The management of the patient with non-variceal upper gastrointestinal bleeding: from evidence to clinical practice

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ABSTRACT

A multidisciplinary group of 7 experts developed this update and expansion of the recommendations on the management of acute non-variceal upper gastrointestinal hemorrage (NVUGIH) from guidelines published from 2013. The Appraisal of Guidelines for Research and Evaluation (AGREE) process and independent ethics protocols were used. Sources of data included original and published systematic reviews. Recommendations emphasize early risk stratification, by using validated prognostic scales, and early endoscopy (within 24 h). Endoscopic hemostasis remains indicated for high-risk lesions, whereas data support attempts to dislodge clots with hemostatic, pharmacologic, or combination treatment of the underlying stigmata. Clips or thermocoagulation, alone or with epinephrine injection, are effective methods. Second-look endoscopy may be useful in selected high-risk patients, but is not routinely recommended. Intravenous high-dose proton pump inhibitors (PPI) therapy after successful endoscopic hemostasis decreases both rebleeding and mortality in patients with high-risk stigmata. Although selected patients can be discharged promptly after endoscopy, high-risk patients should be hospitalized for at least 72 h after endoscopic hemostasis. For patients with UGIH who require a nonsteroidal anti-inflammatory drug, a PPI is preferred to reduce the rebleeding. Patients with NVUGIH needing secondary cardiovascular prophylaxis should start receiving acetylsalicylic acid again as soon as cardiovascular risks outweigh gastrointestinal risks (usually within 7 days).

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Introduction

Acute upper gastrointestinal hemorrhage (UGIH) is defined as bleeding proximal to the ligament of Treitz. UGIH is the most common cause of acute hospital admission to the units of gastroenterology and also of admission in internal medicine departments. This is why a clinical competence of the internist is mandatory. Acute UGIH is mostly non-variceal (NVUGIH) and especially comes from peptic ulcers. Other causes include mucosal erosive disease of the esophagus/stomach/duodenum, Mallory-Weiss syndrome and upper GI tract malignancy. In the last decades, we can observe a decreased tendency of the overall incidence and hospitalization for NVUGIH, thanks to the introduction of effective drug treatments (proton pump inhibitors, *Helicobacter pylori* eradication therapy) and endoscopic (injective, thermal, mechanical). However, mortality associated with NVUGIH remains still significant, despite the therapeutic advances,[1-5] although appropriate management of NVUGIH has been demonstrated to improve patient outcomes.[6] Mortality for UGIH is still about 5% and is usually related to multiorgan failure, cardiopulmonary conditions and end-stage malignancy. Recent epidemiological data show that patients with NVUGIH are aged and with a

higher prevalence of severe comorbidities. This might explain the failure to reduce mortality, despite the improvements of the therapeutic offer. The use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of NVUGIH provoked by peptic ulcer of 4.8 times.[7] NSAIDs are the most frequently assumed drugs by elderly patients in polytherapy. For this group it is mandatory to assess the risk of NVUGIH in order to consider the use of gastric mucosal protective agents. Some diagnostic scores have been developed and validated (Blatchford score, Rockall score), which, starting from predictors of severity of NVUGIH, facilitate triage and identification of those in need of urgent endoscopic treatments.[1,8] The factors directly correlated to an increased mortality rate in case of NVUGIH are: age, comorbidity, hemodynamic instability and rebleeding. From the above, it is understandable how NVUGIH represents an interesting pathological condition to the internist that is, nowadays, dealing with elderly and multi-pathological patients.

Rationale and objective

Acute UGIH is a common worldwide condition, frequently leading to hospital admission. It has reported an annual incidence of 50 to 150 cases per 100,000 adults. Despite improvements in medical therapy and endoscopic interventions, a mortality rate of around 8% is registered, with some reports noting up to 27% mortality rates in elderly patients or in those with significant comorbid conditions. The most common causes of acute UGIH are non-variceal,[2,9] including: peptic ulcers, 28%-59% (duodenal ulcer 17%-37% and gastric ulcer 11%-24%); mucosal erosive disease of the esophagus/stomach/duodenum, 1%-47%; Mallory-Weiss syndrome, 4%-7%; upper GI tract malignancy, 2%-4%; other diagnosis, 2%-7%; or no exact cause identified, 7%-25%[2,9] (Figure 1). Moreover, in 16%-20% of acute UGIH cases, more than one endoscopic procedure are necessary to identify the origin of bleeding. For these reasons the diagnosis and the management of NVUGIH should be a competence of internists.

Methodology

In order to provide evidence-based recommendations for the management of patients with NVUGIH, we preliminary verified the existence of guidelines on the issue. Therefore, we led a search activity using the following database guidelines:

- The role of endoscopy in the management of acute non-variceal upper GI bleeding. Gastrointest Endosc 2012:75:1132-1138 (ASGE - American Society for Gastrointestinal Endoscopy);[10]
- Livio Cipolletta, Gianluca Rotondano. La gestione delle emorragie alte non da varici. Giornale Italiano endoscopia digestiva 2012:35;17-22 (SIED - *Società Italiana Endoscopia Digestiva*);[11]

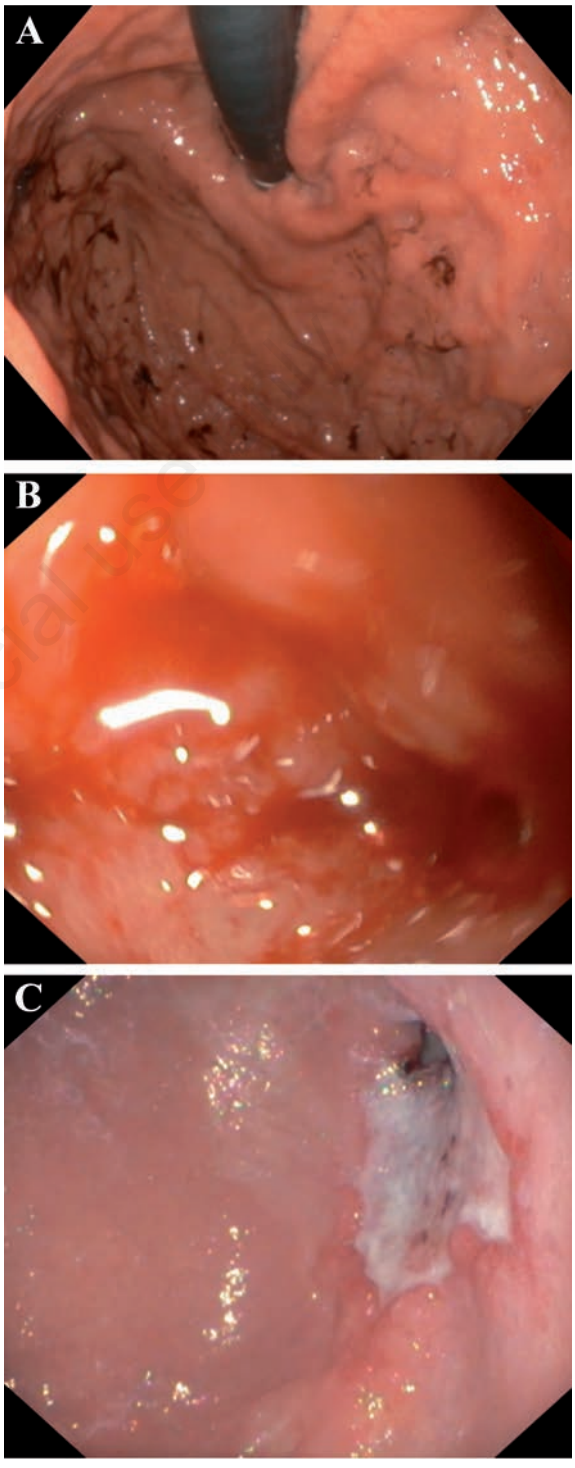

Figure 1. Endoscopic view of: A) erosive gastritis of the gastric fundus; B) ulcer of the bulb with active bleeding (Forrest Ib;); C) ulcer of the gastric antrum with fibrin and hematin (Forrest IIc).

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- NICE Guidelines;[13]
- International Consensus Recommendations on the Management of Patients With Non-variceal Upper Gastrointestinal Bleeding.[14]

The research was carried out by seven independent authors, using as key words the following terms: gastro-intestinal bleeding, non-variceal upper gastro-intestinal bleeding, acute upper gastrointestinal hemorrhage, acute non-variceal upper gastrointestinal bleeding. The results obtained separately were then compared and discussed together. The guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument,[15] by the seven independent authors, in order to identify the best one. AGREE II assesses compliance with 23 requirements, meeting 6 domains such as the explanation of the purpose, the clarity, the involvement of all stakeholders, the rigor of development, the applicability and its editorial independence. Each author evaluated the adherence of individual requirements with a score from 1 (disagree completely) to 7 (complete agreement). The scores assigned by each author were added within individual domains and reported with the highest and the lowest score possible within the domain based on the number of the assessors and of the requirements included.

Results

By the above listed databases, we identified five guidelines, taking into account the works published in literature during the last three years. Among them, three studies prevalently evaluate the endoscopic management of NVUGIH, being commissioned by the scientific societies of endoscopy, and two investigate the management of the disease by a general approach both medical (internal) and endoscopic. The overall quality of selected guidelines was assessed by 7 authors using the AGREE instrument II. In view of these concerns and on the basis of the assessment of guidelines within the AGREE method, the ones produced by NICE[13] are qualitatively the best and their implementation in clinical practice is deemed to be desirable (score 7). The NICE guidelines analyzed the cost-effectiveness only in their appendix; they are more complete, but difficult to manage, due to the length and the large amount of tables and appendices they include.[13]

The *Diagnosis and management of non-variceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline*[12] published by Endoscopy 2015 is excellent from the quality point of view (score 7), well written and full of information about the studies on NVUGIH, starting from the prophylaxis to the treatment of its complications, and also careful to give appropriate advice for choosing between them. Sometimes, however, it seems to be a bit too detailed. The guideline of the *International Consensus Recommendations on the Management of Patients With Non-variceal Upper Gastrointestinal Bleeding*[14] is of good quality (score 7) and it is shown to include clear expression of the goals and the motivations of the document, good methodological rigor and fair application. Moreover, the *International Consensus Recommendations on the Management of Patients With Non-variceal Upper Gastrointestinal Bleeding* guidelines explore their applicability in clinical practice. They notice that initiatives on dissemination and economics are ongoing. In the same guidelines it is stated that in a separate paper the criteria for quality indicators and the analysis of cost will be issued in the near future. The other ones do not analyze the cost-effectiveness and the applicability in real life.[14]

The *Role of endoscopy in the management of acute non-variceal upper GI bleeding*. Gastrointest. Endosc. 2012:75:1132-1138 (ASGE - American Society for Gastrointestinal Endoscopy)[10] (score 5.5) possesses discrete features of applicability, but less clearly explained clinical and medical aspects of the disease. Moreover, it is prevalently specific for the endoscopic treatment of NVUIGH. The national guidelines issued by the SIED[11] are of good quality (score 4.5), easily applicable, but their only Italian version restricts their diffusion. The target population is not clearly declared in all the guidelines: we speculated about the fact that the guidelines are useful for physicians involved in the management of gastro-intestinal bleedings.

After a preliminary evaluation of the literature guidelines, the coordinating team was divided into four subgroups, each one following a topic, according to various key questions (Table 1).

Topics

The management of NVUIGH consisted of four steps: i) initial patients' evaluation, hemodynamic resuscitation and risk evaluation; ii) pre-endoscopic management; iii) endoscopic management; iv) post-endoscopic management.

Initial patients' evaluation, hemodynamic resuscitation and risk evaluation

Who needs resuscitation?

Immediate assessment of hemodynamic status with intravascular volume replacement initially using crystalloid fluids in case of hemodynamic instability is recommended.

Who needs blood product transfusion?

Level of hemoglobin between 7 g/dL and 9 g/dL should be taken into account as a target, when higher values occur in patients with significant co-morbidity (*e.g.*, ischemic cardiovascular disease).

Which are the reliable risk stratification score(s)?

The Glasgow-Blatchford score is suggested for pre-endoscopy risk stratification (Table 2).[16]

Score is equal to *0* when all the following parameters are present: i) hemoglobin level >12.9 g/dL (men) or >11.9 g/dL (women); ii) systolic blood pressure >109 mmHg; iii) pulse <100/min; iv) blood urea nitrogen level <18.2 mg/dL; v) neither melena nor syncope; vi) neither past or present liver disease nor heart failure.

Pre-endoscopic management

How to manage patient using antiplatelet and anticoagulant drugs?

Antiplatelet and anticoagulant drugs, including direct oral anticoagulants, should be discontinued and coagulopathy should be corrected, according to the patient's cardiovascular risk. Basing up the clinical situation, an international normalized ratio value <2.5 is recommended before performing endoscopy with or without endoscopic hemostasis.

What is the role of pre-endoscopy proton pump inhibitor therapy?

A high dose of intravenous proton pump inhibitors (PPI) followed by PPI continuous infusion (80 mg daily) in patients awaiting endoscopy should be performed but, in any case, PPI infusion should not delay the performance of early endoscopy.

Table 1. Non-variceal upper gastrointestinal hemorrhage (NVUGIH): task forces and key questions.

Topics	Key questions
Initial patients evaluation, hemodynamic resuscitation and risk evaluation	Who needs resuscitation? Who needs blood product transfusion? What are the reliable risk stratification score(s)?
Pre-endoscopic management	How to manage patient using antiplatelet and anticoagulant drugs? What is the role of pre-endoscopy proton pump inhibitor therapy? What is the role of pre-endoscopy somatostatin therapy? What is the role of naso-/orogastric tube aspiration/lavage? What is the role of endotracheal intubation before upper endoscopy? Is there a role for antifibrinolytic medications? What is appropriate timing for upper endoscopy?
Endoscopic management	Which endoscopic classification should be used for describing endoscopic stigmata of recent hemorrhage? Is there a role for doppler ultrasonography, magnification endoscopy, and chromoendoscopy in recent hemorrhage for peptic ulcer bleeding? Which ulcer stigmata require endoscopic hemostasis? Injection therapy? Thermal contact therapy? Thermal noncontact therapy? Mechanical therapy? Combination therapy?
Post-endoscopic management	What is the medical management post endoscopic hemostasis? What to do when rebleeding occurs? Is there a role for scheduled second-look endoscopy? When should the radiologist/surgeon be involved? Diagnosis and treatment of *Helicobacter pylori*? When? In whom? How to manage the non-variceal upper gastrointestinal hemorrhage patient using antiplatelet and anticoagulant drugs post endoscopy? How and when to reinstitute these medications? When to discharge patients home?

What is the role of pre-endoscopy somatostatin therapy?

The use of somatostatin, or its analogue octreotide, is not appropriate in this kind of patients.

What is the role of naso-/orogastric tube aspiration/lavage?

The routine use of nasogastric or orogastric aspiration/lavage should not be carried out.

What is the role of endotracheal intubation before upper endoscopy?

Endotracheal intubation prior to endoscopy should be executed in patients with ongoing active hematemesis, encephalopathy, or agitation.

Is there a role for antifibrinolytic medications?

The use of tranexamic acid is not recommended.

What is appropriate timing for upper endoscopy?

After hemodynamic resuscitation, upper GI endoscopy should be done early (≤24 h). Very early (<12 h) upper GI endoscopy may be considered in high risk patients, such as those with hemodynamic instability, despite volume resuscitation, active hematemesis or bloody nasogastric aspirate, contraindication to the interruption of anticoagulant therapy.

Table 2. The Glasgow-Blatchford score for pre-endoscopy risk stratification.

Glasgow-Blatchford score	
Admission risk marker	**Score component value**
Blood urea (mmol/L)	
6.5-8.0	2
8.0-10.0	3
10.0-25	4
>25	6
Hemoglobin (g/L) for men	
12.0-12.9	1
10.0-11.9	3
<10.0	6
Hemoglobin (g/L) for women	
10.0-11.9	1
<10.0	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Other markers	
Pulse ≥100 (per min)	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

Endoscopic management

Which endoscopic classification should be used for describing endoscopic stigmata of recent hemorrhage?

The Forrest (F) classification should be applied to differentiate low- and high-risk endoscopic stigmata.

Is there a role for Doppler ultrasonography, magnification endoscopy, and chromoendoscopy in recent hemorrhage for peptic ulcer bleeding?

Doppler ultrasounds or magnification endoscopy in the evaluation of endoscopic stigmata of peptic ulcer bleeding are not applicable.

Which ulcer stigmata require endoscopic hemostasis?

Forrest Ia, Ib and IIa lesions should receive endoscopic hemostasis because of the high risk for bleeding or rebleeding. Forrest IIb (adherent clot) lesions should be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding or nonbleeding visible vessel should receive endoscopic hemostasis.

Injection therapy?

Epinephrine injection should not be given as endoscopic monotherapy.

Combination therapy?

For patients with active bleeding ulcers epinephrine injection should be combined with a second hemostasis modality (contact thermal, mechanical therapy, or injection of a sclerosing agent). In case of bleeding not controlled by standard endoscopic hemostasis therapies, topical hemostatic spray or over-the-scope clip should be taken into account, if available.

Post-endoscopic management

What is the medical management post endoscopic hemostasis?

In patients who receive endoscopic hemostasis and in those ones with adherent clot not receiving endoscopic hemostasis PPI therapy should be administered by an intravenous bolus followed by continuous infusion (80 mg then 8 mg/h) for at least 72 h post endoscopy.

What to do when rebleeding occurs?

In patients with clinical evidence of rebleeding upper endoscopy with hemostasis should be repeated.

Is there a role for scheduled second-look endoscopy?

Only in patients with high risk of rebleeding second-look endoscopy should be considered.

When should the radiologist/surgeon be involved?

In case of failure of a second attempt of hemostasis, transcatheter angiographic embolization or surgery should be evaluated.

Diagnosis and treatment of* Helicobacter pylori*? When? In whom?

In patients with bleeding secondary to peptic ulcer, investigation for the presence of *H. pylori* in the acute setting is recommended, starting an appropriate antibiotic therapy if *H. pylori* is detected. Patients with a negative test in the acute setting should be re-tested. However, documentation of successful *H. pylori* eradication is recommended.

How to manage the non-variceal upper gastrointestinal hemorrhage patient using antiplatelet and anticoagulant drugs post endoscopy?

In patients with an indication for long-term anticoagulation, this kind of therapy should be restarted as soon as possible, but the timing should be decided on a patient-by-patient basis. Early restoring of anticoagulation (<7 days from bleeding) may be considered in patients at high thrombotic risk.

In patients receiving low dose aspirin for primary cardiovascular prophylaxis, who develop peptic ulcer bleeding, the risks/benefits of ongoing aspirin use in consultation with a cardiologist should be considered and low dose aspirin should be resumed after ulcer healing or earlier if clinically indicated. In case of assumption of low dose aspirin for secondary cardiovascular prophylaxis aspirin should be resumed immediately, following index endoscopy if the risk of rebleeding is low (*e.g.*, FIIc, FIII). In patients with high-risk peptic ulcer (FIa, FIb, FIIa, FIIb), early reintroduction of aspirin at least by the third day after index endoscopy is endorsed.

In patients receiving dual antiplatelet therapy, only low dose aspirin should be continued. A cardiological consultation about the timing of resuming the second antiplatelet agent should be obtained and PPI co-therapy should be initiated.

When to discharge patients home?

To date, there is not an established period after which a patient with non-variceal upper gastrointestinal bleeding should be discharged, thus a patient-by-patient strategy, even involving the consult of other specialists (*i.e.*, cardiologist), should be adopted.

Future directions

Although remarkable advances have been made in both endoscopic and pharmacological therapies for NVUGIH, more data are needed in many areas. We plan to facilitate the application of these guidelines by disseminating them to all participating societies and regions, for example by venues as symposia sessions or workshops at society meetings. Other scheduled application initiatives include preparation of an algorithm, a standardized slide presentation and additional relevant peer-reviewed publications (including ethics, diffusion of guidelines, methodology of randomized, controlled trials in NVUGIH, quality indicators, endoscopic classification of ulcer bleeding stigmata and health economics of NVUGIH), posting of major recommendations on society and government health Web sites and translation of the guidelines in society or regional journals. Finally, we anticipate that these guidelines will be periodically updated as soon as new data will become available.

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