepatic encephalopathy.

