

**Review Article**

**The Acute Management of Nonvariceal Upper Gastrointestinal Bleeding**

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**Background.** The mortality from nonvariceal upper gastrointestinal bleeding is still around 5%, despite the increased use of proton-pump inhibitors and the advancement of endoscopic therapeutic modalities. **Aim.** To review the state-of-the-art management of acute non variceal upper gastrointestinal bleeding from the presentation to the emergency department, risk stratification, endoscopic hemostasis, and postendoscopic consolidation management to reduce the risk of recurrent bleeding from peptic ulcers. **Methods.** A PubMed search was performed using the following key words acute management, non variceal upper gastrointestinal bleeding, and bleeding peptic ulcers. **Results.** Risk stratifying patients with acute non variceal upper gastrointestinal bleeding allows the categorization into low risk versus high risk of rebleeding, subsequently safely discharging low risk patients early from the emergency department, while achieving adequate hemostasis in high-risk lesions followed by continuous proton-pump inhibitors for 72 hours. Dual endoscopic therapy still remains the recommended choice in controlling bleeding from peptic ulcers despite the emergence of new endoscopic modalities such as the hemostatic powder. **Conclusion.** The management of nonvariceal upper gastrointestinal bleeding involves adequate resuscitation, preendoscopic risk assessment, endoscopic hemostasis, and postendoscopic pharmacological and nonpharmacological treatment.

**1. Introduction**

About 10% of the population in the Western world will experience peptic ulcer disease at some point during their lives. Individuals with peptic ulcer disease may present with a variety of gastrointestinal (GI) symptoms including abdominal pain, vomiting, and bleeding. Indeed, peptic ulcer disease is the most common cause of conditions such as upper GI hemorrhage and perforation, which are associated with high mortality and morbidity [1].

Acute upper gastrointestinal bleeding (AUGIB) is one of the commonest causes for hospitalization worldwide. In the United States, there are 250,000 to 300,000 hospital admissions and 15,000 to 30,000 deaths each year resulting from acute upper GI hemorrhage [2]. The mortality from bleeding peptic ulcer disease remains unchanged around 5% [3, 4], despite the use of PPI and advances in endoscopic therapy. The unchanged mortality rate might reflect the increased use of aspirin and NSAID in the elderly population with multiple underlying comorbidities that puts such patients at higher risk of both bleeding and death [5]. The incidence of AUGIB ranges from 48 to 160 cases per 100,000 adults per year [6]. For patients with and without complications of nonvariceal upper gastrointestinal bleeding (NVUGIB) in the United States, mean lengths of stay were 4.4 and 2.7 days and hospitalization costs were $5632 and $3402 (2004 US dollars), respectively [6].

Our paper will focus on the state-of-the-art management of bleeding peptic ulcer disease. There are five cornerstone elements critical to the appropriate management of patients with NVUGIB. They are resuscitation, risk assessment, preendoscopic care, endoscopic management, and postendoscopic care including pharmacological and nonpharmacological therapies. The issue of secondary prophylaxis will not be addressed in this particular paper, but readers are referred to a recent narrative review on the topic [7].
2. Resuscitation and Initial Assessment

Patients presenting with upper gastrointestinal bleeding are at risk of hemodynamic shock and airway compromise; therefore, the first priority is to assess the adequacy of the airway, as well as the patient’s breathing and circulation. Venous access should be achieved with at least 2 large-bore cannulae, and patients with active bleeding should be monitored in a high-dependency unit with pulse oximetry, cardiac monitoring, automated blood pressure readings, close monitoring of urine output, and, ideally, central venous pressure monitoring. As a minimum, all patients should be blood typed and cross-matched for an appropriate number of units of packed red blood cells with blood sent for hemoglobin, hematocrit, platelets, coagulation time, and electrolytes [8]. Hemodynamic shock is associated with an increased mortality [9, 10]. There are no studies comparing initial resuscitation with crystalloid or colloid in patients with gastrointestinal bleeding.

Acute upper gastrointestinal bleeding (AUGIB) is a very common indication for transfusion of blood components. A study from the United Kingdom found that this indication alone accounts for 14% of the national red cell supply [11]. There is a widespread variation in clinical practice that influences transfusion threshold, due to several factors including physician, patient factors, and hospital local guidelines. The value of RBC transfusion in exsanguinating NVUGIB is self-evident, and the small proportion of patients requiring massive transfusion should be managed in accordance with local major hemorrhage protocols in close liaison with hospital transfusion teams. Red blood cell transfusion is rarely indicated when hemoglobin (Hg) levels are greater than 100 g/L and is almost always indicated when the levels fall below 60 g/L. The risks associated with the consequences of acute anemia should be weighed against the risks of transfusion. Patients requiring massive transfusion are likely to develop a dilutional coagulopathy and will require transfusion of platelets and fresh frozen plasma, again guided by local hospital protocols. However, in less severe bleeding, the benefit of RBC transfusion is unclear. A retrospective observational study of 4441 patients admitted with AUGIB in the United Kingdom found that for patients presenting with a Hg of > 80 g/L, transfusion within 12 hours was associated with a two-fold increase in the subsequent risk of rebleeding (odds ratio (OR) 2.26, 95% confidence interval (CI) 1.76–2.90), although confounding by indication could not be excluded [12]. A systematic review of 10 RCTs comparing restrictive versus liberal RBC transfusion strategies in 1780 patients from a variety of clinical settings concluded that a restrictive approach led to a 42% reduction in the probability of receiving transfusions with no effect on mortality, rates of cardiac events, morbidity, or length of hospital stay [13]. Therefore, in patients presenting with AUGIB who are not massively bleeding, transfusion can probably be withheld in the presence of Hg levels as low as 70 to 80 g/L, provided there is no evidence of comorbid cardiovascular disease. International guidelines recommend initiating red blood cell transfusions for most critically ill patients when Hg levels decrease to less than 70 g/L, with a target level from 70 to 90 g/L, in the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage [14].

The prognostic value of the international normalized ratio (INR) following presentation with NVUGIB is poorly characterized. In the Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE) cohort of 1869 patients with NVUGIB, a presenting INR of greater than 1.5 was associated with almost a two-fold increased risk of mortality (OR 1.95, 95% CI 1.13–3.41) after adjustment for confounders, but not an increased risk of rebleeding [15]. Another study in patients with upper gastrointestinal bleeding (UGIB), using a historical cohort comparison, suggested that correcting an INR to less than 1.8 as part of intensive resuscitation led to lower mortality and fewer myocardial infarctions in the intervention group [16]. The completeness of correction of a coagulopathy must be considered, but should not delay the performance of endoscopy (defined as within 24 hours of presentation) [6]. This recent consensus recommendation is based on recognition of the benefits of early endoscopic intervention coupled to the decreased tissue damage associated with newer ligation hemostatic techniques such as endoscopic clips or hemostatic powders. Moreover, limited observational data also suggest that endoscopic hemostasis can be safely performed in patients with an elevated INR as long as it is not supratherapeutic (in this study a value of 2.5) [17]. The use of Prothrombin Complex Concentrate (PCC) should be considered in the reversal of Warfarin in patients presenting with life threatening hemorrhage, including gastrointestinal hemorrhage. PCC appeared to be more cost-effective treatment than FFP for the emergency reversal of Warfarin, from the perspective of the UK NHS, in a systemic literature analysis involving 1085 patients in 16 studies [18]. The management of newer anticoagulants that cannot be reversed represents an emerging issue [19].

The role of the nasogastric tube (NGT) in the initial assessment of patients presenting with NVUGIB remains controversial. It carries a prognostic value in identifying high-risk lesions [20], facilitates gastric lavage prior to performing endoscopy which has been shown to improve fundic visualization acutely, but may compromise the airway. The NGT can be negative in up to 15% of upper gastrointestinal bleeding cases, especially when it is from a duodenal source [21]. The presence of fresh red blood in the NGT aspirate has been found to be an independent predictor of adverse outcome on multivariable analysis [22], and is also a predictor of high-risk lesions in patients who are hemodynamically stable without evidence of hematemesis. Indeed a bloody nasogastric aspirate exhibits a specificity for high-risk endoscopic lesions (75.8% : 95% CI 70.0–80.0) with a negative predictive value of 77.9% (95% CI 73.2–82.0) [20].

3. Risk Stratification Scoring Systems

The clinical predictors of increased risk for rebleeding or mortality include age greater than 65 years, shock, poor overall health status, comorbid illnesses, low initial hemoglobin levels, melena, transfusion requirement, fresh
red blood on rectal examination, in the emesis, or in the nasogastric aspirate, sepsis, and elevated urea, creatinine, or serum aminotransferase levels [23]. Other factors predictive of outcomes include chronic alcoholism, active cancer, or unsuitable sociofamily conditions [24], as well as an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 11 or greater [25]. There exists well validated prognostic scoring systems for patients presenting with AUGIB, these scores help to categorize patients into low-risk versus high-risk patients and predict the risk of rebleeding, mortality rates as well as those requiring endoscopic intervention.

The most extensively validated scores are the Rockall (Table 1 and Figure 1) [26] and Blatchford scores (Table 2) [27]. The preendoscopic or clinical Rockall and Blatchford scores use only clinical and laboratory data, whereas the complete Rockall score in addition takes into consideration and uses endoscopic data to predict subsequent rebleeding or mortality.

The complete Rockall score has been said to be superior to both the preendoscopy clinical Rockall scores and Blatchford score in predicting mortality and rebleeding [28], although these findings have been questioned more recently [29].

The Blatchford score is more useful than the clinical Rockall score in identifying low-risk patients who do not require therapeutic endoscopy, and specifically those patients with a score of zero may be safely triaged from the ED to outpatient management [30, 31].

Endoscopically, the following features predict the increased risk of rebleeding: active bleeding at the time of endoscopy, large ulcer size >2 cm, bleeding ulcers located on the lesser curvature or posterior duodenal wall, and high-risk stigmata classified according to the Forrest classification (Table 3) [32].

4. Preendoscopic Medical Therapy

4.1. Proton-Pump Inhibitors. Proton-pump inhibitors (PPIs) play an important role in the stabilization of clot formation in response to bleeding peptic ulcers through pH-dependent factors, by raising the pH to 6, helping in optimizing platelet aggregation [33]. Raising the pH may also decrease pepsin mediated clot lysis and fibrinolytic activity. A Cochrane systematic review and meta-analysis of 6 RCTs including 2223 patients comparing PPI with control administrations (placebo or histamine-2-(H2)receptor antagonists) found no evidence that preendoscopic administration of PPIs led to a reduction in the most important clinical outcomes following AUGIB, namely, rebleeding, mortality, or need for surgery [34]. However, the use of preendoscopic PPI may delay the need for endoscopic intervention by down staging high-risk endoscopic lesions into low risk, that is, downstaging the Forrest classification (Table 3). This may prove beneficial when early endoscopy is not feasible or local expertise is limited, the use of preendoscopic PPI however should replace appropriate initial resuscitation or delay the performance of early endoscopy [35].

Cost-effective scenarios optimizing the possible role of this preemptive pharmacotherapy have been identified and include a high likelihood of bleeding from a nonvariceal source and delayed access to endoscopy [36].

4.2. Octreotide and Somatostatin Analogues. Current international recommendations state that somatostatin or octreotide are not recommended in the routine management of patients with acute NVUGIB [23]. RCT have shown that in patients with a bleeding ulcer following successful endoscopic hemostasis, pantoprazole continuous infusion was superior to somatostatin to prevent bleeding recurrence and promote the disappearance of the endoscopic stigmata. Nevertheless, no differences were seen in the need for surgery or mortality [37]. Such an approach should of course be considered if a variceal cause of bleeding is suspected [38], or if patients are exsanguinating from any upper gastrointestinal tract etiology.

4.3. Prokinetic Agents. The use of prokinetic agents prior to endoscopy may improve diagnostic yield in selected patients; however, they are not warranted for routine use in all patients who present with UGIB. A meta-analysis [39] of 3 trials that evaluated erythromycin [40–42], comprising 316 patients, and 2 abstracts that evaluated metoclopramide [43] found that the use of a prokinetic agent significantly reduced the need for repeated endoscopy (odds ratio (OR), 0.51 (95% CI, 0.30 to 0.88)) [39].

5. Endoscopic Therapy

5.1. Timing of Endoscopy. Early endoscopy (within 24 hours of presentation) is recommended for most patients
Table 1: Points scheme allocation for the complete Rockall score.

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;60</td>
<td>60–79</td>
<td>≥80</td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>No shock</td>
<td>Tachycardia HR &gt; 100</td>
<td>Hypotension SBP &lt; 100</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>none</td>
<td>Cardiac failure/ischemic disease/other conditions</td>
<td>Liver, renal failure, and advanced malignancy</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Mallory Weiss tear, no bleeding or lesions identified</td>
<td>Other diagnosis</td>
<td>Malignancy of upper GI tract</td>
<td></td>
</tr>
<tr>
<td>Stigmata of bleeding</td>
<td>None or dark spot only</td>
<td>Blood in GI tract, active bleeding or visible vessel, or adherent clot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rockall score [8].

Table 2: Points scheme allocation for the Blatchford score.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea mmol/L</td>
<td></td>
</tr>
<tr>
<td>6.5–7.9</td>
<td>2</td>
</tr>
<tr>
<td>8–9.9</td>
<td>3</td>
</tr>
<tr>
<td>10–25</td>
<td>4</td>
</tr>
<tr>
<td>&gt;25</td>
<td>6</td>
</tr>
<tr>
<td>Haemoglobin g/L (for men)</td>
<td></td>
</tr>
<tr>
<td>120–129</td>
<td>1</td>
</tr>
<tr>
<td>110–119</td>
<td>3</td>
</tr>
<tr>
<td>&lt;110</td>
<td>6</td>
</tr>
<tr>
<td>Haemoglobin g/L (for women)</td>
<td></td>
</tr>
<tr>
<td>100–119</td>
<td>1</td>
</tr>
<tr>
<td>&lt;110</td>
<td>6</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td></td>
</tr>
<tr>
<td>100–109</td>
<td>1</td>
</tr>
<tr>
<td>90–99</td>
<td>2</td>
</tr>
<tr>
<td>&lt;90</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Pulse &gt; 100</td>
<td>1</td>
</tr>
<tr>
<td>Melena on presentation</td>
<td>1</td>
</tr>
<tr>
<td>Syncope on presentation</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2</td>
</tr>
</tbody>
</table>

Blatchford score [8].

Table 3: The Forrest classification.

<table>
<thead>
<tr>
<th>Forrest class</th>
<th>Endoscopic appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Active spurting bleeding</td>
</tr>
<tr>
<td>1b</td>
<td>Active oozing bleeding</td>
</tr>
<tr>
<td>2a</td>
<td>Non Bleeding visible vessel</td>
</tr>
<tr>
<td>2b</td>
<td>Adherent clot</td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>Pigmented clot</td>
</tr>
<tr>
<td>3</td>
<td>Clean base ulcer</td>
</tr>
</tbody>
</table>

with acute upper gastrointestinal bleeding. Early endoscopy (within the first 24 hours), using risk classification based on clinical and endoscopic criteria, has been shown to permit the safe and prompt discharge of patients classified as low risk. Furthermore, it also improves patient outcomes for patients classified as high-risk, while reducing use of resources for patients classified as either low or high-risk [6]. Indeed the performance of early endoscopy decreases length of hospital stay in patients at low risk [44], high-risk [45], and combined patient groups [46]. No additional benefit has been shown when using a practice of very early endoscopy at 2 or 12 hours. A systemic review of 3 trials [45, 47], comprising 528 patients, found no significant reduction in rebleeding (OR, 0.71 (CI, 0.28 to 1.81)), surgery (OR, 1.16 (CI, 0.39 to 3.51)), or mortality (OR, 0.70 (CI, 0.14 to 3.57)) with urgent (1 to 12 hours) endoscopy. Recent observational data, however, suggest that earlier endoscopy (at 13 hours) may be beneficial to very ill patients (Blatchford > 12) [48].

5.2. Endoscopic Therapeutic Modalities. There exist many endoscopic modalities for treating bleeding peptic ulcer disease. These include mechanical devices such as endoscopic clips and thermal probes, and it is needless to say that it can inject epinephrine, saline, sclerosing agents, thrombin, and fibrin glue. More recently, hemostatic powders have also been introduced [49].

Endoscopic therapy is warranted for high-risk lesions that is, Forrest classification 1a, 1b, 2a, and 2b because of their greatest propensities for rebleeding if left untreated. Meta-analyses have confirmed that endoscopic hemostasis in this group of patients results in significant improvements in rebleeding, but have been underpowered to show any better improvement in the need for surgery or mortality [32, 36, 38, 50]. Although all endoscopic techniques provide benefit, injection of epinephrine alone is superior to medical management alone, but is inferior to all other methods and should no longer be used as a sole endoscopic treatment when other methods are available. Clinicians should thus favor a sole thermal method, the combination of injection followed by thermal or positioning of a clip, or the injection of a clip followed by injection (studied in this sequence in most trials). Compared with epinephrine, further bleeding was reduced significantly by other monotherapies (relative risk (RR), 0.58 (95% CI, 0.36–0.93) [36]; number-needed-to-treat (NNT), 9 (95% CI, 5–53)), and epinephrine followed by another modality (RR, 0.34 (95% CI, 0.23–0.50); NNT, 5...
showing better and worse results for clips [36, 51]. Therapies, although the latter studies were heterogeneous, endoscopic therapy may be considered, although intensive adherent clots is controversial. Recommendations state that clots. Indeed the role of endoscopic therapy for ulcers with

6.1. Proton-Pump Inhibitors. It has been well documented that high-risk lesions require 72 hours following endoscopic therapy to evolve from a high-risk to a low-risk stigmata, justifying the 3-day duration of the profound acid suppression [58]. High-dose intravenous PPI therapy (e.g., a PPI at a dose of 80 mg bolus dose followed by 8 mg/h infusion over 72 hours) should be administered to patients with high-risk stigmata who have received successful endoscopic therapy. This recommendation is based on a meta-analysis of RCTs including 5792 patients in which PPI therapy reduced the incidence of rebleeding (OR 0.45, 95% CI 0.36–0.57) and needed for surgery (OR 0.56, 95% CI 0.45–0.70), but not mortality (OR 0.90, 95% CI 0.67–1.19) [59, 60]. Furthermore, PPIs improve mortality in patients with HRS, but only if they have initially undergone endoscopic hemostasis (i.e., mainly high dose IV) [6]. These findings have also been confirmed in a “real-life” setting. The optimal dose and route of administration of PPIs, however, remains controversial but the highest quality data apply to the high-dose regimen, thought to be a class effect, as described above [6]. The optimal dose and route of administration, however, remain unclear. The data suggesting lower-dose PPI may be efficacious have been hampered by methodological limitations [61]. All patients should be discharged on a single daily oral dose of a PPI; the duration of PPI is determined by the underlying etiology of the bleeding ulcer, with perhaps a consideration for double-dosing if patients have bled from esophagitis [6].

6.2. Testing for Helicobacter Pylori. All patients with bleeding peptic ulcers should be tested for Helicobacter pylori (depending on the local prevalence) and receive eradication therapy if it is positive. A meta-analysis demonstrated that eradication of H. pylori was significantly more effective than PPI therapy alone in preventing rebleeding from peptic ulcer disease. If Helicobacter pylori is not detected in the acute setting, then repeat testing is indicated. Indeed a systematic review of 23 studies found that diagnostic tests for Helicobacter pylori infection (including serology, histology, urea breath test, rapid urease test, stool antigen, and culture) demonstrate high positive predictive value (0.85 to 0.99) but low negative predictive value (0.45 to 0.75) in the setting of AUGIB, with 25% to 55% of Helicobacter pylori-infected patients yielding false-negative results in the acute context of upper gastrointestinal bleeding [6] (Figure 2). The full reasons for the observed high false negative rate of Helicobacter pylori testing in the acute setting of bleeding are unclear, but in part relate to the alkalotic milieu imparted by the presence of blood in the gastric lumen and the resultant proximal migration of the bacterium in such a setting [62].

6.3. Aspirin in AUGIB. A recent RCT out of Hong Kong has shown that it is more deleterious to withhold ASA amongst patients using it for secondary cardiovascular prophylaxis than to restart it early on. Based on these data, consensus recommendations state that in patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding [63]. ASA is today usually restarted within 3–5 days of the presentation with bleeding, after appropriate
discussions amongst the multidisciplinary treating team that can includes general practitioners, internists, cardiologists, neurologists, gastroenterologists, and intensivists.

7. Summary

Adequate resuscitation and initial risk assessment are crucial in patients presenting with AUGIB. Early endoscopy allows for categorization of patients into low versus high-risk of rebleeding and delivery of endoscopic hemostasis. Prokinetics are helpful in visualizing bleeding lesions at the initial endoscopy. Dual endoscopic modality therapy is superior to epinephrine injection alone followed by continuous PPI infusion for 72 hours should be applied for high-risk stigmata of rebleeding.

All patients should be discharged on a single daily oral dose of a PPI the duration of PPI is determined by the underlying etiology of the bleeding ulcer, while in patients who are on antiplatelet agents, the cardiothrombotic risks should be balanced against the risk of further bleeding or rebleeding. ASA should be soon restarted in patients with nonvariceal upper gastrointestinal bleeding, understanding that there is a high false negative rate in the acute setting of UGIB.

Abbreviations

GI: Gastrointestinal  
AUGIB: Acute upper gastroIntestinal bleeding  
NVUGIB: Nonvariceal upper gastroIntestinal bleeding  
PPI: Proton-pump inhibitors  
PCC: Prothrombin complex concentrate  
NGT: Nasogastric tube  

References


Ulcers


