

Nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Cascade Guideline



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ABBREVIATIONS

APC	argon plasma coagulation
DOAC	direct oral anticoagulants
ESGE	European Society of Gastrointestinal Endoscopy
FFP	fresh frozen plasma
GI	gastrointestinal
IAWG	International Affairs Working Group
NVUGIH	nonvariceal upper gastrointestinal hemorrhage
OTSC	over-the-scope clip
PCC	prothrombin complex concentrate

PPI	proton pump inhibitor
TAE	transcatheter angiographic embolization
UGIH	upper gastrointestinal hemorrhage
VKA	vitamin K antagonist
WEO	World Endoscopy Organization

Introduction

In order to address the status of gastrointestinal (GI) endoscopy in Africa, a European Society of Gastrointestinal Endoscopy (ESGE) International Affairs Working Group (IAWG) was established with participation from the World Endoscopy Organization (WEO) [1]. A previous survey conducted by the IAWG on the main indications of GI endoscopy in African countries showed nonvariceal upper GI hemorrhage (NVUGIH) to be among the top three indications [1]. This indication may reflect the very high prevalence of *Helicobacter pylori* infection, which is well known to be associated with gastroduodenal peptic ulcers and their complications, such as bleeding. In addition, the increased use of aspirin as prevention and treatment of cardiovascular disease, and the increase in life expectancy, may also, at least in part, account for the NVUGIH indication [2–4].

The management of NVUGIH requires a multi-step approach, involving endoscopic factors such as emergency endoscopy with different hemostatic devices, and clinical factors such as hospitalization, blood transfusion, and drugs. Such an approach is clearly sensitive to organizational, medical, pharmaceutical, and technological resources. However, the lack of structural endoscopic and clinical health resources in some underserved African areas is likely to affect the clinical outcome of patients with NVUGIH. In this regard, the previous IAWG survey revealed several critical needs in training, education, and technology that may represent a barrier to adequate NVUGIH management [1].

Most of the respondents from the African countries participating in the IAWG survey reported a lack of national guidelines for GI endoscopy; however, there was interest in the international guidelines, pending adaptation to reflect the endoscopic resources available in their regions. For this reason, the IAWG decided to apply the cascade methodology to adapt ESGE guidelines to resource-sensitive settings in partnership with African experts [1]. Cascade guidelines are resource oriented and provide hierarchical recommendations based on the re-

sources available to the medical care provider [5,6]. In detail, four levels of resource availability—basic, limited, enhanced, and maximal levels—are identified, with most of the interest being in the basic and limited levels.

We aimed to standardize the management of NVUGIH in low-resources setting. Here, we report the cascade adaptation of the ESGE guideline on the diagnosis and management of NVUGIH [7].

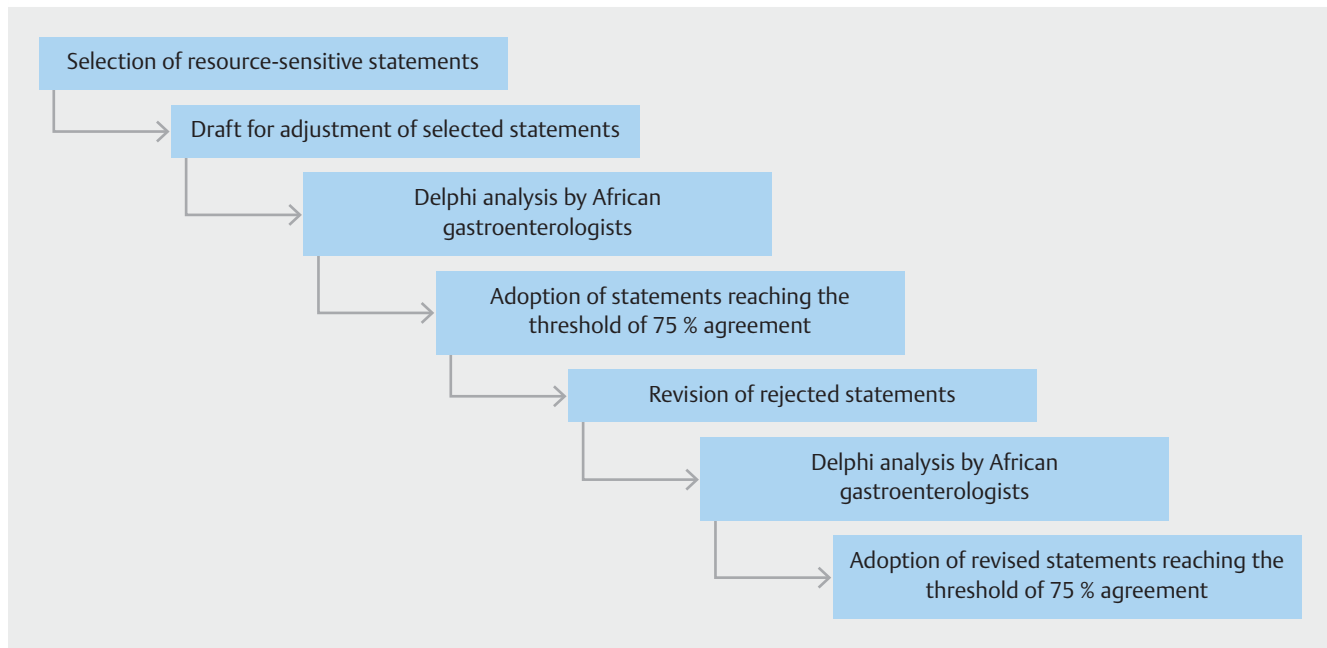
Methods

Implementation of cascade methodology to ESGE guidelines has been detailed in a previous position paper [1]. Briefly, we selected resource-sensitive recommendations from the original ESGE guideline on NVUGIH [7]. Each recommendation was reviewed by four IAWG members. Those statements classified as resource sensitive by at least two reviewers were included in the revision process. The process of identification and selection of resource-sensitive statements from the original ESGE guideline, as well as their categorization into one of the four predefined resource levels, was conducted in close cooperation with four experts from Ghana and Nigeria. Subsequently, the IAWG, together with the first author of the original guideline, drafted a revision of the statements according to cascade methodology, for four predefined levels of resource availability (► **Table 1**) [8].

A modified Delphi process was then carried out with a panel of African gastroenterologists who were invited from a contact list of ESGE, WEO, and European national societies, as previously detailed [1,8]. If a 75% agreement was reached for all four levels of care (adaptations), the statement was accepted [8]. If the panel members disagreed with one of the adaptations, they had the opportunity to add a comment; thus, if an adaptation failed to reach agreement from 75% of the panel, the statement was revised according to the advice from the panel members. Subsequently, a second Delphi round might be conducted to reach an agreement on all of the resource-sensitive state-

► **Table 1** Level of treatment based on resource availability.

Predefined level	Definition
Basic Level I	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 as fundamental monitoring abilities (blood pressure, basic blood biochemistry).
Limited Level II	Limited level: 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).
Enhanced Level III	Enhanced level: 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 improve clinical outcome are available (i. e. biliopancreatic endoscopy, electrosurgical unit, polypectomy/mucosectomy, anaesthesia back-up).
Maximal Level IV	Maximal level: 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.



► **Fig. 1** Methodology of the Delphi process.

ments. Furthermore, if any panel member was not able to respond to specific statements during the Delphi process, they could refuse to answer. The methodology is summarized in ► **Fig. 1**.

► Fig. 1.

In order to describe background details of the Delphi panel, the participants were asked for the socioeconomic status of the location of their hospital and country, and which cascade level they were representing.

Statement selection

Of the 40 recommendations in the original ESGE guideline, 23 were selected as being resource sensitive by the IAWG. Four adapted cascade statements – one for each level – were created for each of the original recommendations, making a total of 92 adapted cascade guideline statements.

The Delphi process

Overall, 144 experts showed an interest in participating in the Delphi process, and 49 finally expressed their degree of agreement for one or more recommendations. Details of the 49 experts are shown in ► **Table 2**.

A $\geq 75\%$ agreement was achieved for 88/92 proposed adaptations. Only four cascade adaptations of two recommendations failed to achieve the $\geq 75\%$ agreement level. One of these failed adaptations was due to a misperceived lack of applicability of the Glasgow–Blatchford score to African settings. The other was a proposed adaptation to carry out endoscopy at the basic care level without INR in patients with coagulopathy due to vitamin antagonist. It was decided to omit the adaptation of these two recommendations.

► **Table 2** Characteristics of the participants in the Delphi process.

	Participants, n (%) (N=49)
Geographical area, n (%)	
▪ North Africa	27 (55)
▪ Central Africa	6 (12)
▪ East Africa	2 (4)
▪ West Africa	14 (29)
▪ Southern Africa	0 (0)
Socioeconomic status of institution/hospital ¹	
▪ High	3 (6)
▪ Mid	26 (53)
▪ Low	20 (41)
Representation of cascade level ^{1,2}	
▪ Basic	9 (18)
▪ Limited	23 (47)
▪ Enhanced	16 (33)
▪ Maximum	1 (2)

¹ Level determined and self-reported by Delphi panel experts.

² See ► **Table 1** for definitions.

Cascade adaptation

Each original recommendation with the accepted adaptations is reported in ► **Table 3**. The main resources on which adaptation was performed may be categorized as follows.

1. Organizational – lack of availability of emergency endoscopy, radiology treatment, cardiologist consultancy, and anesthesiological assistance were reported as possible resource-sensitive limitations.
2. Endoscopy – lack of availability of epinephrine injection and second hemostatic modalities (i. e. thermal, clip, hemostatic spray) were reported as main barriers. In addition, endo-

scopic or histological testing for *H. pylori* was also considered to be resource sensitive.

3. Transfusions and drugs – transfusion strategies were affected at different levels by resource limitations. In detail, lack of biochemical assessment of hemoglobin levels hampers applicability of restrictive transfusion management. In addition, lack of transfusion of either blood, fresh frozen plasma or derivatives, as well as lack of crystalloids, may affect NVUGIH treatment. Proton pump inhibitor (PPI) availability may be limited as either intravenous or oral administration, and vitamin K may be lacking.

► **Table 3** Adapted cascade recommendations for the management of nonvariceal upper gastrointestinal hemorrhage in resource-sensitive settings.

Recommendation in original ESGE guideline ¹	Adapted cascade recommendations
ESGE recommends a restrictive red blood cell transfusion strategy that aims for a target hemoglobin between 7 g/dL and 9 g/dL. A higher target hemoglobin should be considered in patients with significant co-morbidity (e. g. ischemic cardiovascular disease) (strong recommendation, moderate quality evidence).	Level I: Blood pressure monitoring and fluid resuscitation with crystalloid fluids Level II: Restrictive blood transfusion strategy based on clinical judgment Level III: No adjustment
For patients taking vitamin K antagonists (VKAs), ESGE recommends withholding the VKA and correcting coagulopathy while taking into account the patient's cardiovascular risk in consultation with a cardiologist. In patients with hemodynamic instability, administration of vitamin K, supplemented with intravenous prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) if PCC is unavailable, is recommended (strong recommendation, low quality evidence).	Level I: Withhold VKA Level II: Withhold VKA; correct coagulopathy with vitamin K after taking into account the patient's cardiovascular risk Level III: Withhold VKA; correct coagulopathy with vitamin K after taking into account the patient's cardiovascular risk
ESGE recommends temporarily withholding new direct oral anticoagulants (DOACs) in patients with suspected acute NVUGIH in coordination/consultation with the local hematologist/cardiologist (strong recommendation, very low quality evidence).	Level I: Withhold DOACs Level II: Withhold DOACs Level III: Withhold DOACs + consultation with local hematologist and/or cardiologist
For patients using antiplatelet agents, ESGE recommends the management algorithm detailed in ► Fig. 1 ► Fig. 2 (strong recommendation, moderate quality evidence).	Level I: Saline or epinephrine injection; do not remove clot because second modality is not available; high dose oral or intravenous bolus PPI therapy; repeat endoscopy after 2–3 days; empiric/pre-emptive <i>H. pylori</i> treatment; endoscopy together with surgeon; decision for surgery depends on various other factors Level II: Epinephrine injection + second modality if available; do not remove clot if second treatment modality is not available; <i>H. pylori</i> testing and treatment when positive; consider <i>H. pylori</i> treatment if one test is negative Level III: No adjustment, but without topical hemostatic spray, over-the-scope clip (OTSC) or transcatheter angiographic embolization (TAE)
ESGE recommends initiating high dose intravenous proton pump inhibitors (PPI), intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour), in patients presenting with acute UGIH awaiting upper endoscopy. However, PPI infusion should not delay the performance of early endoscopy (strong recommendation, high quality evidence).	Level I: Oral or intravenous bolus PPI Level II: Intravenous bolus PPI Level III: No adjustment
In an effort to protect the patient's airway from potential aspiration of gastric contents, ESGE suggests endotracheal intubation prior to endoscopy in patients with ongoing active hematemesis, encephalopathy, or agitation (weak recommendation, low quality evidence).	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
ESGE recommends the availability of both an on-call GI endoscopist proficient in endoscopic hemostasis and on-call nursing staff with technical expertise in the use of endoscopic devices to allow performance of endoscopy on a 24/7 basis (strong recommendation, moderate quality evidence).	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

► Table 3 (Continuation)

Recommendation in original ESGE guideline ¹	Adapted cascade recommendations
ESGE recommends that peptic ulcers with spurting or oozing bleeding (Forrest classification Ia and Ib, respectively) or with a nonbleeding visible vessel (Forrest classification IIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or rebleeding (strong recommendation, high quality evidence).	<p>Level I: Endoscopic monotherapy; saline injection if no epinephrine; high dose PPI therapy; demonstration of endoscopy to a surgeon and together decide on optimal timing of surgery</p> <p>Level II: Epinephrine injection + second treatment modality such as hemoclips or electrocoagulation; surgical consultation when necessary</p> <p>Level III: No adjustment, but without topical hemostatic spray, OTSC or TAE</p>
ESGE recommends that peptic ulcers with an adherent clot (Forrest classification IIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (Forrest classification Ia or Ib) or nonbleeding visible vessel (Forrest classification IIa) should receive endoscopic hemostasis (weak recommendation, moderate quality evidence).	<p>Level I: Saline or epinephrine injection; do not remove clot because second modality is not available; high dose oral or intravenous bolus PPI therapy; repeat endoscopy after 2–3 days; empiric/pre-emptive <i>H. pylori</i> treatment; endoscopy together with surgeon; decision for surgery depends on various other factors</p> <p>Level II: Epinephrine injection + second modality if available; do not remove clot if second treatment modality is not available; <i>H. pylori</i> testing and treatment when positive; consider <i>H. pylori</i> treatment if only one test was done and was negative; high dose oral or intravenous bolus PPI therapy</p> <p>Level III: No adjustment, but without topical hemostatic spray, OTSC or TAE</p>
For patients with actively bleeding ulcers (IIa, IIb), ESGE recommends combining epinephrine injection with a second hemostasis modality (contact thermal, mechanical therapy, or injection of a sclerosing agent). ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence).	<p>Level I: Endoscopic monotherapy; saline injection if no epinephrine; high dose PPI therapy; demonstration of endoscopy to a surgeon and together decide on optimal timing of surgery. Also, consider endoscopic injection monotherapy using a sclerosing agent, e. g. alcohol, polidocanol, ethanolamine</p> <p>Level II: Dilute epinephrine injection + second treatment modality such as hemoclips or electrocoagulation; surgical consultation when necessary</p> <p>Level III: No adjustment</p>
For patients with nonbleeding visible vessel (IIa), ESGE recommends mechanical therapy, thermal therapy, or injection of a sclerosing agent as monotherapy or in combination with epinephrine injection. ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence).	<p>Level I: Endoscopic monotherapy (if available); saline injection if no epinephrine; high dose oral or intravenous bolus PPI therapy twice daily; consider repeat endoscopy after 2–3 days; empiric/pre-emptive <i>H. pylori</i> treatment; endoscopy together with surgeon</p> <p>Level II: Endoscopic monotherapy (if available), saline injection if no epinephrine; second treatment modality (mechanical, contact thermal, sclerosing agent) if available; <i>H. pylori</i> testing and treatment when positive; however, consider <i>H. pylori</i> treatment if only one test was done and was negative; high dose oral or intravenous bolus PPI therapy twice daily</p> <p>Level III: No adjustment</p>
For patients with active NVUGIH bleeding not controlled by standard endoscopic hemostasis therapies, ESGE suggests the use of a topical hemostatic spray or over-the-scope clip as salvage endoscopic therapy (weak recommendation, low quality evidence).	<p>Level I: Surgery</p> <p>Level II: Surgery</p> <p>Level III: Surgery or no adjustment</p>
For patients with acid-related causes of NVUGIH different from peptic ulcers (e. g. erosive esophagitis, gastritis, duodenitis), ESGE recommends treatment with high dose PPI. Endoscopic hemostasis is usually not required and selected patients may be discharged early (strong recommendation, low quality evidence).	<p>Level I: High dose oral PPI therapy twice daily</p> <p>Level II and Level III: No adjustment</p>
ESGE recommends that patients with a Mallory–Weiss lesion that is actively bleeding receive endoscopic hemostasis. There is currently inadequate evidence to recommend a specific endoscopic hemostasis modality. Patients with a Mallory–Weiss lesion and no active bleeding can receive high dose PPI therapy alone (strong recommendation, moderate quality evidence).	<p>Level I: Injection therapy (or what is available); high dose PPI</p> <p>Level II: Injection therapy and/or second modality such as hemoclips or electrocoagulation (or what is available); high dose PPI</p> <p>Level III: No adjustment</p>

► **Table 3** (Continuation)

Recommendation in original ESGE guideline ¹	Adapted cascade recommendations
ESGE recommends that a Dieulafoy lesion receive endoscopic hemostasis using thermal, mechanical (hemoclip or band ligation), or combination therapy (dilute epinephrine injection combined with contact thermal or mechanical therapy) (strong recommendation, moderate quality evidence). Transcatheter angiographic embolization (TAE) or surgery should be considered if endoscopic treatment fails or is not technically feasible (strong recommendation, low quality evidence).	Level I: Injection therapy (or what is available); surgery if TAE unavailable Level II: Injection therapy and second treatment modality (mechanical, contact thermal) if available; surgery if TAE unavailable Level III: No adjustment; surgery if TAE unavailable
In patients bleeding from upper GI angioectasias, ESGE recommends endoscopic hemostasis therapy. However, there is currently inadequate evidence to recommend a specific endoscopic hemostasis modality (strong recommendation, low quality evidence).	Level I: Argon plasma coagulation (APC) or contact thermal therapy, e. g. bipolar or heat probe Level II: APC or contact thermal therapy, e. g. bipolar or heat probe Level III: No adjustment
In patients bleeding from upper GI neoplasia, ESGE recommends considering endoscopic hemostasis in order to avert urgent surgery and reduce blood transfusion requirements. However, no currently available endoscopic treatment appears to have long-term efficacy (weak recommendation, low quality evidence).	Level I: Endoscopic monotherapy (if available); saline injection if no epinephrine available Level II: Endoscopic monotherapy (if available); saline injection if no epinephrine available; consider APC of tumor bleeding Level III: No adjustment; hemostatic spray if available
ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose and administered as an intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour) for 72 hours post endoscopy (strong recommendation, high quality evidence).	Level I: Intravenous bolus PPI twice daily instead of continuous infusion; if intravenous not available, use high dose oral PPI twice daily Level II and Level III: No adjustment
ESGE suggests considering PPI therapy as intermittent intravenous bolus dosing (at least twice daily) for 72 hours post endoscopy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. If the patient's condition permits, high dose oral PPI may also be an option in those able to tolerate oral medications (weak recommendation, moderate quality evidence).	Level I: Intravenous PPI bolus twice daily instead of continuous infusion Level II and Level III: No adjustment
In patients with clinical evidence of rebleeding following successful initial endoscopic hemostasis, ESGE recommends repeat upper endoscopy with hemostasis if indicated. In the case of failure of this second attempt at hemostasis, transcatheter angiographic embolization (TAE) or surgery should be considered (strong recommendation, high quality evidence).	Level I: Endoscopic monotherapy; saline injection if no epinephrine is available; conventional histopathology for <i>H. pylori</i> ; empiric antibiotics for <i>H. pylori</i> ; intravenous PPI bolus if continuous infusion is impossible; surgery when TAE is unavailable Level II: Endoscopic monotherapy; saline injection if no epinephrine is available; conventional histopathology for <i>H. pylori</i> ; empiric antibiotics for <i>H. pylori</i> ; intravenous PPI bolus if continuous infusion is impossible; surgery when TAE is unavailable Level III: Surgery when TAE is unavailable
In patients with NVUGIH secondary to peptic ulcer, ESGE recommends investigating for the presence of <i>Helicobacter pylori</i> in the acute setting with initiation of appropriate antibiotic therapy when <i>H. pylori</i> is detected. Re-testing for <i>H. pylori</i> should be performed in those patients with a negative test in the acute setting. Documentation of successful <i>H. pylori</i> eradication is recommended (strong recommendation, high quality evidence).	Level I: Conventional histopathology; consider empiric treatment when test is not available or if only one test was done and was negative Level II: Conventional histopathology and rapid urease test; consider empiric treatment if only one negative test was done Level III: No adjustment

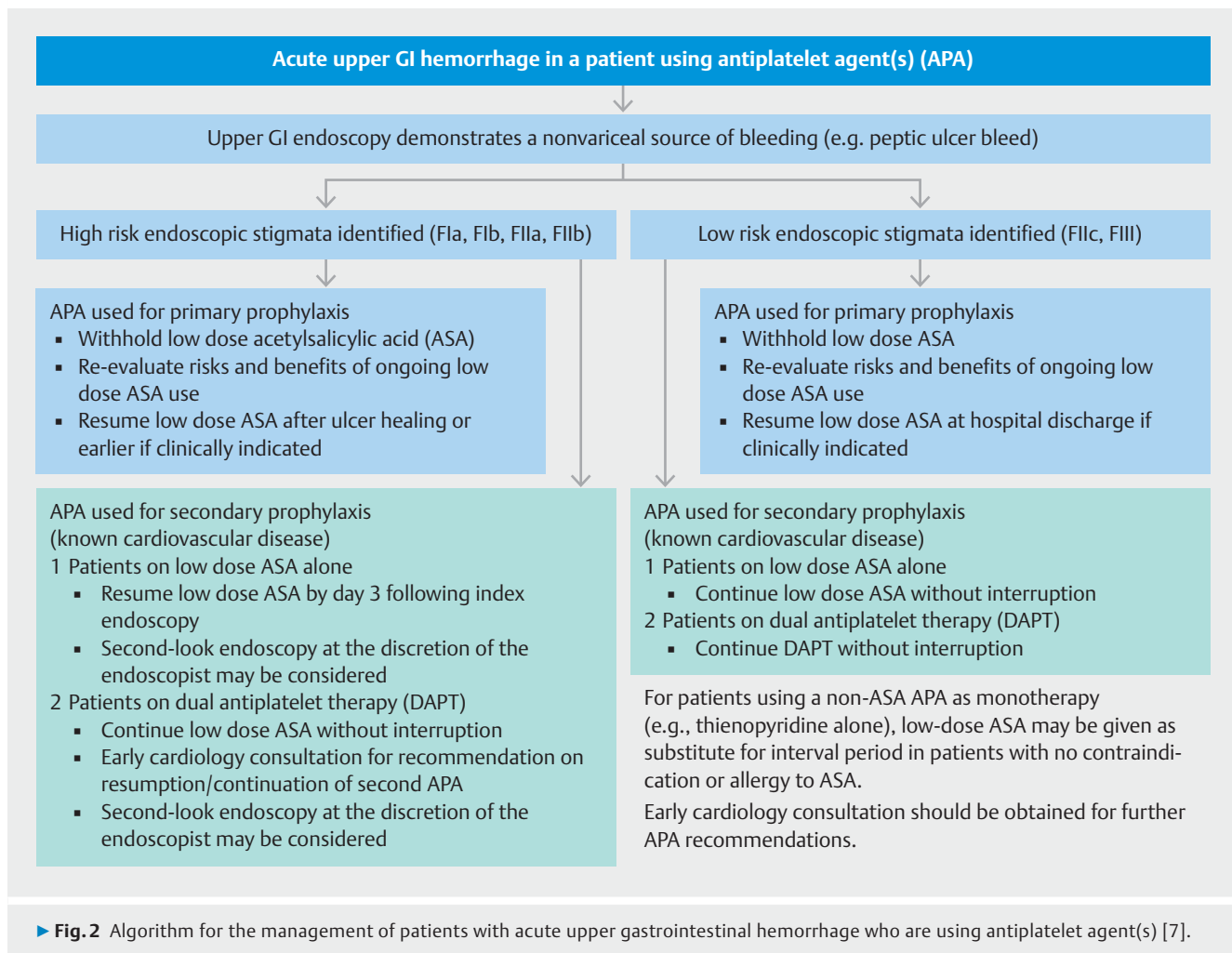
ESGE, European Society of Gastrointestinal Endoscopy; GI, gastrointestinal; NVUGIH, nonvariceal upper gastrointestinal hemorrhage.

¹ Gralnek IM, Dumonceau JM, Kuipers EJ et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; 47: a1–46

Conclusions

Our cascade approach was strengthened by the high rate of participating physicians practicing in low-to-mid socioeconomic areas, which corresponded closely with our definition of basic-to-limited settings of the cascade levels. Most of the original recommendations for NVUGIH management were successfully adapted to underserved areas, addressing limitations that mainly relate to infrastructural, pharmacological, and

technological factors. For example, at the basic level, emergency endoscopy is not fully available, and pharmacological and surgical resources may therefore become more relevant. However, when emergency endoscopy is available, a lack of devices may reduce its efficacy; more affordable devices for a second thermal or mechanical hemostatic modality may then be more relevant for the outcome of these patients.



Disclaimer

ESGE position statements and guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of the statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE position statements and guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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Competing interests

None

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