

Recent advances on the management of patients with non-variceal upper gastrointestinal bleeding

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Abstract

Non-variceal upper gastrointestinal bleeding is a common emergency associated with significant morbidity and mortality. The mainstays of therapy include prompt resuscitation, early risk stratification, and appropriate access to endoscopy. Patients with high-risk endoscopic findings should receive endoscopic hemostasis with a modality of established efficacy. The pillar of post-endoscopic therapy is acid-suppression via proton pump inhibitors (PPI), although the optimal dose and route of administration are still unclear. Post-discharge management of patients with peptic ulcers includes standard oral PPI treatment and eradication of *Helicobacter pylori* infection. The risk of recurrent bleeding should be carefully considered and appropriate gastroprotection should be offered when non-steroid anti-inflammatory drugs, anti-platelet agents, and/or anticoagulation need to be used. This review seeks to survey new evidence in the management of non-variceal upper gastrointestinal bleeding that has emerged in the past 3 years and put it into context with recommendations from recent practice guidelines.

Keywords Non-variceal upper gastrointestinal bleeding, risk stratification, proton pump inhibitors, endoscopic hemostasis

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Introduction

Non-variceal upper gastrointestinal (GI) bleeding (NVUGIB) is a common emergency, affecting 44 to 99 per 100,000 persons every year [1,2]. Peptic ulcer bleeding is the principal cause of NVUGIB [3]. Significant bleeding can result in major consequences, such as acute coronary syndromes [4]. The mortality from NVUGIB remains high. A recent UK national audit found a 9.6% in-hospital mortality rate [5]. Recurrence of bleeding occurs in 8-26% of patients [6,7], and is associated with an even higher mortality. Mortality is also increased in the elderly [8].

Such a serious disease inspires constant research in the hope of decreasing complications and mortality. A number of practice guidelines have been developed to help clinicians

manage patients with NVUGIB, including those issued by the UK National Institute for Health and Clinical Excellence (NICE) [9], an International Consensus meeting [10], and the American College of Gastroenterology (ACG) [11]. Of note, the Hellenic Society of Gastroenterology held a national consensus meeting on NVUGIB in Athens on June 8, 2008; the recommendations have not been published, but were remarkably similar to the International Consensus recommendations that were formed a few months later [10]. The principle components of management include resuscitation, risk-stratification, endoscopy for diagnosis and appropriate intervention, and post-endoscopic acid-suppression. All of these factors are the subject of constant revision and rigorous testing to improve outcomes and, in the last three years in particular, the literature has grown considerably. This review serves to survey the most recent evidence to emerge in the management of NVUGIB and put in into context with recommendations from the recent practice guidelines.

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Pre-endoscopic approach and management

Resuscitation

All management guidelines recommend prompt assessment of hemodynamic status and resuscitation if required. Generally, the guidelines agree that red blood cell transfusions should be administered to patients whose hemoglobin levels drop to 70

g/L or less [10,11]. In 2010, Hearnshaw *et al* [12] published a prospective cohort study assessing outcomes in patients who received blood transfusions within 12 h of presentation. They found that, regardless of the initial hemoglobin level (greater than or less than 80 g/L), the rates of rebleeding were higher in those who received early transfusion. The odds ratio (OR) for rebleeding was 2.26, adjusted for Rockall score and initial hemoglobin level. Mortality at 30 days was greater in those receiving transfusion, but not significantly so when adjusted for initial hemoglobin level and Rockall score. Previous randomized controlled trials (RCTs) had shown comparable results, but these were performed over a decade ago when appropriate endoscopic hemostasis was not offered in all high-risk patients [13,14].

However, a more recent RCT on this topic was published by Villanueva *et al* [15] who randomized 921 patients (bleeding peptic ulcer 48%, variceal bleeding 24%) with upper GI bleeding to either a restrictive (transfuse at a hemoglobin level of 70 g/L) or liberal (transfuse at a hemoglobin level of 90 g/L) transfusion strategy. The patients were treated according to current standards of care with regards to proton pump inhibitor (PPI) treatment and endoscopic hemostasis. Patients treated with the restrictive strategy had significantly lower mortality at 45 days [hazard ratio (HR) =0.55; 95% confidence interval (CI) 0.33 to 0.92], less rebleeding, and experienced fewer overall adverse events. These findings attracted high publicity but should be interpreted with caution because of high risk of performance bias (due to lack of blinding) and limited generalizability (many potentially eligible patients were either not screened or excluded for reasons such as “massive” bleeding or severe comorbidity). Furthermore, the subgroup analyses on peptic ulcer bleeding versus variceal bleeding, albeit important, were underpowered; therefore, no conclusion could be drawn specifically for patients with peptic ulcer bleeding [15].

Considerations

All patients should be assessed for evidence of hemodynamic compromise and low hemoglobin levels. The decision to transfuse should take into account the hemoglobin level, but practitioners should keep in mind that transfusion may carry the risks of complications. This decision should be weighed carefully for each individual patient. As common sense dictates, hypovolemic patients with acute massive blood loss who may only show a spuriously small drop in hemoglobin on presentation should be managed proactively according to the hemoglobin levels that are anticipated to show following volume resuscitation. Similarly, a higher target level of hemoglobin should be pursued in patients who have low tolerance to anemia because of comorbidities such as coronary artery disease, cardiac or renal failure. More research is necessary before sound recommendations can be made about the hemoglobin threshold for transfusion and the target hemoglobin levels.

Risk stratification, management of co-morbidities, and time to endoscopy

Many patients who experience upper GI bleeding have other medical co-morbidities which can affect their outcomes. Anticoagulation, in particular, is a treatment for many medical conditions, and recent guidelines recommend reversal of coagulopathy when it is identified [9]. They make note, however, that reversal should not delay endoscopy [10].

There exists general consensus that patients presenting with upper GI bleeding should be considered for risk-stratification using an evidence-based scoring system such as the Rockall score [16] or the Blatchford score [17]. The two scores differ in their clinical predictions. The complete (post-endoscopy) Rockall score predicts the occurrence of rebleeding and mortality, and those patients who are at low risk for rebleeding and death can be safely discharged after endoscopy [10]. The Blatchford score can be completed prior to endoscopy and predicts the need for intervention. There are no guidelines that recommend one particular risk-assessment score, though the NICE guidelines recommend performing the Blatchford score at first assessment and the complete Rockall score after endoscopy [9]. NICE performed a rigorous systematic review and meta-analysis on the prognostic accuracy of these scoring systems. Both of them have higher sensitivity than specificity and therefore are mainly useful for ruling out high risk patients. The Blatchford score is extremely sensitive (99-100%), but the quality of evidence for this result is “low” according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [18]; the Rockall is slightly less sensitive (98%), but the quality of evidence for this is somehow better (“moderate” according to GRADE) [9].

Schiefer *et al* [19] assessed the utility of the Blatchford score in a retrospective cohort study that was published in 2012. They reviewed the cases of 478 patients who presented to the emergency departments of 2 centres in the Netherlands with acute upper GI bleeding and scored them by the Blatchford score and other scoring systems. 104 patients had a Blatchford score of 2 or less. Of those, only 2 required endoscopic intervention (neither died). This resulted in 99.2% sensitivity and 42.9% specificity for intervention when a score of 2 was used as a cut-off. This further strengthens previously published guideline recommendations that patients with a low Blatchford score can be safely managed as outpatients [11]. Those who do not meet these criteria are recommended to proceed to endoscopy for diagnosis and possible therapy within 24 h or immediately after resuscitation [9-11].

Considerations

Clinicians should assess their patients for presence or history of other medical co-morbidities, particularly coagulopathy. Consideration should be given to the patient’s clinical risk as predicted by tools such as the Blatchford Score and/or Rockall Score. These scores should also direct management in the post-endoscopic period. Patients deemed to be at low risk can be managed as outpatients, whereas those at higher risk should proceed to endoscopy within 24 h.

Pre-endoscopic management

There are a number of interventions that can be considered prior to endoscopy for patients experiencing upper GI bleeding. Nasogastric tubes or orogastric tubes have been used for gastric lavage in the past, but there is no evidence that this improves outcomes and the recommendations are conflicting regarding their utility in terms of diagnosis or improvement of visualization at the time of endoscopy [10,11]. Pre-endoscopic PPI treatment can be considered, as it reduces the severity of bleeding lesions at the time of endoscopy but has not been shown to improve important clinical outcomes (such as rebleeding and mortality) and it should not replace or delay endoscopy [10,11,20]. Pre-endoscopic PPI treatment would theoretically be most beneficial when endoscopy is expected to be delayed or when the endoscopists have limited experience in endoscopic hemostasis [10].

The question of pre-endoscopic medical management frequently involves the decision to administer prokinetic agents prior to endoscopy. This can be considered in patients presenting with upper GI bleeding, but should not necessarily be used in all patients [11]. Barkun *et al* [21] published a meta-analysis of RCTs on the use of prokinetics (erythromycin or metoclopramide) in upper GI bleeding in 2010. This included 3 full publications and 2 abstracts with a combined total of 319 patients. They found that use of prokinetics prior to endoscopy significantly decreased the need for repeat endoscopy to determine the source of bleeding (OR 0.55; 95% CI 0.32-0.94). No significant difference was found regarding number of units of blood transfused or length of hospital stay. Previously published guidelines recommend erythromycin as the prokinetic agent of choice [10].

Considerations

Clinicians should consider the use of pre-endoscopic PPIs, particularly for those patients in whom endoscopy will be temporarily or indefinitely delayed. Naso- or orogastric tube placement is rarely useful. Prokinetic agents should be considered to reduce the need for repeat diagnostic endoscopy in patients when large amount of fresh blood or clots are anticipated to be present in the stomach.

Endoscopic management

For those patients who require endoscopy, the decision to intervene depends on the severity of the lesion(s) found. Major guidelines generally proscribe that low-risk lesions, such as a clean-based ulcer or non-protuberant pigmented dot, do not require endoscopic intervention. Ulcers with adherent clots, however, require a more nuanced approach. Recent guidelines [10,11] recommend attempting to dislodge any adherent clot via irrigation and treating the underlying lesion based on its appearance.

Higher-risk lesions, such as spurting or oozing lesions

and non-bleeding visible vessels, should be treated endoscopically. However, which modality results in the highest rates of hemostasis is still debated. Generally, the use of thermocoagulation (no specific thermal coaptive therapy has been shown to be superior to others) or sclerosant are recommended as useful modalities. Clips can be used as well, though the ACG guidelines note that studies comparing clips to other hemostatic modalities are lacking [11]. Most guidelines include injection of epinephrine (adrenaline) as an acceptable mode of achieving hemostasis, but strictly as an adjunctive therapy [10].

In the past few years, a number of articles have been published that provide new evidence for the effectiveness of the various endoscopic treatment modalities. The most recent of these concerns one of the newest modalities to be developed: the nanopowder TC-325 (Hemospray™, Cook Endoscopy). This granular powder is sprayed upon lesions where it coalesces to form a mechanical barrier that adheres to the mucosa and it is thought not to be systemically absorbed or have systemic toxicity [22].

In 2011, Sung *et al* [23] conducted a single arm phase II clinical trial in Hong Kong. They included patients who presented with upper GI bleeding and were found to have active bleeding (spurting or oozing) at endoscopy that was performed within 24 h. None of the patients were hemodynamically unstable or coagulopathic. Hemospray was applied to the identified lesion until hemostasis was controlled. If rebleeding occurred within the following 5-min observation period, the Hemospray was applied again. If rebleeding occurred again, Hemospray was abandoned and a standard hemostatic modality was used. Second-look endoscopy was performed at 72 h or upon suspicion of rebleeding. Using this technique, 19 of the 20 patients achieved hemostasis. Two of the remaining patients experienced rebleeding. No intervention-related complications were reported by 30 days.

Ljubicic *et al* [24] published an RCT in 2012 looking at the effectiveness of endoclips versus large (30-40 mL) or small-volume (15-20 mL) epinephrine injection of 1:10,000 for achieving hemostasis in 150 patients with non-bleeding visible vessel found on endoscopy. All patients were started on intensive PPI therapy after endoscopy. All patients underwent repeat endoscopy at 4-5 days or upon suspicion of rebleeding (based on well-defined criteria). There was significantly less early rebleeding in the hemoclip group compared to either of the epinephrine injection groups. Unfortunately, late rebleeding rates were not reported. The duration of hospital stay was also shorter in patients receiving hemoclips. There were no statistical differences between the groups with regards to transfusion requirements or 30-day mortality.

Over the past decade, interest has piqued for a novel endoscopic method for assessment of bleeding lesions. Doppler ultrasound method for assessment of bleeding lesions. Doppler ultrasound probes (DUP) can be introduced through the biopsy channel of an endoscope and applied directly onto a lesion; movement of blood through vessels underneath the mucosa is picked up and converted to an audible signal. There is older data to suggest that utilization of DUP to guide endoscopic hemostatic therapy can reduce the rates of recurrent bleeding

[25]. More recently, an abstract published by Pekárdi *et al* [26] showed that, in 44 patients with bleeding peptic ulcers, DUP findings were not always consistent with the endoscopic appearance (Forrest classification). DUP findings required re-stratification of rebleeding risk in 30% of the patients.

Specific to the problem of bleeding Dieulafoy lesions, Cui *et al* [27] published an RCT in 2011 comparing the efficacy of sclerosant injection to hemoclips or both in 107 patients with upper GI bleeding due to Dieulafoy lesions. The combination therapy group achieved significantly higher hemostasis at a rate of 96.7%, compared to 77.4% for hemoclips alone and 71.7% for sclerosis alone. Two previously published, smaller RCTs had shown that epinephrine alone should not be used for bleeding Dieulafoy lesions, as it results in inferior hemostasis rates compared to hemoclips [28] or band ligation [29], respectively.

Considerations

Patients with lesions found on endoscopy should be treated based on the appearance of the lesion. Lower-risk lesions should be treated medically. Higher-risk lesions should be treated with endoscopic intervention such as hemoclip or thermocoagulation. While there are no strict guidelines on the use of one modality over another, for Dieulafoy lesions, clinicians can consider the combined use of hemoclip and sclerosant injection for more definitive therapy, though there is not yet enough evidence to recommend this as standard therapy. Finally, Hemospray, a relatively novel mechanical hemostatic therapy, has some evidence to suggest it is a useful modality for non-variceal upper GI bleeding, especially in bleeding from wide-spread malignant lesions. However, even in jurisdictions where it is approved for use, consideration should be paid to more standard treatments first, until comparative trials of Hemospray to other modalities provides evidence for its non-inferiority or superiority compared to existing modalities.

Post-endoscopic in-hospital management

The mainstay of medical therapy after endoscopy is acid suppression. To this end, histamine-2 receptor antagonists (H₂RAs) are not recommended, as PPIs can have greater efficacy [10,30,31]. PPIs have been shown to reduce rebleeding and the need for urgent surgery compared to either H₂RAs or placebo in patients with peptic ulcer bleeding [30]. A recently updated Cochrane review of 34 RCTs (comprising a total of more than 6000 patients with peptic ulcer bleeding) showed that PPIs compared to control treatment (H₂RAs or placebo) significantly reduced rebleeding (OR 0.45, 95% CI 0.36-0.56), the need for urgent surgery (OR 0.58, 95% CI 0.46-0.72) and the need for repeat endoscopic treatment (OR 0.53, 95% CI 0.41-0.68) [32]. There was no demonstrable effect on mortality in the overall analysis (OR 0.83, 95% CI 0.60-1.14); however,

mortality was significantly reduced by PPI treatment in patients who received endoscopic treatment at the initial endoscopy (OR 0.62, 95% CI 0.42-0.91) [32].

All consensus guidelines concur in their recommendation to use PPIs in patients with peptic ulcer bleeding [9-11]. However, consensus is lacking among the different guidelines with regards to the optimal dose and route of administration of PPIs. The NICE guidelines recommend PPI treatment following endoscopy but consider the current evidence as inadequate to support a recommendation on the optimal dose and optimal route of administration [9]. In contrast, an international consensus group of experts and the ACG recommend that patients with high-risk lesions requiring endoscopic treatment should receive high-dose IV PPI treatment (80 mg IV bolus followed by continuous IV infusion of 8 mg/h) for 72 h [10,11]. As for patients with low-risk lesions (ulcers with pigmented flat spots or clean base), the international guidelines leave the dose and route of PPI treatment at the discretion of the clinicians [10], while the ACG recommends oral PPIs [11].

The question of the optimal dose and route of PPI treatment in patients with endoscopically diagnosed peptic ulcer bleeding remains open. Three relevant systematic reviews and meta-analyses of RCTs have been conducted recently. In 2010, Wang *et al* [33] included 7 RCTs that were of “high quality” according to the Jadad scale (however, as we have previously pointed out [34], the evidence derived from these studies was “low quality” according to the GRADE approach [18]). These 7 RCTs had compared the high dose IV PPI regimen (80 mg bolus followed by 8 mg/h) with other lower dose PPI regimens (IV or oral). Also in 2010, Wu *et al* [35] included 9 RCTs that compared two regimens of PPIs provided that one was at least twice the dose of the other. A 2013 Cochrane review included 22 RCTs [36] (many of these studies had been missed by the previous reviews, while others were published subsequent to the search dates of the previous reviews). All three reviews reached very similar results: high-dose PPI treatment was not significantly better than lower-dose PPI treatment with regards to any clinical outcome, including mortality, rebleeding and surgery, but the 95% CIs were very wide. The two reviews that were published in 2010 interpreted these results as evidence of equivalence or non-inferiority [33,35]. In contrast, the Cochrane review concluded there was “insufficient evidence for concluding superiority, inferiority or equivalence of high dose PPI treatment over lower doses in peptic ulcer bleeding” [36].

Unfortunately, individual RCTs that compared different regimens of PPIs in peptic ulcer bleeding and even the meta-analysis of these trials remain severely underpowered. What is worse, it is not likely that an adequately powered RCT will be conducted in the near future due to feasibility issues and lack of funding from pharmaceutical companies facing increasing generic competition. Then how will we be able to decide on this issue? It seems that, for the time being, a reasonable approach is the approach chosen by the international consensus group who stated that “strong evidence

demonstrates the efficacy of high-dose IV PPI therapy after successful endoscopy, but it is not possible to make conclusions regarding the efficacy of either lower intravenous doses or high-dose oral therapy” [10]. This statement was largely based on the results of a 2006 Cochrane review that showed that, among patients with high-risk endoscopic lesions who had received endoscopic hemostatic therapy, high dose IV PPI therapy (80 mg bolus plus 8 mg/h continuous infusion) significantly reduced rebleeding and mortality, while lower doses (IV or oral) significantly reduced rebleeding but had no demonstrable effect on mortality [30]. The 2013 update of that review showed very similar results [32].

It is important to note that even if the guideline recommendations are followed, a significant proportion of patients will rebleed; there is still room for improvement in the management of patients with NVUGIB, especially in those who have been found to have high-risk endoscopic lesions. A recent RCT attempted to improve outcomes for these patients [37]. 105 patients with upper GI bleeding and high-risk endoscopic lesions were treated successfully with endoscopic combination treatment and were started on IV PPI treatment. Then, they were randomized to either receive supplementary (preventive) transcatheter arterial embolization or continue standard treatment. The group that received preventive embolization therapy experienced less rebleeding episodes (2 versus 8 patients). The results did not reach statistical significance as the study was underpowered, but the concept is worth further research.

Consensus guidelines suggest that clinicians not routinely perform a repeat endoscopy during hospital admission unless the patient experiences evidence of rebleeding [10,11]. This recommendation was reached despite the fact that two systematic review and meta-analyses of RCTs [38,39] had suggested some benefits. The main reason for this apparent discrepancy between guidelines and meta-analyses was that the vast majority of the RCTs included in these meta-analyses had used endoscopic and medical treatments that would have been considered suboptimal nowadays; therefore their results are not applicable to current practice.

When endoscopic therapy fails a second time, guidelines suggest pursuing alternative measures of hemostasis, such as surgical or radiological intervention. In 2010, Lenhart *et al* [40] retrospectively analyzed 16 cases of patients who failed endoscopic therapy for NVUGIB. The patients underwent emergency arterial embolization therapy with a new agent: liquid polyvinyl alcohol copolymer (Onyx®). The authors were able to achieve hemostasis in all 16 cases. No significant side effects such as bowel necrosis were reported, however, the follow-up period was only up to one month.

Considerations

After endoscopy, clinicians should start their patients on PPI therapy. Patients who have received endoscopic hemostasis for high risk lesions should receive IV infusion of high-dose PPI. Patients should only undergo repeat endoscopy if they exhibit signs of recurrent bleeding [10].

Post-discharge management

For patients with lesions identified on endoscopy, it is recommended they be started on an oral anti-secretory agent. PPIs are the pharmacologic agent of choice in these patients; H₂RAs are generally regarded as inadequate. This was demonstrated most recently by an excellent publication by Ng *et al* [41] in 2010. 130 patients who experienced dyspepsia or bleeding while taking acetylsalicylic acid (ASA) and were found to have peptic ulcers or multiple erosions at endoscopy were randomized to receive either famotidine 40 mg twice daily or pantoprazole 20 mg once daily (with evening placebo) for 7 weeks. All patients remained on ASA (160 mg daily), and were treated for *Helicobacter pylori* (*H. pylori*) infection if this was present. Patients on pantoprazole experienced significantly fewer symptoms from ulcers or erosions and, most importantly, significantly fewer bleeding episodes.

Practice guidelines recommend the use of PPI for all patients with previous ulcer bleeding who require treatment with any non-steroid anti-inflammatory drug (NSAID) [10,11,42]. They make particular note that the use of clopidogrel alone presents a greater risk for rebleeding than does the use of ASA combined with a PPI.

Many patients who experience upper GI bleeding are already taking or will eventually require treatment with ASA. While ASA is a known risk factor for the development of peptic ulcer disease [42], many patients should be taking ASA for primary or secondary prevention of cardiovascular disease. As weighing the risks of bleeding versus coronary artery disease can be difficult, Sung *et al* [43] recently performed a single-center, non-inferiority double blind RCT in Hong Kong wherein they randomized 156 patients who developed peptic ulcer bleeding while prescribed ASA to restart (immediately after endoscopic hemostasis) taking ASA 80 mg daily over 8 weeks or switch to placebo for 8 weeks. All patients were given daily omeprazole. Patients taking ASA had a non-significant increase in the rate of rebleeding, but also a significantly lower all-cause mortality rate (HR 0.2, 95% CI 0.05-0.90). This lends more credibility to the idea that ASA should be resumed in patients even after experiencing a bleeding ulcer. It would be useful if future studies compare less extreme strategies (e.g. restarting ASA immediately or 2 days after endoscopic hemostasis versus restarting in 7 days).

Considerations

Patients who experience peptic ulcer bleeding should be discharged home on oral PPI treatment. H₂RA use is not an equivalent alternative. Attention should be paid to patients' concurrent medications, particularly the use of NSAIDs; they should be discontinued if possible. For those patients who require long-term ASA use, these drugs should be restarted as soon as the risk of cardiovascular complications outweighs the risk of rebleeding. PPIs should be administered for as long as ASA is used, but even so, patients should be made aware the risk of rebleeding is significantly reduced but not eliminated. Patients should be tested for *H. pylori* via endoscopic biopsy, be treated if infection is diagnosed, and undergo confirmation of eradication.

Conclusions

NVUGIB is a common and serious condition that, unfortunately, still carries a high degree of mortality. While the advances of the past few years promise to improve management, they also open up new questions and avenues for investigation. There is now growing evidence that the use of prokinetic agents can benefit certain subsets of patients with upper GI bleeding, but more research will likely be required before their use is adopted by all major guideline committees. The introduction of novel hemostatic methods, such as nanopowders, offers exciting new possibilities for the mechanical management of bleeding lesions. More research should also be devoted to investigating the various other mechanical and injectable hemostatic modalities that are already more widely in use. The appropriate hemoglobin level for consideration of red blood cell transfusion and the optimal dose and route of administration for PPI after endoscopy are unclear, but stronger evidence is required before firm changes can be made to practice guidelines. Finally, much of the data that exists focuses specifically on the treatment of peptic ulcer bleeding; studies on the optimal ways to manage the other entities that result in upper GI bleeding require strong consideration as well.

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