ABSTRACT

- **Objective:** To provide an overview of management of nonvariceal upper gastrointestinal bleeding (NVUGIB).
- **Methods:** Literature review in the context of a clinical case.
- **Results:** NVUGIB is a common condition, with approximately 30% to 50% of cases attributable to peptic ulcer disease. Endoscopy is the cornerstone of management. Comprehensive evidence-based guidelines exist to direct appropriate care for persons with NVUGIB. Adherence to these guidelines will promote the delivery of the most cost-effective care, allowing high-risk patients to receive appropriate management to reduce the risk of rebleeding and its complications and allow low-risk patients to be managed in the outpatient setting.
- **Conclusion:** Improvements in medical and endoscopic management have led to a decrease in the morbidity and mortality associated with gastrointestinal bleeding. It is hoped that further research will help better differentiate low-risk and high-risk patients and that further improvements in endoscopic techniques and post-endoscopic medical therapy may lead to a further reduction in rebleeding rates and mortality.

CASE STUDY

**Initial Presentation and History**

An 81-year-old man with a past medical history of type 2 diabetes mellitus, hypertension, ischemic heart disease (on aspirin), and gastroesophageal reflux disease presents to the emergency department with 2 episodes of melena.

**Physical Examination**

Blood pressure is 95/63 mm Hg and heart rate is 120 bpm. Hemoglobin has dropped from 79 g/L to 59 g/L, blood urea nitrogen is 20.1 mmol/L, and INR is 1.2.

**What clinical features are associated with UGIB?**

A retrospective analysis of risk predictors of UGIB reports the most common presenting symptoms as hematemesis (59%), followed by melena (29%) [8]. Hematochezia (passage of bright red blood per rectum) has been noted as a less common but more severe presentation of UGIB [9]. A recent review by Srygley et al [1] has shown that having a history of melena, epigastric pain, a positive nasogastric lavage, and melena on exam are strongly predictive of an UGI source, whereas finding clots in the stool is suggestive of the lower GI tract being the site of bleeding [1]. Elevation of the urea/creatinine ratio also is much more common in UGIB, with persons with a urea/creatinine ratio of 30 or greater having 7.5 times increased odds of having an upper GI bleed. Having a
normal hemoglobin also decreased the likelihood of an upper GI source by 75%.

- What are risk factors for UGIB?

Approximately 30% to 50% of NVUGIB cases can be attributed to peptic ulcer disease [7,10]. Peptic ulcer disease can have up to a 5% to 10% mortality rate, some of which may be credited to its prevalence in the geriatric population. Other causes of NVUGIB include (in order of decreasing incidence) erosive gastritis, esophagitis, Mallory-Weiss tear, malignancy, and miscellaneous (Dieulafoy’s lesion, hemobilia, angiodysplasia, vasoenteric fistula, gastric antral vascular ectasia) [10].

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin (ASA) has been well documented to be a leading cause of NVUGIB [11,12]. Colonization of the gastrointestinal tract with Helicobacter pylori is another important risk factor that may eventually lead to peptic ulcer disease, which in turn may cause NVUGIB [13]. The use of anticoagulants has also shown to be a cause of NVUGIB [14]. The introduction of acid suppression therapy with proton pump inhibitors (PPIs) and proper eradication of H. pylori with triple therapy has proven to be beneficial in reducing the incidence of NVUGIB [15,16].

- What are important components of preendoscopic management?

Preendoscopic Treatment

Pre-endoscopic treatment is an essential component of the management of NVUGIB. When patients present with signs and symptoms suggestive of any UGIB, they should be immediately resuscitated to maintain adequate blood pressure. If the patient’s hemoglobin is less than or equal to 70 g/L, it is recommended that they be transfused with packed red blood cells, though transfusion at higher hemoglobin levels should probably be avoided [17]. It is often recommended to correct elevated INRs. If patients are on warfarin, their INR should be corrected with intravenous vitamin K (for those on warfarin) or replacement of fresh frozen plasma (for those with liver disease, or other coagulopathies). The use of concentrated clotting factors (eg, octoplex) can also be considered when coagulopathy is present and bleeding is ongoing and/or leading to hemodynamic instability [18]. However, a high INR does not warrant the need to delay endoscopic intervention if bleeding is severe [19,20]. There is also little evidence on how to best manage UGIB patients who are using the new oral factor Xa inhibiting anticoagulants, such as dabigatran and/or rivaroxiban, as the effect of factor Xa inhibitors cannot be reversed with vitamin K or clotting factor replacement [21]. Although guidelines do not exist for patients who develop UGIB in this setting, one should proceed with urgent endoscopy if significant UGI bleeding has occurred.

Risk Stratification

Risk stratification is an essential component of the assessment of a patient with UGIB, both to determine which patients require a more urgent endoscopic assessment and also to better identify low-risk patients who may be able to be investigated electively. Several pre-endoscopic risk assessment tools have been created to help physicians decide whether

<table>
<thead>
<tr>
<th>Admission risk marker</th>
<th>Score</th>
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<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>≥ 6.5–7.9</td>
<td>2</td>
</tr>
<tr>
<td>8.0–9.9</td>
<td>3</td>
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<tr>
<td>10.0–24.9</td>
<td>4</td>
</tr>
<tr>
<td>≥ 25</td>
<td>6</td>
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<tr>
<td>Hemoglobin, male (g/L)</td>
<td></td>
</tr>
<tr>
<td>&gt; 120–130</td>
<td>1</td>
</tr>
<tr>
<td>100–119</td>
<td>3</td>
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<tr>
<td>&lt; 100</td>
<td>6</td>
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<tr>
<td>Hemoglobin, female (g/L)</td>
<td></td>
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<tr>
<td>≥ 100–120</td>
<td>1</td>
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<tr>
<td>&lt; 100</td>
<td>6</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
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<tr>
<td>100–109</td>
<td>1</td>
</tr>
<tr>
<td>90–99</td>
<td>2</td>
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<td>&lt; 90</td>
<td>3</td>
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<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Pulse &gt; 100</td>
<td>1</td>
</tr>
<tr>
<td>Melena</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac disease</td>
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or not the patient needs urgent intervention. The 2 most widely used and evaluated pre-endoscopic risk stratification scoring systems are the Glasgow-Blatchford bleeding score (GBS) and the Rockall pre-endoscopic risk score [23].

Glasgow-Blatchford Score
The GBS (Table 1) uses clinical and laboratory data to predict the need for blood transfusion, endoscopy, or surgery. The advantage of this scoring tool is in its simplicity, thus making it popular, even to medical students and junior residents. Using GBS, patients are classified as low risk and can be treated as outpatients if they meet the following criteria: blood urea nitrogen less than 6.5 mmol/L, hemoglobin more than 130 g/L (male) or 120 g/L (female), systolic blood pressure greater than or equal to 110 mm Hg, and pulse less than 100 beats per minute. A recent article validated the use of GBS in successfully identifying low-risk patients and therefore reducing the number of unnecessary admissions to hospital, demonstrating that a score of 0 or 1 on admission is associated with a 99% probability of not requiring an endoscopic intervention or transfusion [24]. Its main limitation is its poor specificity in identifying low risk patients, as the vast majority of persons with a GBS of 2 or greater will also not require an intervention.

Rockall Score
Another risk stratification tool that is widely used in clinical practice is the pre-endoscopy Rockall score (Table 2).

This is essentially a modified version of the Rockall scoring tool, which requires a diagnosis and endoscopy to predict the risk of rebleeding [25]. The pre-endoscopy Rockall score uses the patient’s age, presence of shock and comorbidity to determine if a patient is low risk for rebleeding and death, and therefore eligible to be treated as an outpatient (similar to the GBS). However, more recent studies have reported this scoring tool as being less accurate than the GBS at predicting the need for intervention [26].

Pharmacologic Therapy
Pharmacologic therapy is often used prior to performance of endoscopy in order to better prepare the upper GI tract for optimal visualization. During large UGIB episodes, parts of the stomach, especially the fundus, may be difficult to optimally evaluate due to the presence of retained blood clots. Therefore, agents that improve gastric emptying, specifically erythromycin and metoclopramide, have been evaluated in the pre-endoscopic setting in order to improve visualization of the upper GI tract. Erythromycin, given at a dose of 250 mg 20 minutes prior to endoscopy, has been shown to improve upper GI visualization compared to no therapy [27]. Metoclopramide has been less widely evaluated, but appears to also improve gastric visualization compared to placebo [28]. While pro-motility agents are not routinely recommended prior to endoscopy in UGIB, their use should be considered when large volume bleeding is suspected or when

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**Table 2. Rockall Risk Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>Age (years)*</td>
<td>&lt; 60</td>
<td>60–79</td>
<td>≥ 80</td>
<td></td>
</tr>
<tr>
<td>Shock*</td>
<td>Systolic BP ≥ 100</td>
<td>Systolic BP ≥ 100</td>
<td>Systolic BP &lt; 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart rate &lt; 100</td>
<td>Heart rate ≥ 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity*</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease, cardiac failure, other major comorbidity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Renal failure, hepatic failure, disseminated malignancy</td>
<td></td>
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<tr>
<td>Diagnosis</td>
<td>Mallory-Weiss tear, no lesion, or no stigmata of hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All other diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignancy of UGI tract</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stigmata of hemorrhage</td>
<td>None, or dark spot</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Blood in UGI tract, adherent clot, visible or spurting vessel</td>
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*These variables used to calculate pre-endoscopy risk score.
there are signs of ongoing bleeding and performance of endoscopy is imminent [7,29].

PPIs are also widely used prior to endoscopy. The evidence supporting the use of pre-endoscopic PPI emerged from a large trial where patients who presented with suspected UGIB were randomized to receive 80 mg IV pantoprazole, followed by an 8 mg per hour infusion or placebo [30]. It was determined that patients who received pre-endoscopic PPI therapy were less likely to require endoscopic hemostatic therapy (19.1% vs. 28.4% in the placebo group), more likely to have ulcers with clean bases (120 vs. 90 patients in the placebo group), and had shorter hospital stays. Pre-endoscopic PPI had no effects on rates of rebleeding or mortality. In spite of the lack of a demonstrable benefit on rebleeding rates, PPIs are still routinely recommended prior to endoscopy because of their relatively low cost, limited side-effect profile, and the potential to downgrade high-risk lesions may lead to cost-savings in prevented hospital admissions [31].

**Case Continued**

The patient was resuscitated with intravenous fluids, transfused 3 units of packed red blood cells, was given 80 mg IV pantoprazole bolus, and then started on an 8 mg per hour infusion. His aspirin was held. The patient’s Glasgow-Blatchford bleeding score was 10 and pre-endoscopy Rockall score was 6.

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• **What are guidelines for the use of endoscopy?**

Endoscopy is the cornerstone of management of patients with NVUGIB. The benefits of endoscopy are twofold. First, it allows direct visualization of the source of bleeding, providing a definitive diagnosis. Second, prognostic information of the likelihood of continued bleeding or recurrent bleeding is obtained, which may allow for more intensive therapy for persons at high risk of recurrent bleeding or UGIB-related complications as well as outpatient management of low-risk patients. Furthermore, endoscopy facilitates the delivery of direct therapeutic hemostasis, so that persons with ongoing bleeding or at high-risk of recurrent bleeding can undergo hemostatic treatment to prevent future bleeding episodes.

The time frame during which to perform endoscopy is controversial. Most recent guidelines recommend that patients with NVUGIB have endoscopy within 24 hours of presentation [32,33]. A recent prospective national audit done in the UK showed a direct correlation between late endoscopy (greater than 24 hours) and increased length of hospital stay and a higher rebleeding rate [34]. Conversely, urgent endoscopy (less than 12 hours) was not associated with decrease in mortality but did show improved effectiveness of treatment, and decreased need for surgical intervention [35]. On the contrary, other retrospective analyses did not demonstrate that endoscopy within 6 hours of presentation was associated with decreased rates of mortality or the need for blood transfusions or surgery [36]. It is important to note that most patients undergoing urgent endoscopy are those with severe bleeding. Therefore, the lack of benefit seen with urgent endoscopy may be related to the patient population rather than the procedure itself. A few studies analyzed patients admitted on weekends with NVUGIB; they concluded that these patients are less like to get an endoscopy within 24 hours of presentation and are therefore associated with a higher in-hospital mortality [37,38]. In rare circumstances such as the patient having an acute coronary syndrome, it is recommended to delay endoscopy until the patient has been adequately stabilized [39].

**Classification of Peptic Ulcers**

The main predictor of the risk of rebleeding is the appearance of the ulcer base at the time of initial endoscopy. The Forrest classification (Table 3) uses the characteristics of the lesion found on endoscopy to place patients into high-, intermediate-, or low-risk groups [40]. Forrest Ia lesions (active arterial spurting) are associated with an 85% to 100% risk of recurrent/ongoing bleeding in the absence of endoscopic hemostasis, whereas only one-quarter of Forrest Ib lesions (arterial oozing) will have recurrent bleeding. Forrest IIa (non-bleeding visible vessels) are associated with a 50% risk of recurrent bleeding if left untreated. All of these lesions should be considered for endoscopic hemostasis in order to decrease the risk of further hemorrhage. Conversely, Forrest IIc (hematin flat spot) and Forrest III (clean based) ulcers do not require application of hemostasis, as only 3% to 5% of these lesions will re-bleed [41]. Persons with Forrest IIb (adherent clots) are at intermediate risk of rebleeding, though it is recommended that clots should be removed after first injecting the surrounding tissue with 1:10000 epinephrine to determine if an underlying non-bleeding visible vessel is present [42].
• **What endoscopic treatment modalities are utilized?**

There are many different modalities of treatment using endoscopy. It is generally recommended that patients with Forrest Ia and IIa lesions be considered for endoscopic hemostasis [32]. Forrest IIb lesions may also require endoscopic hemostasis if a visible vessel is apparent following removal of the overlying clot. The common modes of endoscopic hemostasis include epinephrine injection, thermal coaptive coagulation, and application of mechanical clip devices [43]. Endoscopic therapy has been shown to decrease the risk of rebleeding and mortality in patients with active arterial bleeding and those with non-bleeding visible vessels. The application of epinephrine in combination with either thermal therapy or mechanical therapy has been shown to be superior to epinephrine monotherapy [44,45]. The choice of endoscopic technique is generally left to the discretion of the endoscopist. In the event of recurrent bleeding following performance of endoscopic hemostasis, repeating endoscopy and reapplying hemostatic techniques has been shown to prevent surgery in approximately ¾ of cases [46]. Some studies have suggested that a routine second-look endoscopy may be useful even in the absence of signs of recurrent bleeding to identify occult ongoing bleeding and the continuing presence of high-risk lesions amenable to endoscopic therapy. While there is evidence that second-look endoscopy may decrease rebleeding rates, these studies come from an era where PPI therapy was not routinely used, so it is unclear whether these results are generalizable to patients in the current day [47]. Should initial hemostasis be unsuccessful or if rebleeding occurs after a second attempt at endoscopic hemostasis, the patient should receive urgent consultation with a surgeon for performance of surgical ligation of the bleeding vessel [48]. Alternatively, angiographic embolization has been shown to be effective in achieving hemostasis in patients with recurrent peptic ulcer bleeding, and can be considered if local expertise is available [49].

• **What is post-endoscopic management?**

The main goal of post-endoscopic management of NVUGIB is to determine which patients are at highest risk of rebleeding and continuing inpatient observation, preventing short-term rebleeding, and decreasing the risk of recurrent bleeding over the long term.

It is now generally accepted that patients who are believed to be at low risk for recurrent bleeding should be discharged immediately following recovery from endoscopy [32]. There are several risk scores and treatment algorithms which have been used to better identify patients who are at low risk for recurrent hemorrhage [50–52]. In general, patients with lesions at low risk for rebleeding (esophagitis, Mallory-Weiss tears, and peptic ulcers without high-risk stigmata [Forrest IIc/III]) do not require admission to hospital. However, hospitalization should be considered for patients with severe concomitant comorbidities, those with poor social support, and persons who require reinitiation of anticoagulation, even if only low-risk findings are present on endoscopy. Moreover, patients who are discharged may be adequately treated using oral PPIs [53].

Persons with higher-risk lesions, and thus at a higher risk of rebleeding in the short term, should be hospitalized, primarily for close observation and to allow the
provision of IV PPI infusions. Continuous infusions of PPI are able to maintain an elevated intragastric pH, which promotes clot stability [54]. The initial evidence supporting the use of IV PPIs following endoscopy comes from the study by Lau et al [55], where persons with peptic ulcers with active bleeding or non-bleeding visible vessel were randomized to receive IV infusion of a placebo or omeprazole given as a 80-mg bolus and then 8 mg/hour infusion which was carried on for a total of 72 hours post endoscopy, followed by oral PPIs at 20 mg daily for the next 8 weeks. Subjects who received IV PPI therapy were significantly less likely to have rebleeding (7% vs. 23%) and also had shorter length of hospital stay following endoscopy. Similar findings have been reported in other studies of IV PPI for high-risk ulcers, including in North American and European populations. Because of the costs associated with IV PPI therapy, attempts have been made to look at the role of high-dose oral PPIs in reducing the risk of recurrent bleeding [56]. While there is some evidence that oral PPIs may be equally efficacious as IV PPIs [57,58], the evidence is not currently strong enough to recommend their routine use. IV H2-receptor antagonists (H2RAs) are likely ineffective for prevention of ulcer rebleeding; if IV PPIs are not available, it is preferable to substitute an oral PPI over administering an IV H2RA, as H2RAs have been proven to be ineffective in preventing recurrent bleeding. Lastly, IV PPIs are not sufficient on their own to prevent rebleeding, and are not a substitute for the performance of prompt endoscopy [59].

Following discharge, the goals of therapy are to eliminate or mediate the effects of the modifiable risk factors which are associated with the source of NVUGIB. This includes detection and treatment of *H. pylori*, discontinuation of ASA/NSAIDs/anticoagulants when possible, or decreasing the gastrointestinal toxicity of these agents when they cannot be discontinued. Testing for *H. pylori* is most commonly performed in the acute setting by obtaining gastric biopsies at the time of endoscopy, which can then be analyzed for *H. pylori* histologically or with rapid urease testing [32,60]. However, the false-negative rate for *H. pylori* has been reported to be high in the setting of an acute bleed, and repeat testing in the outpatient setting is recommended if *H. pylori* testing is negative, either with urea breath testing or serologic evaluation [61]. Serologic testing for *H. pylori* is very specific and is not affected by acute bleeding, though patients with prior *H. pylori* eradication may be falsely positive [62]. Eradication of *H. pylori* once detected is of paramount importance as those with proven *H. pylori* have shown up to a 20% rate of rebleeding, which drops to 2.7% if eradication is undertaken, and 1.1% if eradication is confirmed [63]. Following treatment, successful eradication should be confirmed either with urea breath testing, stool antigen testing, or via gastric biopsy. Chronic maintenance therapy with oral PPIs is not generally required following *H. pylori* eradication unless the patient is on chronic ASA, NSAIDs, or anticoagulation [15].

Patients using an NSAID when they developed a NVUGIB should ideally discontinue its use. However, if they need to continue for some reason, the use of COX-2 inhibitors in combination with an oral PPI has been shown to be superior to either a COX-2 inhibitor or PPI as monotherapy [64,65]. However, patients with known cardiovascular disease should not be given COX-2 inhibitors as they have been shown to increase the risk of MI [66]. In this case, continued use of an NSAID, preferably naproxen, with a PPI, is acceptable, though ideally the NSAID should be discontinued [67].

Patients who continue ASA following acute NVUGIB have been shown to have a high rate of recurrent bleeding if there is no co-prescription of a PPI [68]. However, patients at high risk of cardiovascular disease may have an increased risk of coronary events if ASA is discontinued [69,70]. Persons with acute NVUGIB who had ASA discontinued have been shown to have a higher rate of cardiovascular-associated mortality at 8 weeks compared with those in whom ASA was continued, while recurrent gastrointestinal bleeding was nonsignificantly greater among those who continued ASA [71]. As the risk of bleeding was highest in the first few days, it seems reasonable to hold ASA for approximately 3 to 5 days following a bleeding event before restarting [72]. If the patient is on ASA for primary prevention, then it may be discontinued as evidence shows that the risk of recurrent gastrointestinal bleeding outweighs the cardiovascular benefits of continuing the medication.

Clopidogrel, another antiplatelet agent used for cardio-prophylaxis, has been reported to cause higher rebleeding rates than those on ASA combined with a PPI [73]. However, clopidogrel is often required for patients with recent coronary stenting and those at high risk of recurrent stroke. The bleeding risk associated with clopidogrel can be reduced through concomitant therapy with a PPI [74]. However, there is controversy as to whether PPIs may interfere with the antiplatelet effects of clopidogrel, increas-
ing the risk of cardiovascular events [75]. The most recent data from well-designed observational trials suggests that although PPIs appear to inhibit clopidogrel action in vitro, the effect on cardiovascular outcomes is no different than those not given PPI [76,77]. Therefore, PPIs should still be used long term in persons who have a history of NVUGIB who require chronic clopidogrel therapy.

Case Continued

The patient was taken for an endoscopy within 24 hours of presentation. Endoscopy revealed an ulcer in the duodenum and some old blood was seen in the stomach. The ulcer was classified as Forrest Class IIA (non-bleeding visible vessel) and endoscopic hemostasis was performed by injecting the area surrounding the ulcer with 10 cc of 1:10000 epinephrine and applying a hemostatic clip. A biopsy was taken from the antrum and body of the stomach and was sent for H. pylori testing (later came back as negative). The IV pantoprazole infusion was continued for a total of 48 hours after which the patient was started on an oral PPI. He was discharged home 2 days after endoscopy and instructed to continue taking the PPI. Aspirin was restarted a week after due to the patient’s extensive cardiovascular disease.

CONCLUSION

NVUGIB is a common problem that health care professionals encounter every day. Comprehensive evidence-based guidelines exist to direct appropriate care for persons with NVUGIB, and it has been demonstrated that improvements in the medical and endoscopic management have led to a decrease in the morbidity and mortality associated with gastrointestinal bleeding. Adherence to these guidelines will promote the delivery of the most cost-effective care of these patients, allowing high-risk patients to receive appropriate management to reduce the risk of rebleeding and its complications, and allow low-risk patients to be managed in the outpatient setting, limiting the use of scarce healthcare resources. It is hoped that further research will help better differentiate low-risk and high-risk patients, and that further improvements in endoscopic techniques and post-endoscopic medical therapy may lead to a further reduction in rebleeding rates and mortality. Finally, greater efforts are required on the part of caregivers to better identify patients at risk of NVUGIB so that risk factors may be eliminated or their effects reduced through the preventative use of PPIs.

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