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Endoscopic treatment of variceal upper gastrointestinal bleeding: European Society of Gastrointestinal Endoscopy (ESGE) Cascade Guideline

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ESGE

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Introduction

Patients with variceal gastrointestinal bleeding are encountered daily in endoscopic departments around the world. Risk factors include infectious diseases such as hepatitis B and C virus and schistosomiasis, as well as alcohol consumption and metabolic syndrome with development of nonalcoholic fatty liver disease [1]. Globally, prevalence and incidence of chronic liver disease and cirrhosis varies markedly between countries [2]. High-quality epidemiological data from the majority of African countries are lacking; nevertheless, development of cirrhosis and related consequences are a major burden for public health systems in the continent [2–4]. In Africa, mortality from cirrhosis is estimated at 12.9 to 24.2 per 100,000 person-years range and prevalence of hepatitis B virus is among the highest in the world at 6,100 per 100,000 inhabitants [5, 6].

The latest update of the Baveno guideline describes in detail how to prevent and manage variceal bleeding, as well as how to avoid recurrent bleeding [7]. The majority of recommendations in the guideline are based on high levels of evidence and many years of practice. However, some of the recommendations are resource-sensitive and may be unavailable in low-resource settings due to factors such as extensive costs, lack of sufficient health professional training and logistical limitations.

The European Society of Gastrointestinal Endoscopy (ESGE) has implemented a cascade methodology in a joint effort with the World Endoscopy Organization (WEO), aiming to adapt existing guidelines to make them applicable to resource-limited regions (including some African countries) [8]. Previously, two cascade guidelines have been published focusing on endoscopic management of non-variceal upper gastrointestinal bleeding and upper gastrointestinal obstruction, respectively [8–10]. This ESGE cascade guideline aims to standardize endoscopic management of patients with variceal gastrointestinal bleeding.

Methods

The methodology of the cascade guidelines has been described in the ESGE position paper [8]. Briefly, endoscopy-related statements from the Baveno VI guideline were extracted after agreement with the European Association for the Study of Liver [7]. Following that step, members of the International Affairs Working Group (IAWG) independently categorized the statements as resource-sensitive or not. Those with an agreement of 50 % or more for being resource-sensitive were selected for the revision process and subsequently, adaptions were suggested for the four previously defined resource levels (▶ **Table 1**) [8]. The selection of statements, as well as the adaption process, was guided by an external panel of five colleagues from Nigeria, Ghana, and Ethiopia, as well as collaborating WEO outreach committee members.

The modified statements were then subject to a Delphi process with local doctors invited by a dedicated mailing list representative of gastroenterology specialists in different areas of Africa, where a rate of agreement of 75 % or higher of all adaptions for all resource levels led to acceptance of the cascade statement [11]. If a 75 % agreement was not reached, the statement was subject to another round of modification before a final Delphi process was carried out.

Results

Cascade statements

Statement selection: 50 of 199 statements from the original BAVENO VI guideline were selected as resource-sensitive. Three adapted cascade statements – one for each level, excluding the IV as corresponding to the original guideline – were created for each of the original recommendations, making a total of 150 adapted cascade guideline statements.

Delphi process: Overall, 205 experts showed an interest in participating in the Delphi process. Finally, 38 experts from 16 countries participated in the Delphi process, expressing their degree of agreement with one or more recommendations. Details of the participants are provided in ▶ **Table 2**. A ≥ 75 % agreement was achieved for 49 of 50 proposed adaptations.

▶ **Table 1** Level of treatment care.

I: Basic	Core resources or fundamental services absolutely necessary for an endoscopy care system to function. By definition, a health care system lacking any basic level resource would be unable to provide endoscopic service to its patient population. It includes diagnostic procedures (gastroscopy and colonoscopy) as well and fundamental monitoring abilities (blood pressure, basic blood biochemistry).
II: Limited	Second-tier resources or services that produce major improvements in outcome, such as increased survival, but that are attainable with limited financial means and modest infrastructure. It includes minor endoscopic procedures to improve major clinical outcomes (i. e. sclerotherapy/adrenaline injection, band ligation, plasma expanders, basic surgical interventions).
III: Enhanced	Third-tier resources or services that are optional but important. Enhanced-level resources may produce minor improvements in outcome but increase the number and quality of therapeutic options. Most procedures that improves clinical outcome are available (i. e. biliopancreatic endoscopy, electrosurgical unit, polypectomy/mucosectomy, anaesthesia back-up).
IV: Maximal	High-level resources or services that may be used in some high-resource countries or be recommended in guidelines that assume unlimited resources. To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

▶ **Table 2** Characteristics of the participants in the Delphi Process.

	Number of participants N = 38
Geographical area	
North Africa (%)	20 (52.6 %)
Central Africa (%)	3 (7.9 %)
East Africa (%)	6 (15.8 %)
West Africa (%)	8 (21 %)
South Africa (%)	1 (2.6 %)
Socioeconomic status of institution/hospital	
High (%)	1 (2.6 %)
Mid (%)	14 (36,8 %)
Low (%)	23 (60.5 %)

One cascade adaptation recommendation on the role of covered self-expanding metal stents (C-SEMS) for refractory bleeding failed to achieve the ≥ 75 % agreement level. The comments provided by the participants pointed towards the unavailability of C-SEMS and balloon tamponade for treatment of refractory variceal bleeding. For that reason, the statements were revised to include best supportive care and non-selective beta blocker (NSBB) treatment in Levels I and II.

Cascade adaptation: Each original recommendation with the accepted adaptations is reported in ▶ **Table 3**. It was assumed that basic endoscopy is available at all levels of care. However, added to the availability of endoscopy, some specific resources influenced the adaptation of the original guidelines and can be categorized as follows:

1. Pharmacological treatment
2. Therapeutic endoscopy
3. Interventional radiology and surgery
4. Pharmacological treatment

At the basic level, best supportive care and NSBB treatment were recommended as adaptations for primary as well as secondary prophylaxis of variceal hemorrhage. Octreotide was the recommended adaptation when urgent endoscopic treatment of active bleeding episodes was not available.

1. Endoscopic treatment
   a) Esophageal varices
      At the most basic level, band ligation of varices is the treatment of choice in our adaptation. It is available in most centers and represents the most effective endoscopic treatment for acute esophageal variceal bleeding and for secondary prophylaxis. However, round-the-clock availability of emergency endoscopic services may be limited, representing the main difference between Levels I and II. Thus, timing of endoscopy may be delayed, worsened by a lack of availability of blood transfusion at Level 1. Thus, we recommended as a possible adaptation use of octreotide and supportive care.
   b) Gastric varices
      Injection of tissue adhesive (cyanoacrylate) does not require a high level of technical expertise. Unfortunately, it is not available at the basic and limited levels. For that reason, treatment of acute bleeding from isolated gastric varices with band ligation can be considered even though evidence for this procedure is limited [12].
   c) Refractory bleeding
      For endoscopic rescue treatment, balloon tamponade and SEMS are not available at the basic level. They can be recommended only in some centers at the limited level, but in all centers at the enhanced level.
2. Radiologic and surgical treatment

Transjugular intrahepatic portosystemic shunt (TIPS), balloon-occluded retrograde transvenous obliteration (BRTO), and surgical options such as the mesenteric-left portal vein bypass (Meso-Rex operation) are not available except at the enhanced resource level. For prevention of recurrent variceal hemorrhage, maximal endoscopic and pharmacological treatment options should be exhausted.

Endoscopic treatment of gastroesophageal varices represents by far the most life-saving endoscopic intervention in most of developing African countries given the high prevalence of viral and parasitic liver infections. For that reason, primary endoscopic treatment – i. e. band ligation – has become available also at Level II in most centers, providing a favorable prognosis for patients with active bleeding. However, technical feasibility may be hampered by irregular provision of endoscopic resources such as training, scope maintenance, and availability of ligators.

Despite endoscopy's prominent role in this condition, resources for it are not easily accessible for most patients with gastroesophageal varices due to limited capacity, long distances or costs. In this context, use of NSBB is consistently recommended through Level I and II as a less effective but more widely available resource.

Treatment of gastric varices remains challenging. The main priority is adequate and cost-effective supply of tissue adhesive to developing countries as the technical feasibility for its injection is available. Alternatively, band ligation or NSBB may represent surrogate treatments.

Conclusion

In conclusion, endoscopic treatment of variceal bleeding represents the most life-saving endoscopic intervention in most developing countries. In a resource-limited situation, adaptation of general guidelines may help optimize endoscopic care in this patient group.

▶ **Table 3** Adaptation of recommendations according to level of treatment care.

	Original statements	Suggested modifications
	Surveillance of esophageal varices	
1	In compensated patients with no varices at screening endoscopy and with ongoing liver injury (e. g. active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 2-year intervals.	Level I/II/III: No adjustment
2	In compensated patients with small varices and with ongoing liver injury (e. g. active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 1-year intervals.	Level I/II/III: No adjustment
3	In compensated patients with no varices at screening endoscopy in whom the aetiological factor has been removed (e. g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors (e. g. obesity), surveillance endoscopy should be repeated at three year intervals.	Level I/II/III: No adjustment
4	In compensated patients with small varices at screening endoscopy in whom the etiological factor has been removed (e. g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors (e. g. obesity), surveillance endoscopy should be repeated at 2-year intervals).	Level I/II/III: No adjustment
	Patients with no varices or small varices	
5	Patients with small varices with red whale marks or Child-Pugh C class have an increased risk of bleeding and should be treated with non-selective beta blockers (NSBB).	Level I/II/III: No adjustment
6	Patients with small varices without signs of increased risk may be treated with NSBB to prevent bleeding. Further studies are required to confirm their benefit.	Level I/II/III: No adjustment
	Patients with medium-large varices	
7	Either NSBB or endoscopic band ligation is recommended for the prevention of the first variceal bleeding of medium or large varices.	Level I: NSBB and endoscopic surveillance every 6 months Level II: No adjustment Level III: No adjustment
8	The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events.	Level I/II/III: No adjustment
	Patients with gastric varices	
9	Although a single study suggested that cyanoacrylate injection is more effective than beta blockers in preventing first bleeding in patients with large gastroesophageal varices type 2 or isolated gastric varices type 1, further studies are needed to evaluate the risk/benefit ratio of using cyanoacrylate in this setting before a recommendation can be made).	Level I: NSBB Level II: NSBB and sclerotherapy e. g. submucosal ethanol injection Level III: No adjustment
	Management of the acute bleeding episode	
	Blood volume restitution	
10	The goal of resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability.	Level I/II/III: No adjustment
11	Packed red blood cells transfusion should be done conservatively at a target haemoglobin level between 7 and 8 g/ dl, although transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding).	Level I: Blood pressure monitoring and fluid resuscitation with crystalloid fluids Level II: Restrictive blood transfusion strategy based on clinical judgement Level III: No adjustment
12	Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data.	Level I/II/III: No adjustment
13	PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis.	Level I/II/III: No adjustment
	Antibiotic prophylaxis	
14	Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted from admission.	Level I: No adjustment Level II: No adjustment Level III: No adjustment

▶ **Table 3** (Continuation)

	Original statements	Suggested modifications
15	The risk of bacterial infection and mortality are very low in patients with Child-Pugh A cirrhosis, but more prospective studies are needed to assess whether antibiotic prophylaxis can be avoided in this subgroup of patients.	Level I/II/III: No adjustment
16	Individual patient risk characteristics and local antimicrobial susceptibility patterns must be considered when determining appropriate first line acute variceal hemorrhage antimicrobial prophylaxis at each center.	Level I/II/III: No adjustment
17	Intravenous ceftriaxone 1 g/24 h should be considered in patients with advanced cirrhosis, in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis.	Level I: Intravenous antibiotics after local preferences and availability Level II: No adjustment Level III: No adjustment
	Prevention of hepatic encephalopathy	
18	Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding. However, further studies are needed to evaluate the risk/benefit ratio and to identify high risk patients before a formal recommendation can be made.	Level I: Lactulose and antibiotics according to local preferences and availability Level II: Lactulose and nonabsorbable antibiotics Level III: No adjustment
19	Although, there are no specific studies in acute variceal bleeding, it is recommended to adopt the recent EASL/AASLD HE guidelines which state that episodic HE should be treated with lactulose (25 ml q 12 h until 2–3 soft bowel movements are produced, followed by dose titration to maintain 2–3 soft bowel movements per day).	Level I: Lactulose and best supportive care Level II: No adjustment Level III: No adjustment
20	Child-Pugh class C, the updated MELD score, and failure to achieve primary haemostasis are the variables most consistently found to predict six week mortality.	Level I/II/III: No adjustment
	Pharmacological treatment	
21	In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy.	Level I: Octreotide Level II: Octreotide Level III: No adjustment
22	Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to five days.	Level I: Octreotide Level II: Octreotide and endoscopic therapy is recommended Level III: No adjustment
23	Hyponatremia has been described in patients under terlipressin, especially in patients with preserved liver function. Therefore, sodium levels must be monitored.	Level I/II/III: No adjustment
	Endoscopy	
24	Following hemodynamic resuscitation, patients with upper gastrointestinal bleeding and features suggesting cirrhosis should undergo esophagogastroduodenoscopy within 12 h of presentation.	Level I. Technical expertise may not be available on a 24 /7 basis Level II. Endoscopy within 24 hours; trained emergency team with necessary technical expertise available Level III. No adjustment
25	In the absence of contraindications (QT prolongation), pre-endoscopy infusion of erythromycin (250 mg IV 30–120 min before endoscopy) should be considered.	Level I: Endoscopy even when pre-endoscopic erythromycin infusion is not available. Level II: No adjustment Level III: No adjustment
26	The availability both of an on-call gastrointestinal endoscopist proficient in endoscopic haemostasis and on-call support staff with technical expertise in the usage of endoscopic devices enables performance of endoscopy on a 24 /7 basis and is recommended.	Level I. Technical expertise may not be available on a round-the clock basis Level II. Endoscopy within 24 hours; trained emergency team with necessary technical expertise available Level III. No adjustment
27	Patients with acute variceal hemorrhage should be considered for ICU or other well monitored units.	Level I: Best supportive care Level II: Best supportive care with best available monitoring of vital parameters Level III: No adjustment

▶ **Table 3** (Continuation)

	Original statements	Suggested modifications
28	In patients with altered consciousness, endoscopy should be performed with protection of the airway.	Level I: Patients with ongoing active hematemesis should be placed in a stable side position immediately; continuous active suction of blood and gastric contents Level II: Stable side position; continuous sedation; continuous active suction of blood and gastric contents; emergency endoscopy Level III: No adjustment
29	Ligation is the recommended form of endoscopic therapy for acute oesophageal variceal bleeding.	Level I: Best supportive and octreotide Level II: No adjustment Level III: No adjustment
30	Endoscopic therapy with tissue adhesive (e. g. N-butyl-cyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) and those gastroesophageal varices type 2 (GOV2) that extend beyond the cardia.	Level I: Best supportive care and NSBB Level II: Endoscopic band ligation can be considered as a salvage treatment in case of acute bleeding from small gastric varices when tissue adhesive is not available Level III: No adjustment
31	To prevent rebleeding from gastric varices, consideration should be given to additional glue injection (after 2 to 4 weeks), beta-blocker treatment or both combined or TIPS. More data in this area are needed.	Level I: Best supportive care and NSBB Level II: NSBB and endoscopic band ligation when tissue adhesive or TIPS are not available Level III: No adjustment
32	EVL or tissue adhesive can be used in bleeding from gastroesophageal varices type 1 (GOV1).	Level I: Best supportive care and NSBB Level II: No adjustment Level III: No adjustment
	Early TIPS placement	
33	An early TIPS with PTFE-covered stents within 72 h (ideally < 24 h) must be considered in patients bleeding from EV, GOV1 and GOV2 at high risk of treatment failure (e. g. Child-Pugh class C < 14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy. Criteria for high-risk patients should be refined.	Level I: Best supportive care and NSBB Level II: Maximal endoscopic and pharmacological therapy including NSBB when TIPS is not available Level III: No adjustment
	Balloon tamponade	
34	Balloon tamponade, given the high incidence of its severe adverse events, should only be used in refractory oesophageal bleeding, as a temporary ''bridge'' (for a maximum of 24 h) with intensive care monitoring and considering intubation, until definitive treatment can be instituted.	Level I: Best supportive care and NSBB Level II: No adjustment Level III: No adjustment
	Use of self-expandable metal stents	
35	Data suggest that self-expanding covered esophageal metal stents may be as efficacious and a safer option than balloon tamponade in refractory oesophageal variceal bleeding.	Level I: Best supportive care and NSBB Level II: No adjustment Level III: No adjustment
	Management of treatment failures	
36	Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by PTFE-covered TIPS.	Level I: Best supportive care and NSBB Level II: Maximal endoscopic and pharmacological therapy including NSBB when TIPS is not available Level III: No adjustment
37	Rebleeding during the first 5 days may be managed by a second attempt at endoscopic therapy. If rebleeding is severe, PTFE-covered TIPS is likely the best option.	Level I: Best supportive care and NSBB Level II: Maximal endoscopic and pharmacological therapy including NSBB when TIPS is not available Level III: No adjustment
	Preventing recurrent variceal haemorrhage and other decompensating events	
	Prevention of recurrent variceal haemorrhage	
38	First line therapy for all patients is the combination of NSBB (propranolol or nadolol) + EVL.	Level I: NSBB Level II: No adjustment Level III: No adjustment

▶ **Table 3** (Continuation)

	Original statements	Suggested modifications
39	EVL should not be used as monotherapy unless there is intolerance/contraindications to NSBB.	Level I: No adjustment Level II: No adjustment Level III: No adjustment
40	NSBB should be used as monotherapy in patients with cirrhosis who are unable or unwilling to be treated with EVL.	Level I: No adjustment Level II: No adjustment Level III: No adjustment
41	Covered TIPS is the treatment of choice in patients that fail first-line therapy (NSBB + EVL).	Level I: Best supportive care and NSBB Level II: NSBB, EVL, and SEMS Level III: No adjustment
42	Because carvedilol has not been compared to current standard of care, its use cannot be recommended in the prevention of rebleeding.	Level I/II/III: No adjustment
	Secondary prophylaxis of portal hypertensive gastropathy (PHG)	
43	PHG has to be distinguished from gastric antral vascular ectasia because treatments are different.	Level I/II/III: No adjustment
44	NSBB are first-line therapy in preventing recurrent bleeding from PHG.	Level I: No adjustment Level II: No adjustment Level III: No adjustment
45	TIPS might be considered in patients with transfusion-dependent PHG in whom NSBB and/or endoscopic therapies fail.	Level I: NSBB Level II: NSBB when TIPS is not available Level III: No adjustment
	Treatment of portal hypertension in EHPVO	
46	All patients in whom thrombosis has not been recanalized should be screened for gastroesophageal varices within 6 months of the acute episode. In the absence of varices, endoscopy should be repeated at 12 months and 2 years thereafter.	Level I: No adjustment Level II: No adjustment Level III: No adjustment
47	There is insufficient data on whether beta blockers or endoscopic therapy should be preferred for primary prophylaxis. Thus, guidelines for cirrhosis should be applied.	Level I/II/III: No adjustment
48	For the control of acute variceal bleeding, endoscopic therapy is effective.	Level I/II/III: No adjustment
49	Evidence suggests that beta blockers are as effective as endoscopic ligation therapy for secondary prophylaxis.	Level I/II/III: No adjustment
50	Mesenteric-left portal vein bypass (Meso-Rex operation) should be considered in all children with complications of chronic EHPVO, who should be referred to centres with experience in treating this condition.	Level I: Best supportive care and NSBB Level II: Maximal endoscopic and pharmacological therapy including NSBB Level III: No adjustment

SVR, sustained virological response; HCV, hepatitis C virus; NSBB, nonselective beta blockers; EASL, European Association for the Study of Liver; AASLD, American Association for the Study of Liver Diseases; HE, hepatic encephalopathy; ICU, intensive care unit; IGV, isolated gastric varices; GOV2, gastroesophageal varices type 2; TIPS, transjugular intrahepatic portosystemic shunt; EVL, endoscopic variceal ligation; GOV1, gastroesophageal varices type 1; PTFE, polytetrafluoroethylene; SEMS, self-expanding metal stent; PHG, portal hypertensive gastropathy; EHPVO, extrahepatic portal vein obstruction

Competing interests

The authors declare that they have no conflict of interest.

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