

A summary of recent recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding

Joshua Greenspoon, Alan Barkun

Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital, Montreal, Canada

KEY WORDS

endoscopy, guidelines, hemorrhage, proton pump inhibitor, upper gastrointestinal bleeding

ABSTRACT

Recommendations in managing patients with nonvariceal upper gastrointestinal bleeding were recently updated, addressing resuscitation, risk assessment and pre-endoscopic care, endoscopy, pharmacotherapy, and secondary prophylaxis. Initial adequate resuscitation and risk stratification using validated scales remain critical. Intravenous erythromycin improves visualization when likely to find blood in the stomach. Pre-endoscopic proton pump inhibition (PPI) does not improve outcomes, but downstages high-risk endoscopic lesions and may be considered. In patients on anticoagulants, correction of a coagulopathy is recommended, but should not delay early endoscopy (within 24 h), as it improves clinical outcomes. In patients with high-risk endoscopic stigmata, although better than doing nothing, epinephrine injection alone provides suboptimal efficacy and should be combined with another modality such as clips, thermal or sclerosant injection, which are also efficacious alone. Following an attempt at dislodgment, adherent clots can be treated with high-dose intravenous PPI infusion alone (80 mg bolus and 8 mg/h for 3 days) or following endoscopic hemostasis. The combination is indicated for all other patients with high-risk stigmata as there is currently a lack of high-quality generalizable data supporting other intravenous or oral PPI regimens. A second-look endoscopy is recommended only selectively after endoscopic hemostasis. A negative *Helicobacter pylori* test requires confirmation in the acute setting. Following appropriate discussions, acetylsalicylic acid (ASA) can soon be restarted acutely after bleeding; long-term PPI co-therapy is imperative in patients having bled on nonsteroidal anti-inflammatory drugs if still needed (preferably with a cyclooxygenase-2, if appropriate) or ASA (not clopidogrel alone). Further work is needed to implement and disseminate these recommendations.

Correspondence to:

Alan Barkun, MD, CM, MSc,
Division of Gastroenterology,
The McGill University Health Center,
Montreal General Hospital, 1650
Cedar Avenue, Montréal, Canada
H3G 1A4, phone: +1-514-934-8309,
fax: +1-514-934-8532,
e-mail: alan.barkun@mhuc.mcgill.ca

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Introduction Upper gastrointestinal bleeding (UGIB) represents a substantial economic and clinical burden, with incidence ranging from 48 to 160 cases per 100,000 adults per year, and mortality ranging from 10% to 14%.¹ A multidisciplinary group of 34 experts from 15 countries met in late 2008 to develop international guidelines to help clinicians in making informed decisions regarding the optimal management of patients who present with nonvariceal UGIB. These consensus recommendations were subsequently published in early 2010. The guidelines are summarized below.

Recommendations relating to initial resuscitation of the patient

Upon presentation, appropriate initial resuscitation should precede any further diagnostic measures. Initial resuscitation includes stabilization of blood pressure and adequate restoration of intravascular volume. Patients with hemoglobin levels of 70 g/l or less should be administered blood transfusions to increase hemoglobin levels to the range of 70 to 90 g/l in the absence of coronary artery disease, tissue hypoperfusion, or acute hemorrhage.¹ A greater target hemoglobin level may be required in patients with cardiorespiratory morbidities. In patients receiving anticoagulants, correction of coagulopathy should be

TABLE 1 Clinical predictors of rebleeding and mortality

age > 65 y
comorbidities
fresh red blood emesis
poor overall health status
finding of fresh red blood on rectal examination
finding of fresh red blood in the nasogastric aspirate
low initial hemoglobin level
increased transfusion requirements

considered. A baseline international normalized ratio (INR) less than 1.3 vs. 1.3 or greater does not predict mortality, surgery, rebleeding, transfusion requirements, or length of stay² suggesting that it is not necessary to delay endoscopic therapy unless the INR (or prothrombin time) is supratherapeutic. The reader is cautioned that for patients with cirrhosis, neither the INR nor the prothrombin time have been shown to accurately predict the risk of bleeding;³ therefore, the approach suggested above should not be applied to these patients.

Early risk stratification and initial management

Placement of a nasogastric tube should be considered in patients, as the presence of blood in the nasogastric aspirate confirms an upper gastrointestinal source.⁴

Prognostic scales should be used to stratify patients into high- and low-risk categories for rebleeding and mortality.¹ Important clinical predictors of rebleeding and mortality include comorbid illness, low initial hemoglobin levels, transfusion requirements, finding of fresh red blood upon rectal examination or nasogastric aspirate or in the emesis, age over 65 years, and poor overall health status (TABLE 1). Endoscopic predictors of increased risk of rebleeding and mortality include active bleeding, ulcer size larger than 2 cm, ulcer location, and the presence of high risk stigmata (TABLE 2).¹ High risk lesions include those actively spurting (Forrest class IA) or oozing of blood (IB), a nonbleeding visible vessel (IIA), and adherent clots (IIB). Low-risk lesions include flat, pigmented spots (grade IIC) and clean-base ulcers (grade III). The Blatchford or preendoscopic Rockall score (based on age, comorbidity, and the presence or absence of hemodynamic instability) should initially be used to aid in stratification and in determining which patients require urgent endoscopy, or conversely, suitability for early discharge. The complete Rockall score should be used at endoscopy (add to the clinical Rockall score the nature and appearance of the bleeding lesion), as this score best identifies patients at low risk.⁵

Neither somatostatin nor octreotide have been found in contemporary summary analyses to improve patient outcomes compared with other pharmacotherapy or endoscopic therapy,⁶ and are therefore not recommended for routine use

TABLE 2 Endoscopic predictors of rebleeding and mortality

the presence of high risk stigmata in the ulcer base
– active bleeding
– spurting
– oozing
– nonbleeding visible vessel
– adherent clot
ulcer size > 2 cm
ulcer location (posterior in mid-gastric body and posterior in duodenal bulb)

in patients with nonvariceal bleeding.¹ The selective use of these agents can be considered for patients with massive unresponsive bleeding. They are indicated, of course, in the management of patients with variceal bleeding in conjunction with endoscopic ligation,⁷ but this indication was outside the scope of the Consensus document. Proton pump inhibitors are not promoted for routine use; however, patients suspected of having large amounts of blood or clots in the stomach or who have recently eaten should receive a prokinetic agent to improve visualization.¹ The administration of a proton pump inhibitor (PPI) prior to endoscopy should be considered as it downstages the bleeding lesion and decreases the need for endoscopic intervention.¹ Although administration of pre-endoscopic PPIs has not been shown to affect rates of rebleeding, surgery, or mortality, recent evidence has suggested that PPIs may have beneficial biological properties.⁸ The most cost-effective scenarios in which pre-endoscopic PPI use may be administered include treating a patient likely to be bleeding from a nonvariceal source, especially if it is likely to be a high-risk lesion, and if a delay to early endoscopy is likely to occur.¹ TABLE 3 summarizes the role of pharmacological agents in nonvariceal UGIB.

Endoscopic therapy Early endoscopy, defined as within the 24 hours following presentation, should be performed when possible, because early endoscopy is associated with improved patient outcomes, and, consequently, reductions in length of hospitalization for both low- and high-risk patients compared with delayed endoscopy.¹ Endoscopy may need to be delayed in rare patients, including those with suspected perforation or active acute coronary syndrome. Patients classified at very low risk for rebleeding may be discharged home immediately after an early endoscopy. Both this latter group and those patients exhibiting low-risk stigmata at endoscopy do not require endoscopic therapy and can be put on a single daily dose oral PPI; more complete postendoscopic pharmacological management is discussed below. All patients exhibiting high-risk lesions should receive endoscopic hemostasis.

Various endoscopic hemostatic techniques are available for use, including injection, thermocoagulation, and the use of clips. When a high-risk

TABLE 3 Summary of role of pharmacological agents in nonvariceal upper gastrointestinal bleeding

Medication	Recommendation
octreotide/somatostatin	Not recommended (can consider in cases of massive bleeding).
prokinetic agents (especially erythromycin)	Can be used selectively if suspecting blood in the stomach.
pre-endoscopy PPI	Can be used, especially if early endoscopy may be delayed, if the patient is likely to be bleeding from a nonvariceal source, and if a high-risk lesion is likely to be found.
H ₂ receptor antagonists	Not recommended.
postendoscopic hemostasis PPI	Administration of high-dose intravenous PPI 80 mg bolus + 8 mg/h for 72 hours is indicated. Low-dose intravenous regimens may be as effective as the high dose, yet more definitive evidence showing equivalence between the 2 regimens is needed before a low-dose regimen can be recommended. High-dose oral PPI can be considered in Asian populations.
PPI use upon discharge	All patients should be discharged on an oral PPI with dosage and duration dependent on the underlying etiology to decrease the risk of rebleeding.

Abbreviations: PPI – proton pump inhibitor

endoscopic stigma is noted, although better than doing nothing, epinephrine injection alone provides suboptimal efficacy and should be used in combination with another modality such as clips, thermal or sclerosant injection, which are also efficacious alone.^{10,11} Endoscopists should opt for an efficacious hemostatic method that they are most comfortable with. Finding a clot in an ulcer bed requires an attempt at dislodgement in order to treat the underlying lesion. Optimal treatment of adherent clots remains controversial; endoscopic therapy should be considered but high-dose intravenous PPI therapy may be sufficient.¹ Routine second-look endoscopy is not recommended.¹ Two meta-analyses^{12,13} had suggested marginal benefits in rebleeding rates; however, these analyses had significant methodological limitations and included trials in which patients were not treated in accordance with contemporary clinical guidelines. Second-look endoscopy

should be considered on a case-by-case basis, if the effectiveness of endoscopic hemostasis is in question or for patients at particularly high risk for rebleeding. The principles of endoscopic management are listed in **TABLE 4**.

Pharmacologic therapy Acid has been shown to inhibit platelet aggregation¹⁴ and to facilitate clot lysis through the activation of pepsin.¹⁵ Therefore, acid-suppressing agents are commonly used to stabilize intraluminal clots and improve patient outcomes. H₂-receptor antagonists (H₂RA) are not efficacious in maintaining the necessary acid suppression due to the development of pharmacological tolerance to these medications.^{16,17} One large randomized clinical trial¹⁸ and 2 meta-analyses^{19,20} have now confirmed that there are no overall benefits attributable to the acute use of intravenous or oral H₂RA in patients with peptic ulcer bleeding; thus, they are not recommended for routine management of patients with acute peptic ulcer bleeding.¹

Intravenous PPIs achieve more profound and sustained acid suppression than H₂RA without the development of tolerance.^{21–23} Meta-analyses^{24,25} have confirmed that administration of high-dose (80 mg bolus + 8 mg/h for 72 h) intravenous PPI to high-risk patients reduces the rate of rebleeding, surgery, and, in patients having undergone successful endoscopic therapy, even mortality. Low-dose intravenous regimens may be as effective as the high dose, yet more definitive evidence showing equivalence between the 2 regimens is necessary before a low-dose regimen can be recommended.¹ Few head-to-head gastric pH studies or clinical trials comparing oral and intravenous routes have been conducted; thus, conclusions regarding the effectiveness of oral PPI administration cannot be drawn at this time, although high-dose oral PPI has been shown effective in Asian patients. These benefits are unclear in a Caucasian population owing to differences in pharmacokinetics, parietal cell mass, *Helicobacter pylori* (*H. pylori*) carriage rates, and overall disease acuity of enrolled patients. Current consensus guidelines recommend the intravenous high-dose regimen to reduce rebleeding and mortality among high-risk

TABLE 4 Endoscopic principles of management in nonvariceal upper gastrointestinal bleeding

Endoscopy should be performed within the 24 hours that follow presentation when possible.
All patients exhibiting high-risk endoscopic stigmata should receive endoscopic hemostasis.
Highly selected patients at very low risk for rebleeding (see TABLE 5 for selection criteria) may be discharged home immediately after an early endoscopy.
Patients exhibiting a pigmented dot or clean base ulcer do not require endoscopic hemostasis.
Although better than doing nothing, epinephrine injection alone provides suboptimal efficacy and should be used in combination with another modality such as clips, thermal or sclerosant injection that are also efficacious alone.
Endoscopists should opt for an efficacious hemostatic method, with which they are most comfortable.
Finding a clot in an ulcer bed requires an attempt at dislodgement in order to treat the underlying lesion.
Optimal treatment of adherent clots remains controversial; endoscopic therapy should be considered but intensive intravenous PPI therapy may be sufficient.
Second-look endoscopy should be considered on a case-by-case basis if the effectiveness of endoscopic hemostasis is in question or for patients at particularly high risk of rebleeding.

TABLE 5 Selection criteria for early hospital discharge (following early endoscopy) (adapted from Gralnek et al. N Engl J Med. 2008; 359: 928-937)

age <60 y
no hemodynamic instability
no severe coexisting illness
a hemoglobin level over 80 gm/l after adequate vascular volume expansion
normal coagulation studies
onset of bleeding outside the hospital
presence of a clean-based bleeding lesion
adequate social support at home with an ability to return promptly to a healthcare facility

TABLE 6 Secondary prophylaxis considerations

<i>H. pylori</i> should be tested; if positive, subsequent treatment and confirmation of eradication.
A negative <i>H. pylori</i> diagnostic test should be repeated outside the acute setting.
Patients having experienced a bout of nonvariceal UGIB while on an NSAID require discontinuation of the NSAID or should be put on a COX-2 inhibitor (if no contraindication to its use) and a PPI, because this combination is associated with a decreased risk of rebleeding compared to the combination of a traditional NSAID and PPI or COX-2 inhibitor alone.
Patients requiring low-dose ASA should resume taking ASA as soon as the cardiovascular risks outweigh the risk of rebleeding.
A patient who has had an episode of nonvariceal UGIB while taking ASA, and who still requires cardioprotection, should be prophylaxed with a PPI, because the risk of bleeding persists if switched to clopidogrel alone.

Abbreviations: ASA – acetylsalicylic acid, COX-2 – cyclooxygenase-2, *H. pylori* – *Helicobacter pylori*, NSAID – nonsteroidal anti-inflammatory drugs, others – see [TABLE 3](#)

TABLE 7 The management of patients with nonvariceal upper gastrointestinal bleeding who experience a rebleeding episode

In cases of rebleeding, a second attempt at endoscopic therapy is recommended to reduce the need for surgery.
In patients having failed endoscopic therapy, surgery should be considered.
If available, percutaneous embolization can be considered as an alternative to surgery.

patients.¹ An important point to remember is that if the patient was administered an 80 mg bolus prior to endoscopy, the patient need not receive another bolus after endoscopic therapy.

In-hospital management issues Patients considered at low risk for rebleeding after endoscopy can be fed within 24 hours.¹ Certain patients, including those found to be bleeding from a Mallory-Weiss tear or an ulcer exhibiting a clean base, flat spot, may be discharged within 24 hours. Most high-risk lesions require approximately 72 hours to evolve into a low-risk appearance after endoscopic therapy, and several trials²⁶⁻²⁸ have confirmed that most rebleeding (approximately 80%) in high risk patients occurs within the first 72 hours. Consequently, it is recommended that patients with high-risk stigmata be hospitalized for the full 72 hours of high-dose intravenous PPI therapy following endoscopic hemostasis.

Discharge and subsequent pharmacological management Randomized clinical trials of highly selected patients at very low risk for rebleeding^{1,29} found no difference in outcomes with a policy of very early discharge. Criteria for such early discharge include the finding of a clean ulcer base, adequate sociofamily support at home, accessibility to a hospital, and initial hemodynamic stability. Additional selection criteria are listed in [TABLE 5](#). Patients are not suitable for early discharge if they exhibit serious comorbid illness, have an endoscopic finding of high-risk stigmata as defined previously, are hemodynamically unstable, or have undesirable sociofamily conditions.⁹

All patients should be discharged on an oral PPI with dosage and duration dependent on the underlying etiology to decrease the risk of rebleeding.¹

H. Pylori should be tested for with subsequent eradication if positive, with subsequent confirmation of eradication. Due to tendency of *H. pylori* diagnostic tests to produce false negative results in the acute setting, a negative test should be repeated outside the acute setting. Patients having experienced a bout of nonvariceal UGIB while on a nonsteroidal anti-inflammatory drug (NSAID) require discontinuation of the NSAID or should be put on a COX-2 inhibitor (if no contraindication to its use) and a PPI since this combination is associated with a decreased risk of rebleeding compared to the combination of a traditional NSAID and PPI or cyclooxygenase-2 inhibitor alone.¹ Patients requiring low-dose acetylsalicylic acid (ASA) should resume taking ASA as soon as the cardiovascular risks outweigh the risk of rebleeding.¹ This could be as early as 5 days after the onset of bleeding and should be determined after appropriate discussions with all healthcare professionals involved in the management of the patient. A patient who has had an episode of nonvariceal UGIB while taking ASA and who still requires cardioprotection should be prophylaxed with a PPI as the risk of bleeding persists if switched to clopidogrel alone.¹ In patients having bled on clopidogrel and who are thus at a very high risk for rebleeding, the benefits of the PPI secondary prophylaxis is likely to outweigh any risk attributable to a clopidogrel-PPI interaction with regards to cardiovascular events.

Rebleeding In cases of rebleeding, a second attempt at endoscopic therapy is recommended to reduce the need for surgery.¹ In patients having failed endoscopic therapy, surgery should be considered.¹ If available, percutaneous embolization can be considered as an alternative to surgery.¹

Summary This brief review attempts to summarize the main recommendations recently put forward by an expert group.¹ The guidelines outline general management principles that may need to be individualized and adapted after involvement of the entire healthcare management team, especially considering the increasing complexity of

affected patients. As new research is performed, it is anticipated that the current guidelines will need updating, and the reader is encouraged to keep abreast of evolving literature in this important area.

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Postępowanie u chorych z nieżyłakowym krwawieniem z górnego odcinka przewodu pokarmowego – podsumowanie aktualnych zaleceń

Joshua Greenspoon, Alan Barkun

Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital, Montreal, Kanada

SŁOWA KLUCZOWE

endoskopia, inhibitor pompy protonowej, krwawienie z górnego odcinka przewodu pokarmowego, krwotok, wytyczne

STRESZCZENIE

Niedawno zaktualizowane zalecenia odnośnie do leczenia chorych z nieżyłakowym krwawieniem z górnego odcinka przewodu pokarmowego dotyczą resuscytacji, oceny ryzyka i leczenia przed endoskopią, endoskopii, farmakoterapii i profilaktyki wtórnej. Podstawowe znaczenie ma wciąż właściwa resuscytacja i stratyfikacja ryzyka za pomocą walidowanych skal. Dożylnie podanie erytromycyny poprawia widoczność w przypadku obecności krwi w żołądku. Można rozważyć podanie przed endoskopią inhibitorów pompy protonowej (IPP) – nie poprawiają one rokowania, ale powodują zmniejszenie zmian endoskopowych dużego ryzyka. U chorych przyjmujących antykoagulanty zaleca się skorygowanie koagulopatii, które jednak nie powinno opóźniać wcześniej endoskopii (w ciągu 24 h), ponieważ poprawia ona wyniki kliniczne. W przypadku endoskopowych cech dużego ryzyka nastrzykiwanie adrenaliną nie jest wystarczająco skuteczne i powinno być stosowane w połączeniu z inną metodą, skuteczną również samodzielnie – zakładaniem klipsów, termokoagulacją lub wstrzyknięciem środka obliterującego. W przypadku przylegającego skrzepu, jeżeli nie powiedzie się próba jego usunięcia, można zastosować IPP dożylnie w dużej dawce (bolus 80 mg i 8 mg/h przez 3 dni), sam albo po hemostazie endoskopowej. To ostatnie skojarzenie jest wskazane u wszystkich pozostałych chorych z endoskopowymi cechami dużego ryzyka, ponieważ obecnie brakuje dobrej jakości danych wspierających inne schematy stosowania IPP dożylnie lub doustnie. Kontrolna endoskopia jest wskazana tylko wybiórczo po hemostazie endoskopowej. Ujemny wynik testu w kierunku *Helicobacter pylori* w stanie ostrym wymaga późniejszego potwierdzenia. Po odpowiednich konsultacjach można szybko wznowić stosowanie kwasu acetylosalicylowego (*acetylsalicylic acid* – ASA); u chorych po krwawieniu konieczne jest długoterminowe przyjmowanie IPP w razie stosowania niesteroidowych leków przeciwzapalnych (najlepiej inhibitorów COX-2, jeśli to możliwe) i ASA (nie wystarczy zmiana na kłopidogrel). Konieczne są dalsze prace nad rozpowszechnianiem i wdrażaniem tych wytycznych.

Adres do korespondencji:
Alan Barkun, MD, CM, MSc,
Division of Gastroenterology,
The McGill University Health Center,
Montreal General Hospital site, 1650
Cedar Avenue, Montreal, Kanada
H3G 1A4, tel.: +1-514-934-8309,
fax: +1-514-934-8532,
e-mail: alan.barkun@mhuc.mcgill.ca
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