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Pharmacologic Treatment of Upper Gastrointestinal Bleeding

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Opinion statement

The first goal of therapy is to assess hemodynamic stability in a patient presenting with evidence of upper gastrointestinal bleeding and, second, to maintain hemodynamic stability using crystalloids or packed red blood cells. The diagnosis of the cause of upper gastrointestinal bleeding should be performed using endoscopic techniques, which should be performed early. Therapy directed at treating the cause of upper gastrointestinal bleeding should be initiated at the time of endoscopy. Pharmacologic management should be based on the prevention of ulcer rebleeding and should be initiated at the time of endoscopic diagnosis. Surgery should be considered only in cases when endoscopic and pharmacologic treatments are deemed a failure.

Introduction

Upper gastrointestinal (GI) bleeding is a significant cause of morbidity and mortality in the United States despite our best efforts at preventing the occurrence of ulcerations and advanced endoscopic therapies. Peptic ulcer disease (PUD) and erosive esophagitis remain significant causes of upper GI bleeding in the noncirrhotic patient. Endoscopically directed hemostasis is available with improved techniques and now, with the advent of potent intravenously administered proton pump inhibitors (PPIs), the management of these disorders in patients with upper GI bleeding should be improved.

An identification of the group of patients at greatest risk for the development of upper GI bleeding as well as its complications is important to understand because it will lead to an appreciation of whether prophylaxis is indicated and may help dictate inpatient management of these patients. Furthermore, identifying the group of patients most at risk for the development of gastrointestinal hemorrhage is critical for avoiding high morbidity and mortality, as depicted in Table 1. Clearly, those patients who have had repetitive GI bleeding will have increased likelihood for both the risk of rebleeding from PUD as well as the probability of more severe hemorrhage. A prior hospitalization with an upper GI bleed related to PUD and the requirement of blood transfusions also places a patient into the high-risk category. Other groups of patients who are likely to develop upper GI bleeding are those patients in the perioperative period, especially those patients with burns or neurosurgical procedures. Those patients in the intensive care unit (ICU) are also likely to develop stress

ulcerations in the hospital [1]. Therefore, a careful history with an assessment of past medical history is a key factor in assessing patients at risk for GI bleeding. Infection with the organism *Helicobacter pylori* has been linked to the development of PUD. Similarly, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has led to an increased development of PUD given their overall prevalence as prescription and nonprescription medications. Interestingly, concomitant usage of NSAIDs in patients infected with *H. pylori* has a synergistic effect on the development of PUD [2]. The use of NSAIDs in the elderly population also increases the risk for the development of PUD. A small subsection of patients with PUD have been diagnosed with Zollinger-Ellison syndrome, accounting for less than 1% of patients with documented ulcer disease. Classically, these patients are described as having gastric acid hypersecretion resulting from gastrin hypersecretion from a gastrinoma tumor resulting in symptoms related to gastric hypersecretion and the potential development of postbulbar ulcer disease [3]. Gastric acid hypersecretion, in turn, places the patient at risk for the development of PUD.

At our institution, the most common causes of GI bleeding include PUD involving either the duodenum or stomach (Table 2), followed by erosive esophagitis in the noncirrhotic patient. Although the incidence of *H. pylori* infection is decreasing in our hospital population, the use of NSAIDs is increasing and now accounts for the most common cause for the development of PUD [4]. Erosive esophagitis accounts for approximately a fifth of the cases of upper GI bleeding studied at our institution. Given the high prevalence of gastroesophageal reflux disease (GERD), it is not surprising that the number of cases of erosive esophagitis has been underdiagnosed in most series. Another condition that is frequently diagnosed in approximately 10% of patients presenting with upper GI bleeding is Mallory-Weiss tears, especially in patients with coexistent nausea and vomiting. Given the increasing incidence of cirrhosis related to hepatitis C and alcohol abuse, it is expected that manifestations of this condition will increase in patients with esophageal and gastric varices, and gastritis. In elderly patients, arteriovenous malformations (AVMs) can be a significant cause of upper GI bleeding, and these lesions can occur anywhere in the GI tract. AVMs occurring in the stomach or duodenum may result in upper GI bleeding and should be considered in the differential diagnosis of upper GI bleeding, especially in the elderly population.

Upper GI bleeding may occur in either outpatients or inpatients. Bleeding occurring in hospitalized patients has an increased morbidity compared with patients presenting to the hospital with an upper GI bleed occurring as an outpatient. A history of coffee-ground emesis, melena, and hematochezia or frank hematemesis is most likely. The initial management should be focused on assessment of intravascular blood volume (Table 3). This is best accomplished by assessing blood pressure in both the supine and upright position (if the patient is hemodynamically stable). Measurement of the blood count may not accurately reflect the loss of blood volume in the acute situation because of hemoconcentration. Following the assessment of blood volume status, the next most important step is to stabilize the intravascular volume with either crystalloids (*ie*, normal saline or Ringer's solution) or packed red blood cells. The threshold for when to administer blood products should be dictated by the clinical situation. In a patient with evidence of active ongoing bleeding and hemodynamic instability, a lower threshold should be applied. Maintenance of a hematocrit

above 23% is critical in order to maintain the oxygen delivering capacity of the red blood cells. Generally, in all patients presenting with acute GI bleeding, a type and cross-match of cells should be performed notwithstanding the level of instability. The role of nasogastric lavage is in question, remembering that a negative lavage has little predictive value, whereas a positive lavage helps confirm that the source of bleeding is the upper GI tract.

Once the bleeding is confirmed and there is hemodynamic stability, the next most important aspect to management is to perform an upper endoscopic evaluation (Fig. 1). Endoscopy should be performed for both diagnosis and treatment. In the past, surgery was considered the mainstay of therapy. However, endoscopy has supplanted this modality over the past 30 years. More recently, with the use of hemostasis during endoscopy and more potent antisecretory medications such as the PPIs, the majority of cases can be controlled without the requirement of surgery. The diagnosis of upper GI bleeding is best accomplished using fiberoptic endoscopy, thereby permitting the determination of the cause of bleeding and location of bleeding; it also allows the restoration of hemostasis. Endoscopy with hemostasis can be performed using a heater probe, bicap electrocautery, injection with saline or alcohol, or a combination of both. At our medical center, we frequently inject the ulcer perimeter with a dilute epinephrine solution and subsequently apply electrocautery to the base of the ulcer to permit coaptation of the vessels feeding the ulcer. Endoscopy also permits a follow-up evaluation of the ulcer (*ie*, second-look endoscopy). However, prospective studies have not demonstrated a cost advantage for a second-look procedure except in cases with rebleeding of an ulcer [5]. For gastric ulcers in which a risk of malignancy is present, a repeat endoscopy is indicated to ensure ulcer healing. In addition to assessing the morphology of the ulcer, endoscopic outcome-based studies have permitted a risk assessment for rebleeding based on the ulcer appearance. A clean-based ulcer carries a relatively lower risk for rebleeding (*ie*, < 5%), an ulcer with an overlying clot has an intermediate risk for rebleeding, and an actively bleeding ulcer has a relatively high risk for rebleeding [6••].

Endoscopic hemostasis results in tissue edema with tamponade of the vessel that is feeding the bleeding ulcer. The development of a vessel clot occurs next, which relies on the function of both platelets and activation of the intrinsic and extrinsic coagulation cascade. Therefore, once successful hemostasis is achieved, the next most important step is to prevent clot dissolution. It has been demonstrated in vitro that the platelet plug can be stabilized best if the gastric pH is greater than 6 [6••,7,8]. In humans, this higher pH threshold cannot be achieved by the use of histamine 2 (H₂) receptor antagonists, whereas with the use of intravenously administered PPIs, this pH can be achieved. In one study, intravenous (IV) omeprazole given as an 80-mg loading dose, followed by an 8-mg/h continual infusion, showed significantly lower rates of rebleeding following endoscopic hemostasis compared with placebo, thereby confirming the in vitro pH data and supporting the use of this pharmacologic intervention after hemostasis [9••]. In another clinical trial, IV pantoprazole was studied in a group of 20 normal volunteers receiving a continuous infusion of IV pentagastrin [10]. Pantoprazole (Protonix; Wyeth Pharmaceuticals, Philadelphia, PA) at varying doses was administered as a single dose, and the results of gastric acid output were compared with those of IV saline (placebo). Pantoprazole decreased the rate of gastric acid output in a dose-dependent fashion compared with placebo. Inhibition of gastric acid output

was rapid; it occurred within 1 hour and reached 80% of maximal inhibition by 14 hours. The duration of efficacy that was observed in this study was nearly 24 hours.

The management of non-ulcer-related causes for upper GI bleeding could also be performed endoscopically, except in the case of gastritis and erosive esophagitis, in which medical (*ie*, pharmacologic) management will be more effective. Mallory-Weiss tears can either be followed expectantly if there is no active bleeding or treated with electrocautery if bleeding of a vessel is identified. Similarly, AVMs can be treated with electrocautery. With esophageal varices, the current treatment options include either injection of the varix with a sclerosing agent or banding of the varix. Studies have indicated similar outcomes for either technique [11,12]. Gastric varices are difficult to treat endoscopically, although there have been trials investigating sclerotherapy and banding.

Treatment

- Pharmacologic management of upper GI bleeding can be generally divided into two major categories: H₂ receptor antagonists and PPIs (Table 4).
- No pharmacologic agent has been approved by the US Food and Drug Administration (FDA) for the prevention of PUD rebleeding after endoscopic hemostasis.
- PPIs block the final step in the development of acid and hence, they are more efficacious in attaining higher intragastric pH than H₂ receptor antagonists.
- Recently, an IV formulation for pantoprazole (Protonix) has been approved by the FDA for the inpatient management of erosive esophagitis as well as the gastric acid hypersecretion associated with Zollinger-Ellison syndrome or similar conditions associated with gastric acid hypersecretion.
- The major disadvantage with the PPIs as a group is the lack of safety data for use of the drug during pregnancy.

Diet and lifestyle

- Abstinence from alcohol: Chronic ingestion of ethanol may cause alcohol-induced liver disease and secondary esophagogastric varices, which is an important cause of non-ulcer upper GI bleeding. Alcohol can also induce gastric mucosal injury.
- Avoidance of long-term use of acetylsalicylic acid and NSAIDs: Elderly persons taking NSAIDs with a previous bleeding ulcer disease are at high risk for rebleeding [13,14]. Cardiovascular patients on long-term low-dose aspirin have a stable risk of major upper GI bleeding [15].
- Medications for prophylaxis may protect patients from upper GI bleeding.

Pharmacologic treatment

- Aims of antisecretory therapy:

- Increasing intragastric pH < 6.
- Treatment of peptic ulcer disease.
- Control of symptoms.

Histamine 2 receptor antagonists

- Advantages:
 - Appear to be safe during pregnancy.
- Disadvantages:
 - They have no proven value in the management of upper GI bleeding [16••].
 - Lack of efficacy for increasing gastric pH above 5.

Ranitidine (Zantac; GlaxoSmithKline, Research Triangle Park, NC)

Standard dosage	900 to 1200 mg every 6 hours.
Contraindications	Hypersensitivity to H ₂ receptor antagonists.
Main drug interactions	None.
Main side effects	Lymphopenia (rare).
Special points	The drug has been shown to be safe for use during pregnancy and is available in IV form.
Cost/cost effectiveness	Approximately \$2.00 for 300 mg.

Famotidine (Pepcid; Johnson & Johnson – Merck, Fort Washington, PA)

Standard dosage	80 to 120 mg every 6 hours.
Contraindications	Hypersensitivity to H ₂ receptor antagonists.
Main drug interactions	None.
Main side effects	Lymphopenia (rare).
Special points	Available in IV form.
Cost/cost effectiveness	Approximately \$2.00 for 20 mg.

Proton pump inhibitors

Omeprazole (Prilosec; AstraZeneca LP, Wilmington, DE)

Standard dosage	40 to 80 mg every 12 hours.
Contraindications	Pregnancy and hypersensitivity to PPIs.
Main drug interactions	Increases the serum concentration of following medications: warfarin, phenytoin, carbamazepine, diazepam, nifedipine, digoxin, and cyclosporin A.
Main side effects	Headache.
Special points	Long-term safety and efficacy data are not available in the IV form available in the United States.
Cost/cost effectiveness	Approximately \$8.00 for 20 mg.

Lansoprazole (Prevacid; TAP Pharmaceuticals Inc, Lake Forest, IL)

Standard dosage	30 to 90 mg every 12 hours.
Contraindications	Pregnancy and hypersensitivity to PPIs.
Main drug interactions	Increases the clearance of theophylline, and decreases the clearance of cyclosporin A.
Main side effects	Headache.
Special points	Approved by the FDA; alternative to omeprazole; not yet approved by the FDA in the IV formulation, which is currently undergoing clinical trials.
Cost/cost effectiveness	Approximately \$8.00 for 30 mg.

Rabeprazole (Aciphex; Janssen Pharmaceutica Products, LP, Titusville, NJ)

Standard dosage	20 to 40 mg every 12 hours.
Contraindications	Pregnancy and hypersensitivity to PPIs.
Main drug interactions	Inhibits the hydrolysis of digoxin and increases serum concentration.
Main side effects	Headache.
Special points	Approved by the FDA; alternative to omeprazole; no IV formulation.
Cost/cost effectiveness	Approximately \$8.00 for 20 mg.

Pantoprazole (Protonix PO; Wyeth Pharmaceuticals, Philadelphia, PA)

Standard dosage	40 to 80 mg every 12 hours.
Contraindications	Pregnancy and hypersensitivity to PPIs.
Main drug interactions	May interfere with absorption of ketoconazole, ampicillin esters, and iron salts.
Main side effects	Headache.
Special points	Available in an IV formulation in the United States.
Cost/cost effectiveness	Approximately \$8.00 for 40 mg.

Pantoprazole IV (Protonix IV; Wyeth Pharmaceuticals, Philadelphia, PA)

Standard dosage	40 mg daily.
Contraindications	Pregnancy and hypersensitivity to PPIs.
Main drug interactions	May interfere with absorption of ketoconazole, ampicillin esters, and iron salts.
Main side effects	Headache.
Special points	Approved by the FDA for GERD and Zollinger-Ellison syndrome.
Cost/cost effectiveness	Approximately \$50.00 for 40 mg.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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Figure 1.
Algorithm for nonvariceal acute upper GI bleeding.

Table 1.

Risk for gastrointestinal bleeding

History of gastrointestinal bleeding
Perioperative period
Admission to the intensive care unit
Infection with <i>Helicobacter pylori</i>
Ingestion of acetylsalicylic acid or nonsteroidal anti-inflammatory drugs
Zollinger-Ellison syndrome
Erosive esophagitis
Anticoagulation or antiplatelet therapy

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Table 2.

Causes of gastrointestinal bleeding

Gastric or duodenal ulcer
<i>Helicobacter pylori</i>
Nonsteroidal anti-inflammatory drugs
Erosive esophagitis
Mallory-Weiss tear
Esophageal or gastric varices
Arteriovenous malformations

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Table 3.**Management of gastrointestinal bleeding**

Maintenance of hemodynamic stability
Nasogastric lavage
Endoscopy with hemostasis
Blood products, if necessary
Surgery, if necessary
Antisecretory medications

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Table 4.

Antisecretory medications approved by the US Food and Drug Administration

Histamine 2 receptor antagonists	
Ranitidine (Zantac; GlaxoSmithKline, Research Triangle Park, NC)	
Famotidine (Pepcid; Johnson & Johnson – Merck, Fort Washington, PA)	
Nizatadine (Axid; Reliant Pharmaceuticals, LLC, Liberty Corner, NJ)	
Cimetidine (Tagamet; GlaxoSmithKline, Research Triangle Park, NC)	
Proton pump inhibitors	
Omeprazole (Prilosec; AstraZeneca LP, Wilmington, DE)	
Lansoprazole (Prevacid; TAP Pharmaceuticals Inc, Lake Forest, IL)	
Pantoprazole (Protonix; Wyeth Pharmaceuticals, Philadelphia, PA)	
Rabeprazole (Aciphex; Janssen Pharmaceutica Products, LP, Titusville, NJ)	
Esomeprazole (Nexium; AstraZeneca LP, Wilmington, DE)	