# Management and Prevention of Upper GI Bleeding

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## Learning Objectives

1. Apply an understanding of the pathophysiology and risk factors for upper gastrointestinal (GI) bleeding to patient care.
2. Evaluate the most recent guidelines for management and prevention of upper GI bleeding.
3. Devise a plan to effectively manage acute GI bleeding and optimize treatment responses in the individual patient.
4. Design plans for the prevention of upper GI bleeding caused by commonly associated risk factors.

## Introduction

Upper gastrointestinal bleeding (UGIB) is a potentially life-threatening condition that requires prompt and appropriate management. Representing a significant clinical and economic burden in the United States, UGIB annually produces a hospitalization rate of 165 per 100,000 adults (more than 300,000 hospitalizations) at an estimated cost of $2.5 billion. More people are hospitalized for UGIB than for congestive heart failure or deep venous thrombosis.

Upper gastrointestinal bleeding is defined as bleeding from a source proximal to the ligament of Treitz and can be categorized as either variceal or nonvariceal. Variceal hemorrhage results from complications of end-stage liver disease, and nonvariceal bleeding is associated with peptic ulcer disease (PUD) or other causes of UGIB. Bleeding from the upper gastrointestinal (GI) tract is 4 times as common as bleeding from the lower GI tract. The annual incidence of UGIB ranges from 48 to 160 cases per 100,000 individuals, with a higher incidence in men than in women.

Despite the advances in therapeutic management, mortality has remained unchanged at 10% to 14%, which may be related to longer life expectancy and the higher number of comorbidities in the aging population. In patients with UGIB, comorbid illness is the primary cause of death, not the actual bleeding. Medical comorbid illnesses are reported in 50.9% of patients with UGIB, with a lower rate in men (48.7%) than in women (55.4%). Because rebleeding or continued bleeding is associated with higher mortality, prevention is the most effective strategy in the management of UGIB. This chapter focuses on causes, risk factors, and updated recommendations on the management and prevention of UGIB.

## Pathophysiology

### Peptic Ulcer Disease

Peptic ulcer disease remains the most common cause of UGIB, accounting for 21% to 40% of all bleeding episodes. Recent data suggest a decline in the incidence of bleeding caused by ulcer; this is believed to be partly caused by increased use of *Helicobacter pylori* eradication therapy. *H. pylori* infection and chronic use of

### Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Berardi RR, Fugit RV. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill, 2011:563–86.
- ASHP therapeutic guidelines on stress ulcer prophylaxis. Am J Health Syst Pharm 1999;56:327–79.
- Chey WD, Wong BCY; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* eradication. Am J Gastroenterol 2007;102:1808–25.

**Abbreviations in This Chapter**

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| GI | Gastrointestinal |
| NSAID | Nonsteroidal anti-inflammatory drug |
| PPI | Proton pump inhibitor |
| PUD | Peptic ulcer disease |
| SRMD | Stress-related mucosal damage |
| TIPS | Transjugular intrahepatic portosystemic shunt |
| UGIB | Upper gastrointestinal bleeding |

nonsteroidal anti-inflammatory drugs (NSAIDs) continue to be the predominant causes of PUD leading to bleeding ulcers.

Duodenal ulcers are more common than gastric ulcers with *H. pylori* infection, but the incidence of bleeding is similar for both. Early studies showed that *H. pylori* infection rates were lower in patients with bleeding ulcers (71%) than in those with nonbleeding ulcers (93%). Recent data suggest that this discrepancy is caused by the decrease in sensitivity of biopsy in patients with acute bleeding ulcers. A possible mechanism involved in increased false-negative rates of *H. pylori* testing is the pH buffering effect of blood; higher alkalinity has been associated with higher rates of false-negative results.

Nonsteroidal anti-inflammatory drugs, including aspirin, continue to be a common cause of UGIB. Although most NSAID-associated ulcers are asymptomatic and do not lead to bleeding, elderly patients with a history of bleeding ulcer are at increased risk of rebleeding with continued NSAID use. A long-term prospective study showed that adults older than 65 years receiving chronic NSAID therapy for arthritis and low-dose aspirin therapy were at increased risk of upper GI complications, including UGIB. Aspirin in daily dosages of 75–300 mg has been shown to cause a 2- to 3-fold increased risk of GI bleeding. An important determinant of NSAID-associated bleeding is the therapy duration because a short course (i.e., less than 1 week) of NSAID therapy in healthy individuals is less likely to result in GI bleeding. Other risk factors associated with NSAID-induced UGIB include higher NSAID dosages; history of GI injury from NSAIDs; history of PUD associated with *H. pylori* infection; and concurrent use of corticosteroids, anticoagulants, or bisphosphonates. For some patients, genetic predisposition may also play a role in NSAID-associated GI bleeding. Polymorphism of cytochrome P450 (CYP) 2C9 may delay the metabolism of some NSAIDs and prolong the duration of ulcer-inducing effects. The risk of UGIB is also significantly higher in patients with concomitant use of serotonin reuptake inhibitors and NSAIDs.

The role of *H. pylori* infection in patients with NSAID use is somewhat controversial. Several studies suggest that *H. pylori* infection and NSAID use are independent and synergistic risk factors for bleeding PUD. A meta-analysis showed that preemptive eradication of *H. pylori* in NSAID-naive users before the initiation of NSAIDs was associated with a decrease in the development of peptic ulcers. A more recent meta-analysis concluded that the risk of PUD is significantly higher in patients with *H. pylori* infection who are receiving chronic NSAID therapy than in those on NSAIDs without the infection. However, ulcers were more common in patients with *H. pylori* infection compared with those without the infection, irrespective of NSAID use.

**Esophageal Varices**

A prospective case series from two large tertiary care facilities showed that gastroesophageal varices were the second most common cause of UGIB. Esophageal varices are present in about 50% of patients with cirrhosis, and variceal hemorrhage occurs at a rate of 5% to 15% per year depending on the severity of the liver disease. Gastroesophageal varices develop because of systemic or segmental portal hypertension, leading to obstruction of the portal venous outflow caused by hepatic cirrhosis. Varices develop to decompress the hypertensive portal vein and return blood to the systemic circulation. Six-week mortality with each occurrence of variceal hemorrhage is about 15% to 25%, and late rebleeding (within 1–2 years of the initial bleeding episode) occurs in about 60% to 70% of patients not receiving prophylaxis.

Several clinical and physiologic factors are associated with variceal hemorrhage in patients with end-stage liver disease. Although varices may develop anywhere along the GI tract, the most common sites for liver disease–related varices are the distal esophagus, stomach, and rectum. The gastroesophageal junction has the thinnest tissue layer and the most likely area of variceal hemorrhage. Major risk factors associated with variceal hemorrhage include larger size and/or red appearance of the varices, increasing severity of liver dysfunction, and history of variceal hemorrhage episodes.

**Stress-Related Mucosal Damage**

Stress-related mucosal damage (SRMD) and subsequent bleeding remains the most common cause of acute UGIB in patients with critical illness, with a 1.5% to 8.5% estimated incidence of overt GI bleeding. Two major risk factors for overt GI bleeding in critically ill patients are mechanical ventilation for more than 48 hours and coagulopathy defined as a platelet count less than 50,000/$mm^3$ and/or an international normalized ratio (INR) greater than 1.5. Other risk factors for SRMD and clinically important bleeding include surgery, trauma, organ failure, sepsis, severe burns, and neurologic injuries. In addition, anticoagulants, high-dose corticosteroids, and

prolonged intensive care unit (ICU) stay may increase the risk of SRMD in critically ill patients.

**Other Uncommon Causes of UGIB**

A Mallory-Weiss tear is a longitudinal mucosal laceration in the distal esophagus and proximal stomach. This gastroesophageal tear leads to bleeding from submucosal arteries. The incidence of Mallory-Weiss tears among patients with UGIB is around 5%. These lacerations are usually associated with a sudden increase in intra-abdominal pressure, resulting in a gastric mucosal tear from the forceful distention of the gastroesophageal junction. Precipitating risk factors for Mallory-Weiss tears include vomiting, straining at stool or lifting, coughing, seizures, hiccups, cardiopulmonary resuscitation, blunt abdominal trauma, and colonoscopic preparation with polyethylene glycol electrolyte lavage solutions. Other risk factors include alcoholic binges, diabetic ketoacidosis, and hiatal hernias. A Mallory-Weiss tear is commonly seen in individuals 30–50 years of age, and men have a higher incidence than women.

Aortoenteric fistulas are direct connections between the aorta and GI tract; they are most often associated with prosthetic abdominal aortic vascular grafts, in which necrosis and graft infection are implicated for the development of the fistula. Aortoenteric fistulas usually occur in the third or fourth portion of the duodenum but can also occur in the jejunum and ileum. Other associated factors for the fistula and resultant bleeding include penetrating ulcers, metastatic tumors, trauma, radiation therapy, and foreign body invasion.

Upper GI bleeding caused by a malignant tumor of the GI tract accounts for less than 3% of all UGIB cases. Bleeding usually occurs at a late stage of the malignancy when the tumor outgrows the blood supply, resulting in diffuse mucosal ulceration or an erosion into an underlying vessel. A Dieulafoy lesion is a congenitally dilated submucosal artery that has ulcerated; it is usually located in the upper stomach near the gastroesophageal junction, although it can occur anywhere along the GI tract. The precipitating factors of bleeding in these lesions are not well understood, but bleeding usually occurs in men with comorbid medical conditions such as cardiovascular disease, hypertension, chronic kidney disease, diabetes, or alcoholism. Dieulafoy lesions account for less than 2% to 5% of severe UGIB cases.

## Clinical Evaluation and Diagnosis

The initial evaluation of the patient presenting with features of acute UGIB includes a complete medical history, physical examination, and laboratory assessment with a goal of assessing the severity and urgency of the bleeding. The initial assessment is used to identify high-risk patients who require rapid and appropriate intervention to minimize morbidity and mortality.

The most common clinical presentation of acute UGIB is hematemesis (30% of patients) and/or melena (20% of patients). Around 50% of patients present with both hematemesis and melena, and up to 5% of patients present with hematochezia, which is suggestive of a rapid and significant amount of blood loss. Hematemesis is indicative of bleeding proximal to the ligament of Treitz; frank bloody emesis suggests ongoing bleeding, whereas coffee-ground emesis suggests limited bleeding. Melena usually indicates bleeding proximal to the ligament of Treitz, although in some cases, the small bowel or right colon may also be involved.

In the patient with a bleeding peptic ulcer, epigastric or right upper quadrant pain often accompanies acute bleeding. In patients with Mallory-Weiss tear, emesis, retching, or coughing may have preceded hematemesis. Patients presenting with jaundice, weakness, fatigue, anorexia, and ascites most likely are experiencing variceal hemorrhage. Patients with bleeding from a malignant tumor of the GI tract may present with dysphagia, involuntary weight loss, and cachexia.

Medical history, including previous episodes of UGIB, can identify comorbid medical conditions associated with bleeding and may direct medical management of the bleeding. Up to 60% of patients with a history of UGIB are bleeding from the lesion previously identified. A thorough medication history is also important to identify drug-induced GI bleeding. Nonsteroidal anti-inflammatory drugs, antiplatelet agents, and drugs associated with esophagitis may be identified, and drug therapy can be modified appropriately.

Laboratory values (e.g., complete blood cell count, serum chemistries, liver function tests, coagulation studies) are used to assess the severity of the bleed. Patients with hypovolemia caused by significant blood loss require rapid volume resuscitation to improve hemodynamic stability and to prevent shock; these patients should be immediately transferred to the ICU. Symptoms suggestive of severe bleeding include orthostatic hypotension, confusion, angina, severe palpitation, and cold/clammy extremities. Patients at high risk of rebleeding and increased mortality include those with advanced age, serious chronic medical comorbidities, shock, and coagulopathy.

**Endoscopy**

Although 80% of UGIB resolves spontaneously without treatment, 20% will recur. Patients with low risk of rebleeding on the basis of assessment can be managed as outpatients, but most other patients should receive upper endoscopy within the first 24 hours of a bleeding episode to identify the source of bleeding, look for predictors of recurrent bleeding, and assess the need for endoscopic intervention. Nasogastric lavage can be performed in select patients to remove particulate matter, fresh blood, and clots before endoscopy.

In addition, nasogastric lavage can be used when it is unclear whether a patient with hematemesis has ongoing bleeding and therefore might benefit from an early endoscopy.

Nasogastric lavage appears to be most useful in patients who are hemodynamically stable without evidence of hematemesis; the presence of fresh red blood in nasogastric tube aspirate is a predictor of high-risk lesions. Endoscopic predictors of high risk of rebleeding are listed in Box 1-1. Although data suggest that early endoscopy is safe and effective for patients in all risk groups, endoscopy may be delayed in select high-risk patients, including those with acute coronary syndrome or suspected perforation.

**Prognostic Assessment**

Prognostic scales use clinical, laboratory, and endoscopic criteria to stratify patients as low to high risk of rebleeding and mortality. Prognostic scales allow early identification and appropriate management of high-risk patients.

The Blatchford risk score (Table 1-1) is a validated risk-stratification tool that can accurately identify patient risk using clinical and laboratory variables. The score ranges from 0 to 23. A score of 0 identifies a low-risk patient with a 100% negative predictive value for rebleeding. A patient identified as low risk can be safely managed as an outpatient without the need for early endoscopy. A score of 1 or above identifies a patient as high risk, and a score greater than 6 indicates a recommendation for an intervention such as a blood transfusion or endoscopy. Although externally validated, the Blatchford risk score is useful mostly in identifying low-risk patients suitable for early discharge because the high-risk category encompasses a wide range of scores (1–23).

The Rockall scale (Table 1-2), which makes use of both clinical and endoscopic criteria to predict the risk of rebleeding and mortality, has been validated in several health care settings. The scoring system ranges from 0 to 11 points, with higher scores indicating higher risk and scores of 2 or less indicating low risk of rebleeding and

**Box 1-1.** Predictors of High Risk of Rebleeding or Mortality in Patients with Nonvariceal Upper Gastrointestinal Bleeding

**Endoscopic**

- Active bleeding
- Nonbleeding visible vessel or adherent clot
- Ulcer size greater than 2 cm
- Ulcers located on posterior lesser gastric curvature or posterior duodenal wall

**Clinical**

- Age older than 65 years
- Shock
- Poor overall health status
- Comorbid illnesses
- Low initial hemoglobin concentration
- Melena
- Transfusion requirement
- Fresh red blood on rectal examination, in emesis, or in the nasogastric aspirate
- Sepsis
- Elevated urea, creatinine, or serum aminotransferase concentrations
- APACHE ≥ 11

APACHE = Acute Physiology, Age, and Chronic Health Evaluation.
Information from Barkun A, Bardou M, Kulpers EJ, Sung J, Hunt RH, Marshall JK. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152:101–13.

**Table 1-1.** Blatchford Score

| Variables at Presentation | Points[a] |
|---|---|
| Systolic blood pressure | |
| 100 – 109 mm Hg | 1 |
| 90 – 99 mm Hg | 2 |
| <90 mm Hg | 3 |
| Blood urea nitrogen[b] | |
| 6.5 – 7.9 mmol/L | 2 |
| 8.0 – 9.9 mmol/L | 3 |
| 10.0 – 24.9 mmol/L | 4 |
| ≥25 mmol/L | 6 |
| Hemoglobin (men) | |
| 12.0 – 12.9 g/dL | 1 |
| 10.0 – 11.9 g/dL | 3 |
| <10.0 g/dL | 6 |
| Hemoglobin (women) | |
| 10.0 – 11.9 g/dL | 1 |
| <10 g/dL | 6 |
| Other variables | |
| Pulse ≥ 100 bpm | 1 |
| Melena | 1 |
| Syncope | 2 |
| Hepatic disease | 2 |
| Cardiac failure | 2 |

[a]Scoring; 0 = low risk; 1 or above = high risk.
[b]To convert blood urea nitrogen from mmol/L to mg/dL, divide the number by 0.357.
Reproduced with permission from Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper gastrointestinal haemorrhage. Lancet 2000;356:1318–21.

death. Compared with several other endoscopic prognostic scales, the Rockall system produces a more accurate diagnosis. Both the Blatchford and Rockall scores are useful prognostic tools in patients presenting with acute UGIB and may reduce the need for early medical interventions in patients at low risk of rebleeding.

## Management of UGIB

### Hemodynamic Resuscitation and Preendoscopy Management

The 2003 international consensus recommendations for the medical management of patients with nonvariceal UGIB, updated in 2010, include several changes. Patients with hemodynamic instability require prompt hemodynamic resuscitation, which can decrease mortality and morbidity by reducing the risk of myocardial infarction. Colloids or crystalloid fluids should be administered to restore adequate blood pressure; blood transfusions should be initiated to compensate for ongoing blood loss, substantial hemorrhage, or cardiac ischemia. The consensus guidelines recommend blood transfusion in patients with a hemoglobin concentration of 7 g/dL or lower; however, the threshold may be higher for some patients, such as the elderly and those with comorbid conditions. For patients with coagulopathy, appropriate fractionated blood products should also be administered. In patients with an INR greater than 1.5 due to anticoagulant therapy, measures to correct INR should be initiated.

**Table 1-2.** Rockall Score

| Variables at Presentation | Points[a] |
|---|---|
| Age | |
| <60 years | 0 |
| 60 – 79 years | 1 |
| ≥80 years | 2 |
| Shock | |
| Heart rate >100 beats/min | 1 |
| Systolic blood pressure <100 mm Hg | 2 |
| Coexisting illness | |
| Ischemic heart disease, congestive heart failure, other major illness | 2 |
| Renal failure, hepatic failure, metastatic cancer | 3 |
| Endoscopic diagnosis | |
| No lesion, Mallory-Weiss tear | 0 |
| Peptic ulcer, erosive disease, esophagitis | 1 |
| Cancer of upper GI tract | 2 |
| Endoscopic stigmata of recent hemorrhage | |
| Clean-base ulcer, flat pigmented spot | 0 |
| Blood in upper gastrointestinal tract, active bleeding, visible vessel, clot | 2 |

[a]Scoring: ≤ 2 = low risk; 3–7 = moderate risk; ≥ 8 = high risk.
Reproduced with permission from Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316–21.

### Endoscopic Management

Endoscopic procedures can be used to assess the prognostic indicators, which are described using the Forrest classification. Spurting hemorrhage and oozing hemorrhage are class I and indicate an acute hemorrhage. Class II indicators such as a nonbleeding visible vessel, an adherent clot, and a flat pigmented spot are signs of a recent hemorrhage. Class III indicators such as a clean ulcer base indicate lesions without active bleeding. Clean-base and flat spot ulcers are most commonly seen and are associated with low risk of rebleeding (5% to 10%). Patients with clean-base ulcers can be discharged with a pharmacologic agent. An adherent clot overlying the ulcer bases is associated with a higher risk of rebleeding (22%) and may require endoscopic intervention. Patients with nonbleeding visible vessels or active bleeding, which is associated with the highest risk of rebleeding (43% to 55%), should be admitted to the ICU for appropriate management.

Endoscopic intervention is the method of choice for controlling active GI bleeding. Early endoscopic hemostatic interventions significantly reduce the rate of rebleeding, surgery, and mortality, especially in patients with nonvariceal UGIB. Endoscopic interventions are used either as monotherapy or in combination with other medical procedures. These endoscopic interventions include: application of clips, argon plasma coagulation, injection of epinephrine or sclerosants, bipolar electrocoagulation, band ligation, heater probe coagulation, and laser therapy. Injection therapy, for example, can be first applied to better localize the bleeding site and followed by heater probe or bipolar (gold) probe coagulation.

Injection therapy involves placing 0.5- to 1-mL aliquots of epinephrine (1:10,000 diluted in saline) through a sclerotherapy catheter with a retractable needle in three or four quadrants around the actively bleeding point in the ulcer base. Epinephrine injection induces vasoconstriction and subsequent platelet aggregation. This procedure reduces the volume of bleeding so that the lesion can be better viewed and treated with a heater probe or gold probe. Combining epinephrine injection with human thrombin also reduces the risk of rebleeding, especially in patients with uncontrolled hemorrhage or rebleeding. The sclerosant solutions commonly used in injection therapy include ethanol, polidocanol, ethanolamine, sodium morrhuate, and

sodium tetradecyl sulfate. These agents induce thrombosis, tissue necrosis, and inflammation at the injection site, thereby creating hemostasis. Injection therapy can also be applied before endoscopic hemoclip placement.

The international consensus guidelines on UGIB recommend use of endoscopic clips or thermal therapy for high-risk lesions, such as actively bleeding ulcers. The choice of treatment technique is largely based on the size of the bleeding vessel. Small vessels (less than 2 mm in diameter) can be effectively controlled by a heater probe or bipolar probe. For a larger vessel or vessels that are unapproachable by the heater probe or bipolar probe, clips and band ligation or a combination of techniques is usually necessary. For visible nonbleeding vessels, thermal coagulation or endoscopic hemoclips also significantly reduce the rebleeding rate. An adherent clot over the ulcer base is usually managed with a combination of injection therapy and thermal coagulation.

**Pharmacologic Management**

***Nonvariceal Bleeding***

Pharmacologic management of acute UGIB, described in Figure 1-1, focuses on profound acid suppression with proton pump inhibitors (PPIs). Gastric acid inhibits platelet aggregation, impairs clot formation, and promotes fibrinolysis; therefore, inhibiting gastric acid and raising the intragastric pH to 6 or higher may promote clot formation and decrease the risk of rebleeding. The use of histamine-2 receptor antagonists in patients with acute nonvariceal bleeding is ineffective in sustaining intragastric pH at 6 or higher or producing significant improvement in clinical outcomes and is therefore not recommended.

Several studies evaluating PPIs for bleeding ulcers (with or without endoscopic therapy) found significant reduction in the risk of rebleeding. A 2006 meta-analysis suggested that the use of PPIs substantially decreased the risk of ulcer rebleeding, the need for urgent surgery, and the risk of death compared with histamine-2 receptor antagonists or placebo. The reduction in mortality was shown only in patients with high-risk stigmata (i.e., active hemorrhage, non-bleeding visible vessels, and adherent clots) who had undergone early endoscopic therapy. This supports the use of pharmacologic therapy as an adjunct to endoscopic interventions in patients at high risk of rebleeding. Results from a pooled analysis of 16 randomized controlled trials with more than 3800 subjects support intravenous bolus loading followed by continuous infusion of a PPI (equivalent to omeprazole 80-mg bolus followed by an 8-mg/hour continuous infusion for 72 hours). This regimen is more effective than bolus dosing alone in decreasing the incidence of rebleeding and the need for surgery. Around 72 hours of therapy is required after endoscopic therapy for improvement from high- to low-risk lesion.

The optimal PPI regimen for acute GI bleeding remains debatable because no head-to-head trial has compared the continuous infusion of PPIs with intermittent high-dose intravenous or oral PPIs (equivalent to pantoprazole 40 mg four times/day). The use of high-dose oral PPIs for peptic ulcer bleeding in Asian populations reduced the risk of rebleeding, the need for surgery, and the risk of death compared with low-dose intravenous PPIs. These results may not be generalized to the North American population because of the differences in underlying etiology and higher prevalence of *H. pylori* infection in the Asian population. In addition, genetic polymorphism in CYP metabolism in the Asian population may have produced more potent acid suppression because of the slower clearance of PPIs and a lower parietal cell mass. There could be a significant impact on health care resources if high oral doses were found to be as effective as intravenous administration; therefore, further prospective randomized clinical trials comparing the use of intravenous and oral PPIs are needed.

Pre-endoscopic PPI therapy may be indicated in patients thought to have high-risk stigmata. A meta-analysis of six randomized clinical trials (one study assessed oral PPI therapy, five studies evaluated intravenous PPI therapy) that included 2223 patients suggested that pre-endoscopic PPI treatment significantly reduced the percentage of patients with high-risk stigmata and the need for endoscopic interventions compared with patients who received placebo or histamine-2 receptor antagonists. These findings led to the Asia-Pacific Working Group consensus recommendation for pre-endoscopic PPI when early endoscopy or endoscopic expertise was not available within 24 hours. Cost-effectiveness analyses of pre-endoscopic PPI therapy have shown mixed results; this is because certain model assumptions limit conclusions from studies of pre-endoscopic high-dose intravenous PPI therapy versus oral PPI therapy. If a delay in endoscopy is expected, the most cost-effective strategy may be to employ pre-endoscopic PPI therapy in patients with nonvariceal bleeding from a suspected high-risk lesion.

Octreotide inhibits both acid and pepsin secretion while reducing gastroduodenal mucosal bloodflow. Octreotide is not routinely recommended as a sole or adjunctive agent to endoscopy in patients with nonvariceal bleeding because available data have not shown benefit when it is used alone or in combination with a histamine-2 receptor antagonist. Tranexamic acid is an antifibrinolytic agent that inhibits plasminogen activators. Although a meta-analysis from more than 20 years ago found that tranexamic acid decreased mortality compared with placebo in patients with UGIB, the conclusions were limited because the analysis included studies in which endoscopic interventions were not performed. In addition, more than 43% of the patients

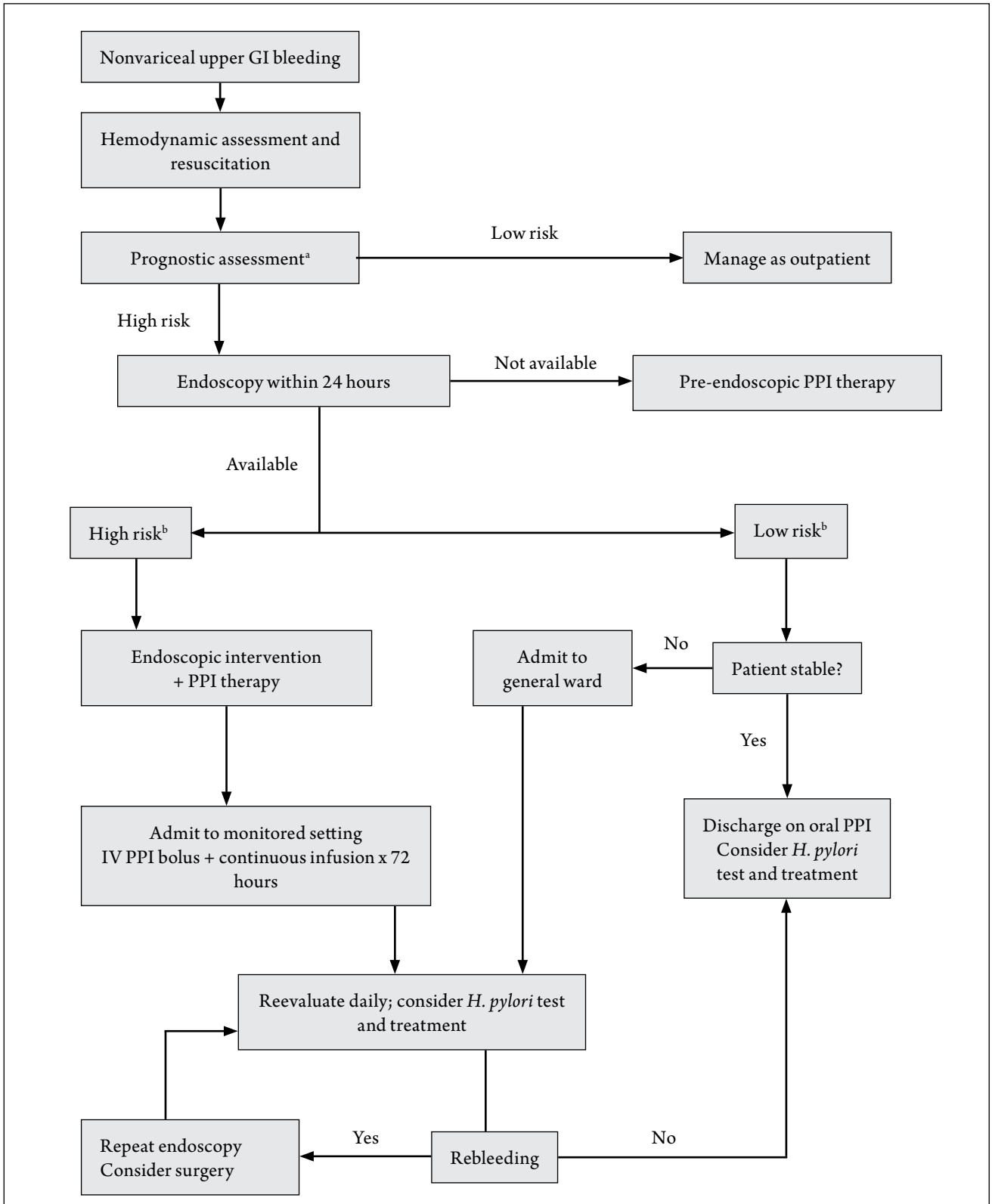


**Figure 1-1.** Algorithm for the management of patients with nonvariceal upper GI bleeding.

[a]Rockall or Blatchford scoring system can be used to categorize patients as low risk or high risk.
[b]Risk assessment based on endoscopy is based on Forrest classification: Class I = low risk; Class II and III = high risk.
GI = gastrointestinal; IV = intravenous; PPI = proton pump inhibitor.

experienced bleeding episodes from sources other than peptic ulcers. Tranexamic acid therefore is not recommended in the acute management of UGIB.

***Variceal Bleeding***

Esophageal variceal hemorrhage is a potentially fatal complication of end-stage liver disease. Mortality rates from a first esophageal bleeding episode are 20% to 35%, and around 30% of further bleeding episodes are fatal. For patients with cirrhosis who present with bloody emesis, antibiotics are initiated on admission; this is because up to 20% of patients with cirrhosis who are hospitalized for bleeding have bacterial infections, and another 50% will develop hospital-acquired infection. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend a short-term course (maximum of 7 days) of prophylaxis with oral norfloxacin or intravenous ciprofloxacin for all patients with cirrhosis who are hospitalized for variceal hemorrhage. Although antibiotic resistance is a growing problem, especially in the acute care setting, prophylactic antibiotics in patients with variceal hemorrhage are associated with a reduction in infectious complications and decreased risk of recurrent hemorrhage. In light of the high mortality associated with variceal hemorrhage, antibiotics should be initiated in all patients, preferably before endoscopy. For patients with advanced liver disease, ceftriaxone may be preferred, especially in regions with a high prevalence of quinolone-resistant organisms. Several studies have suggested that antibiotics prevent rebleeding and decrease infectious complications and mortality in patients with variceal hemorrhage.

When the source of bleeding has been identified and hemodynamic resuscitation achieved, vasoactive drugs are administered to lower portal pressure and pressure in the collateral circulation. Octreotide, the drug of choice, is a synthetic somatostatin that produces selective splanchnic vasoconstriction and decreases portal inflow, thereby indirectly reducing variceal bloodflow. To treat acute variceal hemorrhage, octreotide is administered as a bolus dose of 50 mcg, followed by a 3- to 5-day continuous infusion of 50 mcg/hour. Within seconds after the bolus dose of octreotide, decreases are seen in portal venous inflow, portal pressures, azygos flow (collateral bloodflow that drains the main part of the portal venous system), and intravariceal pressures. Octreotide may be more effective than vasopressin in controlling variceal hemorrhage, with a lower adverse effect profile; however, there is no clear mortality benefit with octreotide.

Another option is vasopressin, a potent vasoconstrictor of mesenteric arterioles that decreases portal venous flow and reduces portal pressures. Vasopressin is administered at a continuous infusion of 0.2–0.4 unit/minute and can be increased to a maximum of 0.8 unit/minute. In several studies, vasopressin achieved initial hemostasis in 60% to 80% of patients with variceal hemorrhage but had a marginal effect on recurrent bleeding episodes and did not improve mortality rates. Vasopressin may increase mortality rates in patients with variceal hemorrhage because of systemic vasoconstriction and subsequent myocardial, cerebral, bowel, and limb ischemia. The many adverse effects of vasopressin caused by systemic vasoconstriction may be managed by use of intravenous nitroglycerin, which reverses the systemic hemodynamic effects of vasopressin while maintaining or enhancing the fall in portal pressure. Nitroglycerin is initiated at 40 mcg/minute and can be increased to a maximum of 400 mcg/minute. Although studies have shown that the combination of vasopressin and nitroglycerin had some benefit in controlling variceal hemorrhage and/or reducing adverse effects of vasopressin, the combination did not improve mortality. Because of these adverse outcomes and the greater benefit seen with octreotide, vasopressin is rarely used in the United States for the management of acute variceal hemorrhage.

Terlipressin is the only pharmacologic agent associated with reduction in mortality compared with placebo. Terlipressin is a vasopressin analog that stimulates vasopressin-1 receptors (located in vascular smooth muscle) and produces vasoconstriction. Terlipressin increases mean arterial pressure and decreases portal flow and pressure, leading to decreased variceal hemorrhage. A meta-analysis of several trials showed a 34% relative risk reduction in mortality with terlipressin use in patients with esophageal variceal hemorrhage compared with placebo. Terlipressin is not available in the United States but is used in several other countries. It is administered as an intermittent intravenous dose of 2 mg every 4 hours and can be titrated down to 1 mg every 4 hours after bleeding is controlled. Compared with somatostatin, octreotide, or endoscopic interventions, terlipressin showed similar efficacy for the control of acute variceal hemorrhage. Compared with octreotide in patients with bleeding varices, terlipressin had more sustained hemodynamic effects.

Patients with cirrhosis and compromised hepatic function experience a reduction in the production of coagulation factors, notably factor VIIa. The resulting coagulopathy may contribute to refractory variceal hemorrhage; therefore, patients may theoretically benefit from recombinant activated factor VIIa. A multicenter placebo-controlled trial found that recombinant factor VIIa had no significant effect on controlling variceal hemorrhage and mortality compared with placebo. Although post hoc subgroup analysis of Child-Pugh class B and C patients with cirrhosis suggested that recombinant factor VIIa decreased the proportion of patients with refractory variceal hemorrhage, confirmatory studies are needed before the use of recombinant factor VIIa can be routinely recommended in this setting.

**Nonpharmacologic Management**

Angiographic interventions have become a vital option for managing nonvariceal bleeding that continues after aggressive endoscopic treatment. Angiographic intervention requires catheterization and angiograms of the celiac, superior mesenteric, and inferior mesenteric arteries to identify abnormalities that are correlated with endoscopic findings.

Angiographic treatment, which involves infusion of intra-arterial vasoconstrictors in the mesentery, is recommended to decrease recurrent bleeding episodes and mortality. Once the selective angiogram identifies the source of bleeding, vasopressin is infused through an infusion catheter near the site of bleeding at a starting rate of 0.2 unit/minute. A mesenteric angiogram is repeated after 20 minutes to see whether bleeding has stopped. Vasopressin infusion rate is increased up to 0.6 unit/minute if bleeding persists. Infusion rates greater than 0.6 unit/minute are associated with increased complications such as intestinal and cardiac ischemia. The intra-arterial vasopressin infusion is continued for up to 36 hours if the bleeding is controlled and slowly tapered off over 24–26 hours. Angiographic interventions successfully control bleeding in 89% to 90% of cases and have an overall success rate of up to 90%. However, rebleeding rates of up to 50% have been reported once the infusion is discontinued.

Transcatheter embolization therapy is also a safe and effective treatment for some patients with peptic ulcers that continue to bleed after endoscopic interventions. Transcatheter embolization therapy selectively reduces blood supply to the source of bleeding; the reduced bloodflow facilitates clot formation. Transcatheter embolization produces an initial bleeding control rate of 89% to 98% and clinical success rates of up to 90%.

Surgical intervention for the management of acute UGIB has declined in popularity. The goal of emergency surgery is to stop the hemorrhage when endoscopic intervention is unavailable or has failed. Surgical intervention remains a safe and effective option for the management of select patients with uncontrollable bleeding or for patients who may not tolerate rebleeding. When patients are unable to tolerate prolonged hemodynamic instability (e.g., those of advanced age or with significant comorbid medical illnesses), early surgery may produce a better clinical outcome than repeat endoscopic hemostasis.

Balloon tamponade is effective in achieving short-term hemostasis in more than 80% of patients with variceal hemorrhage. In this procedure, a large gastric balloon (e.g., Linton tube, Minnesota four-lumen tube, Sengstaken-Blakemore tube) is inserted into the esophagus and inflated to stop refractory esophageal hemorrhage. However, its use is associated with complications such as aspiration, migration, and necrosis and/or perforation of the esophagus; it is also associated with mortality rates as high as 20%. Balloon tamponade is therefore considered a rescue therapy and is reserved for patients with uncontrollable hemorrhage for whom a transjugular intrahepatic portosystemic shunt (TIPS) is planned within 24 hours of placement. Because of the high risk of aspiration, airway protection is recommended when balloon tamponade is used.

## Prevention of UGIB

### Peptic Ulcer–Induced UGIB

Once UGIB has ceased, once-daily PPI therapy has been shown to be effective in healing peptic ulcers. Recurrent bleeding may occur more than 3 days after endoscopic hemostasis has been achieved. Although the 2010 guidelines recommend that patients with UGIB be discharged with a prescription for a once-daily oral PPI, the duration, dosage, and frequency of PPI therapy should be determined by the underlying etiology of the bleeding. Severe or complicated esophagitis may require either twice-daily doses of PPIs or a longer duration of once-daily dosing. In very severe cases, twice-daily doses for a longer duration of therapy are needed to effectively treat esophagitis. Patients who require continued aspirin or NSAID therapy may also require long-term GI prophylaxis with a PPI. Patients who require long-term PPI therapy should be monitored for potential adverse effects of PPIs, including *Clostridium difficile* infection, pneumonia, hypomagnesemia, and osteoporosis-associated fracture.

In patients with NSAID-induced UGIB, NSAID therapy should be discontinued, if possible, and continued PPI therapy should be recommended. For patients with UGIB who require continued NSAID therapy, the combination of a cyclooxygenase-2 (COX-2) inhibitor and a PPI is recommended to reduce the risk of recurrent bleeding. Several studies have shown that in patients with a history of bleeding ulcer who require NSAID therapy, taking a traditional NSAID with a PPI or a COX-2 inhibitor alone is still associated with clinically significant GI toxicity. In addition, the combination of a COX-2 inhibitor and a PPI is associated with a lower risk of GI complications compared with a traditional NSAID plus a PPI or a COX-2 inhibitor alone. However, COX-2 inhibitors, compared with placebo, may be associated with an increased risk of serious cardiovascular events. Therefore, in patients with UGIB who require continued NSAID therapy and may benefit from the combination of a COX-2 inhibitor and a PPI, the potential for both GI and cardiovascular risks should be evaluated.

Patients who require low-dose aspirin therapy and develop UGIB should restart aspirin as soon as the risk of a thromboembolic event outweighs the risk of ulcer bleeding, because in these patients, discontinuation of aspirin is associated with a 3-fold increase in the risk of a major cardiovascular event. The American Heart Association recommends that the decision to withdraw aspirin therapy

for a patient with acute UGIB be based on the patient's cardiovascular and GI risks. Available data suggest that immediately restarting aspirin in combination with intravenous or oral PPI therapy in patients with bleeding ulcers results in a 2-fold increase in the risk of rebleeding, whereas the withdrawal of aspirin therapy is associated with significantly higher mortality at 8 weeks. The international consensus guidelines therefore recommend reinitiating aspirin therapy in patients with UGIB after 7–10 days, when the risks of adverse cardiovascular events are thought to outweigh the risk of recurrent bleeding.

For patients who require NSAID therapy and have not experienced an episode of NSAID-associated GI injury, the American College of Gastroenterology recommends a stepwise approach to evaluation and management of cardiovascular and GI risks. Treatment with naproxen combined with misoprostol or a PPI is recommended for patients with cardiovascular risks who require low-dose aspirin and NSAID therapy. Patients who are at moderate GI risk and high cardiovascular risk are recommended to be managed with naproxen combined with misoprostol or a PPI. Although misoprostol is effective in markedly reducing the incidence of ulcers in patients receiving NSAIDs, its use is limited by significant GI adverse events (cramping and diarrhea) and low adherence because of four times/day dosing. Cyclooxygenase-2 inhibitors and NSAIDs should be avoided in patients at high GI and cardiovascular risk, and alternative drug therapy is recommended. In patients with low risk of cardiovascular events, COX-2 inhibitors can be safely used for the primary prevention of NSAID-associated GI injury.

Clopidogrel is associated with a significant risk of bleeding. Several observational studies suggest that PPIs decrease the antiplatelet effects of clopidogrel through CYP2C19, which is required to convert clopidogrel to its active metabolite. In these studies, PPI use in patients receiving clopidogrel was associated with a significant increase in the risk of cardiovascular events; other studies, however, found no association between PPI use and increased cardiovascular events. No prospective randomized trial data address the clinical outcome of this drug interaction. However, the U.S. Food and Drug Administration has required the clopidogrel product label to include a statement discouraging concomitant administration of drugs that inhibit CYP2C19, such as omeprazole and esomeprazole. For patients who require clopidogrel and GI prophylaxis with a PPI, drugs such as pantoprazole with the least potential for drug interaction may be an option until more studies are available to guide drug therapy.

### *H. pylori* Eradication

The 2010 guidelines recommend that patients with bleeding peptic ulcers be tested for *H. pylori* and receive eradication therapy if positive for the infection, with follow-up confirmation of eradication. *H. pylori* eradication reduces the risk of recurrent peptic ulcers and rebleeding and is markedly more effective than PPI therapy alone. Because up to 55% of *H. pylori*–infected patients may have false-negative results in the setting of acute UGIB, repeat testing is recommended after a negative *H. pylori* test.

Many anti–*H. pylori* regimens have been evaluated. When efficacy, cost, adverse effects, and adherence are considered, triple therapy (i.e., with amoxicillin, clarithromycin, and a PPI) is recommended as the first-line treatment of *H. pylori* eradication. A meta-analysis suggested that 14 days of treatment was more effective than a 10-day regimen, but the associated increase in eradication was only 5%. In patients with penicillin allergy, metronidazole can be substituted for amoxicillin; however, this may compromise the eradication rate because metronidazole resistance is common. In areas where the prevalence of clarithromycin or metronidazole resistance is greater than 20%, a 10- to 14-day course of quadruple therapy (i.e., a PPI, bismuth subsalicylate or bismuth subcitrate, and two antibiotics [metronidazole and tetracycline]) may be appropriate as a first-line treatment for *H. pylori* infection eradication.

Eradication of *H. pylori* infection should be confirmed at least 4 weeks after completion of treatment because initial treatment fails in about 20% of patients, and the risk of rebleeding peptic ulcer may remain. Several studies have evaluated different retreatment regimens; although eradication rates for regimens consisting of two new antimicrobial agents were significantly higher than for regimens with only one new antimicrobial agent, further studies are needed to determine optimal retreatment therapy.

### Prevention of Variceal Bleeding

Primary prophylaxis is recommended in patients with medium or large varices who are at high risk of variceal hemorrhage. Nonselective β-blockers block the adrenergic dilatory tone in mesenteric arterioles, resulting in portal inflow reduction; these agents significantly reduce the risk of first variceal hemorrhage from 24% to 15% over 2 years. Nonselective β-blockers should be targeted to achieve a resting heart rate of 55 beats/minute or a 25% reduction from baseline. Endoscopic variceal ligation may also be an option, particularly in patients who are intolerant of or have contraindications to nonselective β-blockers, because the evidence for superiority of endoscopic variceal ligation compared with nonselective β-blockers is not robust. Propranolol at doses of 20–40 mg twice daily and nadolol at doses of 20–40 mg once daily are commonly used for primary prophylaxis of variceal hemorrhage.

In patients who have recovered from acute variceal hemorrhage, the recurrent bleeding rate is about 60% within 1–2 years, with a mortality rate of 33% without preventive management. The 2007 AASLD

guidelines recommend that patients who survive an episode of active variceal hemorrhage receive a combination of endoscopic variceal ligation and nonselective β-blockers. On the basis of a meta-analysis of 23 trials, combination therapy reduced overall recurrent variceal hemorrhage more than endoscopic therapy or nonselective β-blockers alone in patients who had experienced an episode of bleeding. The combination of a nonselective β-blocker and isosorbide mononitrate has a synergistic portal pressure–reducing effect; however, a study that directly compared this combination with nonselective β-blockers alone failed to show benefit. Other studies found a lower rebleeding rate with the combination therapy than with nonselective β-blocker monotherapy, but combination therapy was associated with greater adverse effects and was not well tolerated.

Transjugular intrahepatic portosystemic shunts (TIPS; which decompress the portal vein but do not require general anesthesia) and shunt surgery (portocaval shunt) should be considered in patients who experience recurrent variceal hemorrhage despite the combination of endoscopic and pharmacologic therapy. Compared with endoscopic therapy, TIPS showed significant improvement in the survival of high-risk patients with acute variceal hemorrhage. However, TIPS procedures are associated with a higher incidence of hepatic encephalopathy, especially in patients who are of advanced age, have liver failure, or have a history of encephalopathy.

**Prevention of SRMD**

In several trials, histamine-2 receptor antagonists, antacids, and PPIs reduced the rate of overt GI bleeding in critically ill patients compared with no prophylaxis. The 1999 American Society of Health-System Pharmacists guidelines recommend that patients at higher risk receive stress ulcer prophylaxis and suggest histamine-2 receptor antagonists as an agent of choice, primarily because of the lack of available data on PPIs at the time. Since the introduction of PPIs in the late 1980s, the use of these agents as the initial choice for stress ulcer prophylaxis has significantly increased (from 3% in 1998 to 23% in 2002), and the use of histamine-2 receptor antagonists noticeably declined (from 77% to 64%) during this same period.

Several studies comparing the safety and efficacy of histamine-2 receptor antagonists and PPIs have reported inconsistent findings, and recent studies also associate increased risk of pneumonia with the use of acid-reducing agents, particularly PPIs. A recent meta-analysis of seven trials comparing histamine-2 receptor antagonists and PPIs for stress ulcer prophylaxis suggested a trend toward less GI bleeding with PPI therapy, but the difference was small. In addition, the study suggested that histamine-2 receptor antagonists and PPIs were similar in rate of UGIB in critically ill patients, despite PPIs' superiority in elevating and maintaining intragastric pH. Histamine-2 receptors and PPIs were also similar with respect to the rate of nosocomial pneumonia and mortality.

The risk of *C. difficile* infection was not addressed in this study; however, several others have associated PPIs with a higher risk of *C. difficile* infection compared with histamine-2 receptor antagonists. Although PPIs are potent antisecretory agents with effective control of gastric pH compared with histamine-2 receptor antagonists, available data do not support the routine use of PPIs as first-line prophylaxis for SRMD. In light of significant clinical complications associated with PPIs, including pneumonia and *C. difficile* infection, histamine-2 receptor antagonists should be considered drugs of choice for stress ulcer prophylaxis in most patients who lack compelling indications for PPIs. The choice of an agent for patients requiring stress ulcer prophylaxis should therefore be made on the basis of the convenience of drug administration (Table 1-3), potential drug-drug interactions, and cost. Oral or nasogastric administration should be used if feasible, reserving the intravenous route for patients without other routes of administration.

Once the risk of stress-related mucosal injury is no longer present, the stress ulcer prophylactic agent should be discontinued promptly. Several studies have found a high rate (40% to 70%) of inappropriate use of stress ulcer prophylactic agents, such as when the drug is continued after a transition from the ICU or continued after discharge from the hospital without appropriate indication. New guidelines on GI stress ulcer prophylaxis from the American Society of Health-System Pharmacists are to be published in 2012 and are eagerly awaited.

## Role of the Pharmacist

The pharmacist can make a significant contribution to the management and prevention of UGIB. The updated international consensus guidelines should be carefully reviewed so that the pharmacist can provide appropriate drug therapy recommendations. Patients at risk of UGIB should be identified in all practice settings, and the optimal treatment plan should be devised for individual patients. Patients at risk of UGIB because of *H. pylori* infection should be screened, and *H. pylori* eradication therapy should be offered to patients who test positive. Pharmacists can play an important role in patient counseling for adherence and favorable therapeutic outcomes.

Patients requiring long-term NSAID therapy should be referred to their primary care physicians for appropriate gastroprotective agents to prevent GI toxicity. For individuals requiring aspirin for cardioprotective effects, the risk of GI complications should be assessed

**Table 1-3.** Pharmacologic Agents for Stress Ulcer Prophylaxis

| Drug | Dose and Frequency | Route | Formulation | Comment |
|---|---|---|---|---|
| **H2 Receptor Antagonists** | | | | |
| Famotidine | 20 mg q12h | Intravenous push<br>Oral<br>Nasogastric | Injection<br>Tablet<br>Powder for suspension | Tablet can be crushed for nasogastric administration |
| Ranitidine | 50 mg q8h IV<br>150 mg q12h orally | Intravenous piggyback<br>Oral<br>Nasogastric | Solution for infusion<br>Tablet<br>Syrup | Tablet can be crushed for nasogastric administration |
| **Proton Pump Inhibitors** | | | | |
| Dexlansoprazole | 30 mg q24h | Oral | DR capsule | Not routinely used for stress ulcer prophylaxis |
| Esomeprazole | 20 mg q24h | Intravenous push<br>Oral<br>Nasogastric | Injection<br>DR capsule<br>Powder for suspension | Many drug interactions (e.g., phenytoin and warfarin)<br>Granules of DR capsule can be mixed with 50 mL of water for nasogastric administration; granules of suspension should be mixed with 15 mL of water for nasogastric administration |
| Lansoprazole | 30 mg q24h | Oral<br>Nasogastric | DR capsule<br>DR OD tablet<br>Powder for suspension | Drug interaction with warfarin<br>OD tablet can be mixed with 10 mL of water for nasogastric administration<br>Granules of DR capsule can be mixed with 40 mL of apple juice for nasogastric administration |
| Omeprazole | 20 mg q24h | Oral<br>Nasogastric | DR capsules<br>DR granules for suspension | Many drug interactions (e.g., phenytoin, cyclosporine, and warfarin)<br>DR omeprazole capsule can be mixed with 10–20 mL of 8.4% sodium bicarbonate or 30 mL of water for nasogastric administration |
| Omeprazole/ sodium bicarbonate | 40 mg q24h | Oral<br>Nasogastric | IR capsule<br>Powder for suspension | Powder for suspension should be mixed with 20 mL of water and administered immediately |
| Pantoprazole | 40 mg q24h | Intravenous push<br>Oral<br>Nasogastric | Injection<br>DR EC tablet<br>Granules for suspension | Drug interaction with warfarin<br>Intact granules should be mixed with 10 mL of apple juice for nasogastric administration |

DR = delayed release; EC = enteric coated; h = hours; IR = immediate release; IV = intravenously; OD = orally disintegrating; q = every.

and guidance provided on the need for GI-protective agents. Patients should also be counseled on modifiable risk factors for UGIB (e.g., smoking). Pharmacists should identify critically ill patients at risk of SRMD and recommend appropriate prophylaxis. In addition, adverse effects, particularly with PPIs (e.g., pneumonia, *C. difficile* infection), can be minimized by pharmacists who are vigilant about the appropriate indications for prophylactic agents. When patients no longer require PPIs for the prevention of UGIB, the agent should be recommended for discontinuation, and discharge counseling should be advocated to prevent the long-term use of PPIs without valid indication.

## Conclusion

Despite the availability of potent antisecretory agents, UGIB continues to be associated with high morbidity and mortality. International consensus guidelines offer a systematic approach to the management of UGIB. *H. pylori* infection and NSAID therapy continue to be the two most common causes of UGIB; fortunately, there are preventive treatments for both conditions that have shown effectiveness in lowering the risk of serious bleeding. Currently available anti–*H. pylori* regimens have high eradication rates with optimal patient adherence. Proton pump inhibitors remain the most effective strategy for the treatment and prevention of NSAID-associated bleeding. On the basis of currently available data, histamine-2 receptor antagonists are recommended in patients at risk of SRMD. Prophylactic agent dosage, formulation, and route should be individualized for each patient to optimize clinical and economic outcomes of stress ulcer prophylaxis.

## Annotated Bibliography


1. Barkun A, Bardou M, Kulpers EJ, Sung J, Hunt RH, Marshall JK, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152:101–13.

   These multidisciplinary consensus recommendations on the medical management of patients with nonvariceal UGIB are updated from the 2003 recommendations. The systematic approach to the management of patients with acute UGIB in these guidelines encompasses resuscitation, risk assessment, and endoscopic management, as well as pharmacologic and nonpharmacologic in-hospital management and recommendations on the prevention of rebleeding with the use of postdischarge NSAIDs. Recommendations revised from the 2003 guidelines include the introduction of prognostic scales, which provide early stratification of patients into categories of low or high risk of rebleeding and death. Patients with acute UGIB who are at low risk of rebleeding on the basis of clinical and endoscopic criteria are recommended to be discharged with PPI therapy. In addition, pre-endoscopic PPI therapy is recommended in select patients thought to have high-risk stigmata, which may downstage the lesion and decrease the need for endoscopic procedures. Pharmacologic management was revised to recommend an intravenous bolus followed by continuous infusion of PPI therapy in patients with high-risk stigmata after successful endoscopic therapy. The guidelines are widely accepted as being evidence-based, especially on the pharmacologic management of acute UGIB. The use of an intravenous bolus followed by a continuous infusion of PPI and *H. pylori* eradication therapy received a grade 1A recommendation (strong recommendation, high-quality evidence), whereas NSAID treatment with a traditional NSAID plus PPI or a COX-2 inhibitor in patients with previously bleeding ulcers received a grade 1B recommendation (strong recommendation, moderate-quality evidence). Use of these guidelines may not be feasible in regions with limited resources where endoscopy may not be available within 24 hours. The updated guidelines incorporate strong data that became available since the 2003 guidelines and provide important information on the effective medical management of patients with UGIB.

2. Sung JJ, Chan FK, Chen M, Ching JY, Ho KY, Kachintorn U, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut 2011;60:1170–7.

   This is another consensus recommendation on the management of nonvariceal UGIB, but the focus is on Asia, where the population has a high prevalence of *H. pylori* infection. In addition, Asians have a different PPI metabolism compared with non-Asians, and varying socioeconomic settings may have an impact on the clinical management of UGIB. The working group is composed of experts from 12 Asian countries, and the emphasis is on data generated from Asian regions. Unlike the international consensus recommendations, this consensus statement recommends the use of the Blatchford score for selecting patients who require endoscopic interventions and low-risk patients who should be discharged early. A pre-endoscopic PPI is recommended when endoscopy is not available within 24 hours. High-dose intravenous PPI (equivalent to omeprazole 80-mg bolus followed by 8-mg/hour continuous infusion for 72 hours) and oral PPI (equivalent to omeprazole 40–80 mg twice daily) are recommended, but low-dose intravenous PPIs should be avoided. The panel recommends COX-2 inhibitors combined with a PPI for patients with high risk of UGIB. As with the international consensus statement, aspirin is recommended to be reinitiated soon after stabilization for patients requiring cardioprotection. For patients who require dual antiplatelet therapy with clopidogrel and aspirin and who are at high risk of GI complications, prophylactic use of a PPI is recommended. Overall, the recommendations of the Asia-Pacific consensus are similar to those of the international guidelines in managing Asian patients with UGIB who may have

different drug metabolism in varying clinical settings. The two recommendations that differ from the international consensus recommendations (i.e., preference for the Blatchford scoring system as a prognostic scale and the use of high-dose oral therapy for managing select patients with acute UGIB) are based on a moderate to high level of evidence.

3. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol 2009;7:33–47.

   The aim of this meta-analysis was to determine an appropriate endoscopic treatment of patients with bleeding ulcers. The analysis included 59 randomized trials that compared thermal therapy; epinephrine injection therapy; sclerosant injection therapy; thrombin/fibrin glue, argon plasma coagulation, or clips for actively bleeding ulcers; visible vessels; and clots. This meta-analysis concluded that thermal devices, sclerosants, clips, and thrombin/fibrin glue were effective endoscopic hemostatic techniques and that epinephrine should not be used alone. More importantly, this study found a significant decrease in rebleeding (relative risk [RR] = 0.40; 95% confidence interval [CI], 0.28–0.59), surgery (RR = 0.43; 95% CI, 0.24–0.58), and mortality (odds ratio [OR] = 0.41; 95% CI, 0.20–0.84) with high-dose intravenous PPI (equivalent to omeprazole 80-mg bolus followed by 8-mg/hour continuous infusion for 72 hours) therapy after endoscopic procedures. Lower doses of PPIs were associated with significant benefits in rebleeding (RR = 0.53; 95% CI, 0.35–0.78) but not surgery or mortality compared with placebo or no treatment. This analysis suggests that epinephrine injection therapy not be used alone and recommends the use of high-dose intravenous PPI therapy in patients with acute UGIB. In addition, the study evaluates comparisons between different endoscopic modalities and provides important information on the efficacy of endoscopic interventions. This analysis provides strong evidence for combination therapy and recommends the use of high-dose intravenous PPI therapy, despite the relatively limited search (i.e., the lack of systematic search for unpublished studies). This meta-analysis is also limited by some heterogeneity across the studies, and careful consideration should be given before an indiscriminate use of combined endoscopic therapy and high-dose infusion of PPIs in all patients with acute UGIB.

4. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc 2007;82:286–96.

   The objective of this meta-analysis was to evaluate the efficacy of PPIs in treating peptic ulcer bleeding. In a previously published study, the authors found that PPIs reduced the rate of rebleeding and surgical interventions after peptic ulcer bleeding compared with placebo or histamine-2 receptor antagonists but did not reduce all-cause mortality. In this updated meta-analysis, which included more recent randomized clinical trials, 24 trials with 4373 participants were included to evaluate 30-day all-cause mortality, rebleeding, surgery, and repeated endoscopic treatment. Treatment with PPIs had no significant effect on mortality (OR = 1.01; 95% CI, 0.74–1.40) but significantly reduced rebleeding (OR = 0.49; 95% CI, 0.37–0.65), the need for surgery (OR = 0.61; 95% CI, 0.48–0.78), and repeated endoscopic interventions (OR = 0.32; 95% CI, 0.20–0.51). Treatment with PPIs significantly reduced mortality in Asian trials (OR = 0.35; 95% CI, 0.16–0.74), which included eight trials from the Asia regions, and in patients with active bleeding or a nonbleeding visible vessel (OR = 0.53; 95% CI, 0.31–0.91). One of the main criticisms of this study is that it included a large number of subgroup analyses, including those of Asian trials and active bleeding or nonbleeding visible vessel trials. In addition, patients with ulcer bleeding represent a heterogeneous population, and the trials of PPI treatment were designed differently with respect to route of drug administration and control treatment used. This study, however, provides important information on the mortality benefits of PPI treatment when used in Asians and patients at high risk of rebleeding.

5. Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. Clin Gastroenterol Hepatol 2006;4:130–42.

   This analysis systematically reviewed the interactions between *H. pylori* infection and NSAID use on the risk of uncomplicated and bleeding peptic ulcer. Twenty-one trials with 10,146 participants were included to evaluate the relationship between the infection and NSAID use. The study found that uncomplicated peptic ulcer was more common in *H. pylori*–positive patients than in *H. pylori*–negative patients. In six age-matched controlled studies, ulcer was more common in *H. pylori*–positive patients than in *H. pylori*–negative patients, irrespective of NSAID use. The risk of ulcer was found to be 17.54-fold higher in *H. pylori*–positive NSAID users compared with *H. pylori*–negative nonusers. Ulcer bleeding was evaluated in 17 trials consisting of 4084 participants. Use of NSAIDs was found to be more common in bleeding patients than in control subjects irrespective of *H. pylori* status. On the contrary, *H. pylori* infection in bleeding patients was less common than in nonbleeding control subjects in eight trials. Both *H. pylori* infection and NSAID use were found to increase bleeding risk 30.83-fold compared with bleeding risk of nonusers without the infection. This study validated the notion that *H. pylori* infection and NSAID use represent independent and synergistic risk factors for bleeding peptic ulcer. One possible reason for the lower frequency of *H. pylori* infection in patients with bleeding ulcers is the high frequency of false negatives from urease-based tests in patients with active bleeding.

6. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: combination endoscopic and drug therapy to

prevent variceal rebleeding in cirrhosis. Ann Intern Med 2008;149:109–22.

The purpose of this analysis was to assess whether a combination of endoscopic and drug therapy could prevent overall and variceal rebleeding and improve survival better than either therapy alone. Twenty-three trials were evaluated, which included 1860 patients; endoscopic plus β-blocker therapy was compared with either therapy alone. The combination therapy with endoscopic interventions and drugs was found to reduce overall rebleeding more than endoscopic therapy alone (RR = 0.68; 95% CI, 0.52–0.89) or β-blocker alone (RR = 0.71; 95% CI, 0.59–0.86). Combination therapy was also found to reduce variceal rebleeding and variceal recurrence. Reduction in mortality from combination therapy was not different from that of endoscopic therapy (OR = 0.79; 95% CI, 0.58–1.07) or drug therapy (OR = 0.70; 95% CI, 0.46–1.06). One criticism of this analysis is that most trials studied variceal sclerotherapy, which has largely been replaced by variceal banding as the standard of care. In addition, the 2007 AASLD practice guidelines published before this study recommended a combination of endoscopic variceal ligation and nonselective β-blockers for patients at risk of rebleeding. Regardless, this study validates current recommendations that combination therapy be employed in patients who have recovered from acute variceal hemorrhage.

7. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al; American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. ACCF/ACG/AHA 2010 expert consensus document on concomitant use of proton pump inhibitors and thienopyridines: a focused update of the 2008 ACCF/ACG/AHA expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use; a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2010;56:1051–66.

This consensus statement updates the 2008 ACCF/ACG/AHA recommendations on the use of PPIs in patients with dual antiplatelet and NSAID therapy. The task force recommends that dual antiplatelet therapy with clopidogrel and aspirin not be routinely used in patients with previous ischemic stroke because of the bleeding risk. Patients with previous GI bleeding are at highest risk of recurrent bleeding on antiplatelet therapy, and PPIs are recommended to reduce GI bleeding in these patients. Patients with several risk factors for GI bleeding (e.g., advanced age; concurrent use of anticoagulants, steroids or NSAIDs including aspirin) are at particularly high risk of rebleeding. The document also recommends against routine use of either a PPI or a histamine-2 receptor antagonist for patients at lower risk of UGIB because these patients have much less potential to benefit from prophylactic therapy. Although clinical significance is unknown, pharmacokinetic and pharmacodynamic studies suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel; therefore, concomitant use should only be considered when overall risks and benefits of cardiovascular and GI complications have been carefully evaluated. The discussion in this updated guideline focuses on the latest scientific data on the clinical implications of the combined use of PPIs and clopidogrel with an extensive expert review of the literature. This updated consensus statement, which was published because of several observational studies that suggested decreased antiplatelet effects of clopidogrel when used concomitantly with PPIs, provides guidance on antiplatelet and NSAID therapy in patients at high risk of GI complications. More importantly, the statement highlights the need to carefully assess the risk of GI complications in each individual patient and to reduce the likelihood of inappropriate use of GI prophylactic agents.

8. Chan FK, Abraham NS, Schieman JM, Laine L. First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Management of patients on non-steroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Am J Gastroenterol 2008;103:2908–18.

This clinical practice recommendation was developed to review the latest clinical evidence regarding NSAID-associated GI complications and cardiovascular risk and to promote discussion on the most appropriate use of NSAIDs. A multidisciplinary group of 19 international experts was selected, which constructed a comprehensive series of possible case scenarios to mirror common clinical cases among patients with different GI and cardiovascular risk factors. Two hundred eighty-eight clinical case scenarios were evaluated for the appropriateness of six therapeutic options: naproxen, non-naproxen NSAID, naproxen plus PPI/misoprostol, non-naproxen NSAID plus PPI/misoprostol, COX-2 inhibitor, or COX-2 inhibitor plus PPI/misoprostol. The panel selected an NSAID appropriate for the patient with low GI risk (younger than 70 years; no previous upper GI complications; no corticosteroids, antithrombotic agents, or anticoagulants). In patients with GI risk factors, concomitant therapy with PPI/misoprostol was determined to be appropriate. Either naproxen or a COX-2 inhibitor was appropriate for patients at low cardiovascular risk, but naproxen was preferred for patients with high cardiovascular risk. None of the six options was determined to be appropriate for patients with several risks of GI complications and high cardiovascular risks. The expert panel concluded that the patient's cardiovascular risk should determine the initial choice of an NSAID, whereas the severity and number of GI risk factors should determine the need for a prophylactic agent to decrease GI complications. In patients who require long-term NSAID therapy but are at high risk of GI complications, this practice recommendation is an important tool for practicing

clinicians in determining appropriate NSAID therapy strategies on the basis of GI and cardiovascular risks.

9. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W; and the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–38.

   These guidelines provide data-supported recommendations on the diagnostic, therapeutic, and preventive care of patients with varices and variceal hemorrhage. The recommendations are based on a formal review and analysis of the recently published literature, consensus among experts, and the guideline policies of AASLD and the American Gastroenterological Association. In patients with cirrhosis and without varices, nonselective β-blockers are not recommended. In patients with cirrhosis and small varices at risk of hemorrhage, nonselective β-blockers are recommended for the prevention of variceal hemorrhage. In patients with medium/large varices at high risk of bleeding, nonselective β-blockers or endoscopic variceal ligation is recommended; for those with low risk of bleeding, nonselective β-blockers are preferred, and endoscopic variceal ligation may be considered when nonselective β-blockers are contraindicated or not tolerated by the patient. Nonselective β-blockers should be adjusted to the maximal tolerated dose. Nitrates, either alone or in combination with nonselective β-antagonists, are not recommended for the prophylaxis of first variceal hemorrhage. For patients with acute esophageal hemorrhage, short-term antibiotic treatment with a fluoroquinolone should be initiated. Drug therapy, including somatostatin, octreotide, or terlipressin, should be initiated promptly and continued for 3–5 days after the diagnosis is confirmed. For patients who have recovered from an episode of esophageal hemorrhage, a combination of nonselective β-blockers and endoscopic variceal band ligation are the treatment of choice for prophylaxis of variceal hemorrhage. These guidelines provide a comprehensive review of management of variceal hemorrhage for practicing clinicians and are an important resource when providing treatment to patients with variceal hemorrhage.

10. Lin PC, Chang CH, Hsu PI, Tseng PL, Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. Crit Care Med 2010;38:1197–205.

    This meta-analysis examined the efficacy and safety of PPIs compared with histamine-2 receptor antagonists for stress-related UGIB prophylaxis in critically ill patients. Included were seven randomized controlled trials that directly compared PPIs with histamine-2 receptor antagonists in 936 ICU patients at risk of stress-related UGIB. When PPIs were compared with histamine-2 receptor antagonists, the difference in the odds ratio of UGIB was −0.04 (95% CI, −0.09 to 0.01), suggesting no difference between PPIs and histamine-2 receptor antagonists. In addition, there was no difference in the risk of pneumonia and ICU mortality between the two drug classes. This meta-analysis therefore found no evidence that PPIs were superior to histamine-2 receptor antagonists in preventing stress-related UGIB and no difference in adverse events (including pneumonia and death) between the two drug classes. A possible explanation for these results is the relatively low incidence of overt or clinically significant bleeding among patients who received histamine-2 receptor antagonists. One of the main criticisms of this study is that most of the trials were of poor quality. The author therefore cautions that there may be no difference in outcomes between the PPIs and histamine-2 receptor antagonists for stress-related UGIB prophylaxis in the ICU setting. In deciding on the appropriate drug for stress ulcer prophylaxis, individual risk of GI bleeding, convenience of drug administration, potential drug interactions, and cost should be considered.

# Self-Assessment Questions

**Questions 1–4 pertain to the following case.**
B.Z. is a 72-year-old African American man who is admitted to the emergency department for a 24-hour history of vomiting coffee-ground material; black, tarry stools; confusion; and dizziness. He has a medical history of hypertension, type 2 diabetes mellitus, hypercholesterolemia, and osteoarthritis. His current drugs include lisinopril 20 mg once daily, amlodipine 10 mg once daily, glipizide 5 mg once daily, lovastatin 20 mg at bedtime, and naproxen 500 mg twice daily. Nasogastric aspiration reveals blood in the stomach. B.Z.'s vital signs include blood pressure (BP) 98/52 mm Hg and heart rate (HR) 101 beats/minute. Pertinent laboratory values include hemoglobin 7.9 g/dL, hematocrit 23.2%, platelet count 190,000/$mm^3$, serum creatinine 1.2 mg/dL, and blood urea nitrogen 19 mg/dL. The patient is sent for emergency endoscopy.

1. **Which one of the following is the best assessment of B.Z.'s risk factors for upper gastrointestinal bleeding (UGIB) secondary to nonsteroidal anti-inflammatory drug (NSAID) use?**
   A. No risk factors.
   B. One risk factor.
   C. Two risk factors.
   D. More than two risk factors.

2. **Which one of the following is the best initial medical management for B.Z.?**
   A. Administer intravenous cimetidine.
   B. Administer 0.9% sodium chloride 500 mL intravenously over 30 minutes.
   C. Administer pre-endoscopic pantoprazole.
   D. Transfuse 2 units of packed red blood cells.

3. **Based on B.Z.'s prognostic assessment, in which one of the following risk categories is he most accurately designated?**
   A. Low risk.
   B. Moderate risk.
   C. High risk.
   D. Prognostic risk assessment indeterminable.

4. **Which one of the following is the best treatment strategy for B.Z.?**
   A. Pantoprazole 80-mg intravenous bolus, followed by an 8-mg/hour continuous infusion for 72 hours.
   B. Octreotide 50-mcg bolus, followed by a 50-mcg/hour continuous infusion until bleeding stops.
   C. Esomeprazole 80-mg intravenous bolus, followed by an 8-mg/hour continuous infusion for 72 hours.
   D. Ranitidine 50-mg intravenous bolus, followed by a 6.25-mg/hour continuous infusion until bleeding stops.

**Questions 5 and 6 pertain to the following case.**
F.E. is a 47-year-old Asian man admitted to the hospital for hematemesis and tarry, black stools. He has a medical history of gastric ulcer and received *Helicobacter pylori* eradication therapy 2 years ago. Since then, he has been taking famotidine 20 mg twice daily for the prevention of recurrent ulcers. He denies taking NSAIDs or aspirin and reports no alcohol use. He smokes an average of 20 cigarettes daily. F.E. reports that he has been experiencing a stressful work environment lately because of inheriting a task to which he was unaccustomed. Endoscopy reveals an open gastric ulcer with a visible vessel.

5. **Which one of the following management strategies is most appropriate for F.E.?**
   A. Discharge home on oral pantoprazole 40 mg four times/day.
   B. Admission as an inpatient and start intravenous proton pump inhibitor (PPI) continuous infusion.
   C. Endoscopic intervention with epinephrine injection therapy followed by high-dose intravenous PPI therapy.
   D. Transfuse 2 units of packed red blood cells.

6. F.E.'s rapid urease test, histology, and bacteriology test are negative for *H. pylori* infection. **Which one of the following is best to recommend for F.E. at this time?**
   A. Twice-daily oral PPI therapy and reassess the patient's risk factors for developing ulcers and bleeding.
   B. Twice-daily oral PPI therapy and counsel on the importance of drug therapy adherence.
   C. Once-daily oral PPI therapy and counsel on smoking cessation for preventing peptic ulcer disease.
   D. Once-daily oral PPI therapy and repeat *H. pylori* testing later to confirm eradication.

7. A 36-year-old woman sustained several fractures and a closed-head injury in a motor vehicle crash. Her medical history is significant only for seasonal allergies, for which she takes daily loratadine with good symptom control. She is admitted to the intensive care unit (ICU) and stabilized on a ventilator. Surgery is performed for her many fractures. By the next morning, she has developed bacteremia requiring intravenous piperacillin/tazobactam 3.375 g every 6 hours (she has normal renal function). A nasogastric tube is placed, and tube feedings are ordered. **Which one of the following is the best recommendation for preventing stress-related mucosal damage (SRMD) in this patient?**

   A. Pantoprazole 40 mg intravenously daily.
   B. Ranitidine 50 mg intravenously twice daily.
   C. Famotidine 20 mg by nasogastric tube twice daily.
   D. Omeprazole 20 mg by nasogastric tube once daily.

8. A 72-year-old woman is admitted to the ICU after an episode of cardiac arrest with successful resuscitation. She was intubated during the code and is being mechanically ventilated. A nasogastric tube is in place, and she is being fed enterally. She is tolerating the tube feedings well without residuals per nasogastric aspirate. Her current drugs include amiodarone 200 mg twice daily, simvastatin 20 mg once daily at bedtime, and subcutaneous heparin 5000 units every 12 hours. Her medical history includes atrial fibrillation, hyperlipidemia, and erosive esophagitis. **Which one of the following is the best agent to recommend for SRMD prophylaxis in this patient?**

   A. Famotidine 20 mg intravenously every 12 hours.
   B. Esomeprazole 20 mg intravenously every 24 hours.
   C. Omeprazole suspension 20 mg once daily by nasogastric tube.
   D. Dexlansoprazole 60 mg once daily by nasogastric tube.

**Questions 9–11 pertain to the following case.**
J.R. is a 41-year-old Hispanic man with a history of alcoholic cirrhosis (Child-Pugh class C). He is admitted to the hospital with abdominal pain, nausea, hematemesis, variceal hemorrhage, and altered mental status. He has had previous episodes of hepatic encephalopathy, ascites, and portal hypertension. J.R.'s oral home drugs include propranolol 40 mg twice daily, lactulose 30 mL three times/day, furosemide 40 mg once daily, spironolactone 50 mg once daily, and rifaximin 550 mg twice daily. Laboratory values include hemoglobin 6.4 g/dL, hematocrit 18.8%, platelet count 60,000/mm$^3$, blood urea nitrogen 26 mg/dL, serum creatinine 1.6 mg/dL, albumin 2.4 g/dL, total bilirubin 1.5 mg/dL, and international normalized ratio (INR) 1.6. His vital signs include BP 105/70 mm Hg and HR 103 beats/minute.

9. **Which one of the following is the most appropriate initial management of J.R.'s UGIB?**

   A. Recombinant factor VIIa.
   B. Transfusion of packed red blood cells.
   C. 0.9% sodium chloride 1000 mL over 2 hours.
   D. 25% albumin 500 mL.

10. **Which one of the following is the most appropriate treatment of J.R. at this time?**

   A. Endoscopic sclerotherapy and terlipressin intermittent infusion.
   B. Combination of vasopressin and nitroglycerin continuous infusions.
   C. Endoscopic variceal ligation and octreotide continuous infusion.
   D. Endoscopic sclerotherapy and vasopressin continuous infusion.

11. **Which one of the following is the most appropriate approach to secondary prevention of esophageal hemorrhage for J.R.?**

   A. Transjugular intrahepatic portosystemic shunts.
   B. Intermittent endoscopic variceal ligation and propranolol 20 mg twice daily.
   C. Nadolol 40 mg once daily.
   D. Portocaval shunt.

12. A 54-year-old man who has been taking ibuprofen 200 mg three times/day for the past 2 weeks presents to the emergency department of a tertiary care university hospital with a 48-hour history of black, tarry stools. The patient denies chest pain, shortness of breath, and dizziness. His medical history is significant only for hypertension, for which he is taking metoprolol 25 mg twice daily, and chronic lower back pain. His vital signs include BP 109/78 mm Hg and HR 89 beats/minute. Laboratory values include hemoglobin 10.1 g/dL, hematocrit 29.8%, and blood urea nitrogen 15.0 mg/dL. **Which one of the following is the most appropriate initial management of this patient?**

   A. Normal saline 1000-mL bolus.
   B. Placement of nasogastric tube.
   C. Pre-endoscopic intravenous pantoprazole continuous infusion.
   D. Evaluation with prognostic scales for risk assessment with Blatchford score.

**Questions 13 and 14 pertain to the following case.**
N.P. is a 59-year-old woman admitted to the ICU with hematemesis, tachycardia, and hypotension. Her medical history includes myocardial infarction 4 years ago and osteoarthritis. She takes aspirin 81 mg once daily, metoprolol 25 mg twice daily, lisinopril 10 mg once daily, naproxen 500 mg twice daily, and atorvastatin 40 mg once daily. Endoscopy reveals a 2-cm gastric ulcer with nonbleeding visible vessel; the biopsy results are negative for *H. pylori*.

13. **Which one of the following is the best medical management of the acute bleeding in N.P. after the initial management of hemodynamic instability?**
    A. Octreotide 50-mcg bolus, followed by a 50 mcg/hour continuous infusion.
    B. Intravenous pantoprazole 80-mg bolus, followed by an 8-mg/hour continuous infusion.
    C. Subcutaneous octreotide 100-mcg injection three times/day.
    D. Intravenous pantoprazole 40 mg twice-daily intermittent infusion.

14. N.P. requires continued NSAID use for her osteoarthritis. **Which one of the following is the best recommendation for N.P.?**
    A. Both naproxen and aspirin should be discontinued until bleeding has ceased and ulcers have healed.
    B. Reinitiate aspirin as soon as possible and initiate combination therapy with a lansoprazole and a cyclooxygenase-2 (COX-2) inhibitor.
    C. Discontinue naproxen and aspirin; initiate ibuprofen and aspirin combined with a pantoprazole once ulcer has healed.
    D. As soon as possible, reinitiate aspirin in combination with omeprazole and reinitiate naproxen.

**Questions 15 and 16 pertain to the following case.**
S.T. is a 61-year-old man (height 5′5″, weight 78 kg) with end-stage liver disease caused by chronic hepatitis C infection and alcohol abuse. He is admitted to the ICU for acute hepatic encephalopathy and variceal hemorrhage, where he is initiated on oral lactulose, oral neomycin, and octreotide continuous intravenous infusion. Shortly after admission, S.T. experiences acute kidney injury and respiratory failure requiring mechanical ventilation. The etiology of respiratory failure is thought to be pneumonia. Pertinent laboratory values include hemoglobin 8.1 g/dL, hematocrit 23.8%, platelet count 52,000/mm$^3$, white blood cell count 8.0 x 10$^3$ cells/mm$^3$, serum creatinine 4.3 mg/dL, and blood urea nitrogen 32 mg/dL.

15. **Which one of the following is the most appropriate intervention for S.T. at this time?**
    A. Cefotaxime 2 g intravenously every 8 hours.
    B. Norfloxacin 400 mg orally twice daily.
    C. Pantoprazole 8-mg/hour intravenous continuous infusion.
    D. Famotidine 20 mg intravenously every 24 hours.

16. **Which one of the following is best to recommend as secondary prophylaxis for esophageal hemorrhage in S.T. once he leaves the hospital?**
    A. Propranolol 40 mg twice daily.
    B. Isosorbide mononitrate 10 mg three times/day.
    C. Nadolol 80 mg once daily.
    D. Nadolol 10 mg once daily with isosorbide mononitrate 10 mg three times/day.

**Questions 17 and 18 pertain to the following case.**
F.G., a 74-year-old man, is brought to the emergency department by his wife, who says he passed out in the bathroom, where she found him lying on the floor. On examination, F.G. admits to experiencing 1 month of increasing weakness and intermittent black, tarry stools. His medical history includes atrial fibrillation, hypercholesterolemia, osteoarthritis, constipation, and hypertension. His drugs include lisinopril 10 mg once daily, amlodipine 10 mg/day, omeprazole 20 mg/day, simvastatin 20 mg/day at bedtime, amiodarone 200 mg twice daily, ferrous sulfate 325 mg twice daily, metoprolol 50 mg twice daily, naproxen 500 mg twice daily, warfarin 2.5 mg/day, and psyllium 1 package daily. F.G. has tried up to 3 g of acetaminophen daily without adequate relief of arthritic pain. F.G. is slowly transfused with 4 units of packed red blood cells on admission. An upper endoscopy is performed, and a hemostatic procedure is completed.

17. The table below summarizes the results of three studies of PPIs.

| Studies | End Point | Relative Risk (95% CI) |
|---|---|---|
| PPI bolus followed by continuous infusion vs. histamine-2 blockers | Mortality | 0.62 (0.20–1.96) |
| | Further bleeding | 0.63 (0.37–1.08) |
| PPI bolus followed by continuous infusion vs. placebo | Mortality | 0.41 (0.20–0.84) |
| | Further bleeding | 0.40 (0.28–0.59) |
| Oral PPI or intermittent intravenous PPI vs. placebo | Mortality | 0.61 (0.18–2.04) |
| | Further bleeding | 0.53 (0.35–0.78) |

**Which one of the following statements best describes the indication for PPI therapy in F.G. based on the correct interpretation of the data?**

A. PPI bolus followed by continuous infusion significantly reduces mortality compared with histamine-2 receptor antagonists.
B. PPI bolus followed by continuous infusion significantly reduces further bleeding compared with histamine-2 receptor antagonists.
C. PPI bolus followed by continuous infusion significantly reduces further bleeding compared with placebo.
D. Oral PPI or intermittent intravenous PPI significantly reduces mortality compared with placebo.

18. **Which one of the following is best to recommend for F.G.'s outpatient drug regimen after discontinuing naproxen?**

A. Increase omeprazole to 20 mg twice daily.
B. Initiate celecoxib 200 mg once daily.
C. Initiate celecoxib 200 mg once daily with twice-daily omeprazole 20 mg.
D. Initiate morphine sulfate controlled-release 15 mg twice daily.

**Questions 19 and 20 pertain to the following case.**
C.O. is a 65-year-old Asian woman who presents to an emergency department for a 24-hour history of black, tarry stools; confusion; dizziness; and hematemesis. She has a medical history of rheumatoid osteoarthritis, hypertension, hyperlipidemia, and myocardial infarction. Her current drugs include ibuprofen 400 mg twice daily, carvedilol 12.5 mg twice daily, clopidogrel 75 mg/day, atorvastatin 20 mg/day, and lisinopril 10 mg/day. She has no known drug allergy and denies ever taking azithromycin. Endoscopy reveals a 2-cm antral ulcer with a visible vessel. C.O.'s vital signs include BP 95/50 mm Hg and HR 102 beats/minute. Pertinent laboratory values include hemoglobin 7.4 g/dL, hematocrit 22.8%, serum creatinine 1.4 mg/dL, and blood urea nitrogen 20 mg/dL.

19. Endoscopic intervention is successful. **Which one of the following is the best recommendation for C.O.?**

A. Omeprazole 40 mg orally twice daily.
B. Pantoprazole 80-mg intravenous bolus, followed by an 8-mg/hour infusion.
C. Esomeprazole 20 mg intravenously once daily.
D. Pantoprazole 40 mg by nasogastric tube twice daily.

20. C.O. tests positive for *H. pylori* infection. **Which one of the following regimens is most appropriate for her?**

A. Omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily.
B. Pantoprazole 40 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily.
C. Esomeprazole 40 mg twice daily, metronidazole 500 mg twice daily, and clarithromycin 500 mg twice daily.
D. Omeprazole 20 mg twice daily, bismuth subsalicylate 262.4 mg four times/day, metronidazole 250 mg four times/day, and tetracycline 500 mg four times/day.