



Clinical Update

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Commentary: Upper GI bleeding is one of the most important therapeutic areas in gastroenterology. Many of the cases fall under the category of an emergency situation and thus require urgent endoscopic intervention. In this review, Dr Loren Laine provides updated information about the epidemiology, the clinical presentation, and therapeutic interventions in various GI bleeding scenarios. In addition, Dr Laine provides a critical review of some of the diagnostic and therapeutic approaches that are commonly pursued despite their very low yield. Lastly, Dr Laine emphasizes, in his review, the importance of combining endoscopic and medical therapeutic interventions in patients who present with upper-GI bleeding.

– Ronnie Fass, MD, Editor

UPPER GASTROINTESTINAL BLEEDING

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EPIDEMIOLOGY

The annual incidence of hospitalizations for upper-GI bleeding (UGIB) is approximately one per thousand adults.¹ Currently, the average mortality is likely to be in the 5% to 10% range. Independent predictors of recurrent bleeding and death include the severity of the bleeding episode as manifested by tachycardia and hypotension, patient age, and comorbidities.² Patients with UGIB rarely die from exsanguination but, rather, death occurs from decompensation of other illnesses. For example, in a large observational study in the United Kingdom, mortality with UGIB in patients <60 years of age with no concurrent illnesses was 0.1%.³

PRESENTATION

UGIB, defined as bleeding from a source in the esophagus, the stomach, or the duodenum, may be overt or occult. Overt bleeding may present as hematemesis (vomiting blood or coffee-ground material), melena (black, tarry stool), or hematochezia (red or maroon blood per rectum). Occult bleeding may present as a positive fecal occult blood test (eg, guaiac testing), laboratory evidence of anemia and iron deficiency, or symptoms of anemia or blood loss (eg, fatigue, lightheadedness, syncope, dyspnea, angina). This update will focus on patients with overt evidence of UGIB.

Hematemesis confirms an upper-GI source of bleeding, assuming that the blood did not originate outside the GI tract (eg, nose, respiratory tract).

Melena is most commonly due to an upper GI source and can result from as little as 50 to 100 mL of blood.⁴ The presence of melena indicates that blood has been in the GI tract for at least 14 hours.⁵ Thus, the more proximal the bleeding lesion in the GI tract, the more likely melena will occur. However, an upper-GI source may occasionally bleed so briskly that the blood does not remain in the GI tract long enough for melena to occur. For example, instillation of a liter of blood into the upper-GI tract leads, at least initially, to hematochezia.⁴ If hematochezia is from an upper-GI site, it reflects major bleeding, with hemodynamic instability and an increased mortality.

INITIAL EVALUATION

Heart rate and blood pressure provide the most important information in the initial assessment of a patient with UGIB. Major bleeding leads to postural changes in heart rate or blood pressure, tachycardia, and, eventually hypotension. The Hb level is less useful at the time of presentation. Even with a major bleeding episode, the Hb level may be normal or only minimally decreased at the time of initial presentation because “people bleed whole blood.” As extravascular fluid enters the vascular space to restore volume, the Hb level falls, but equilibration may take up to 72 hours.⁶

Nasogastric aspirates that are grossly bloody confirm an upper-GI source, but a negative aspirate does not rule out an upper-GI source. Up to 18% of

TABLE 1. OUTCOMES WITH ONLY SUPPORTIVE THERAPY¹⁰ AND RECOMMENDED MANAGEMENT OF PATIENTS WITH BLEEDING ULCER BASED ON ENDOSCOPIC FINDINGS

Endoscopic finding	Mean rate of surgery for bleeding with only supportive therapy, %	Recommended therapy	Length of hospitalization, days*
Clean base	0.5	Oral PPI	≤ 1
Flat pigmented spot	6	Oral PPI	3
Adherent clot	10	IV PPI infusion ± endoscopic therapy	3
Nonbleeding visible vessel	34	Endoscopic therapy + IV PPI infusion	3
Active bleeding	35	Endoscopic therapy + IV PPI infusion	3

*Assuming no other medical problems, no recurrent bleeding, normal vital signs, and stable Hb level.

patients with UGIB have a nonbloody nasogastric aspirate, most commonly because of bleeding from the duodenum.⁷ Although some authors suggest that a nonbloody bile-stained aspirate rules out a duodenal source, physicians are incorrect about 50% of the time when they report bile in the aspirate.⁸

History and physical examination are not usually diagnostic of the source of UGIB, and upper endoscopy is the diagnostic test of choice. Timing of an endoscopy is controversial.⁹ The significant benefit of endoscopic therapy in high-risk patients (discussed below) suggests that early endoscopy should be beneficial in patients with high-risk clinical features. However, no randomized controlled trials have confirmed that early endoscopy improves clinical outcomes. Nevertheless, I suggest that patients with clinical evidence of major bleeding (eg, tachycardia, hypotension, orthostatic changes) undergo an endoscopy soon after resuscitation and volume stabilization. An early endoscopy decreases costs in patients with low-risk clinical features, because patients with normal vital signs, a stable Hb level, and no other medical problems who are found to have low-risk lesions (eg, clean-based ulcers, nonbleeding Mallory-Weiss tears, erosive or hemorrhagic gastropathy) at endoscopy can be discharged home.⁹

SOURCES OF UGIB

Peptic ulcer

A peptic ulcer is the most common cause of UGIB, although the incidence of bleeding ulcers has decreased over the past few decades. Peptic ulcers are responsible for up to approximately 50% of UGIB cases. The decrease in bleeding ulcers is related to the decreasing *Helicobacter pylori* prevalence and possibly the increased use of acid-suppressive medications. An increasing proportion of bleeding ulcers is caused by nonsteroid anti-inflammatory drug (NSAID) use.

In addition to the clinical predictors of outcome discussed above, the appearance of an ulcer at endoscopy provides important prognostic information and is used to guide subsequent management (Table 1). Approximately a third of patients found to have an ulcer with active bleeding or a nonbleeding visible vessel will have further bleeding that requires surgery if treated expectantly.¹⁰ These patients should receive endoscopic therapy and intravenous (IV) infusion of a proton pump inhibitor (PPI) (discussed

below). Patients with adherent clots also should receive IV infusion of a PPI, and some investigators suggest endoscopic therapy as well.^{11,12} Patients with flat pigmented spots and those with clean-based ulcers do not require endoscopic therapy or IV PPIs. Because patients with clean-based ulcers have rates of recurrent bleeding that are close to zero, they can be discharged home once vital signs are normal and the Hb level is stable. Patients with other endoscopic stigmata generally are hospitalized for 3 days after the bleeding episode (assuming no recurrence), because most recurrent bleeding occurs within 3 days.

Randomized controlled trials show that endoscopic therapy significantly improves outcomes, including further bleeding, transfusion, the need for surgery, the length of hospital stay, and costs in patients with high-risk bleeding ulcers (active bleeding, nonbleeding visible vessel, and perhaps adherent clot). Furthermore, meta-analyses indicate that mortality is also significantly decreased with endoscopic therapy.¹³ Standard forms of endoscopic therapy include thermal contact devices that use tamponade and heat to provide hemostasis (bipolar electrocoagulation or heat probe), injection therapy (in which dilute epinephrine and/or sclerosant agents are injected into the base of the bleeding ulcer), and “mechanical” treatment with clips.

Randomized controlled trials also indicate that, even after endoscopic therapy, a bolus of an IV PPI, followed by a constant infusion of PPI for 72 hours will significantly lessen recurrent bleeding (but not mortality).¹⁴ Most studies used IV omeprazole, which is not available in the United States, and the “correct” doses for the available PPIs have not been appropriately studied. Nevertheless, the doses commonly used are a 80-mg bolus and a 8 mg/h infusion for pantoprazole and esomeprazole and a 90-mg bolus and a 6 to 9 mg/h infusion for lansoprazole. The hypothesis behind the use of high-dose constant infusion PPI therapy is based on older experimental studies that suggest that maintaining intragastric pH >6 will enhance clot formation and clot stability.¹⁵ Studies from Kashmir and Iran report significantly less recurrent bleeding with intermittent high-dose oral PPI therapy (omeprazole 40 mg twice a day or 20 mg 4 times a day).^{16,17} However, because PPI therapy also may have greater antisecretory potency in Asian populations, we would not recommend the use of intermittent PPI therapy in place of constant infusion IV therapy unless randomized controlled trials in a Western population document efficacy with intermittent therapy.

Prevention of recurrent ulcer bleeding in the long term should focus on the 3 main factors that cause ulcers: *H pylori*, NSAIDs, and acid. Eradication of *H pylori* in patients with bleeding ulcers decreases the rate of recurrent bleeding to <5%. If a bleeding ulcer develops in a patient taking NSAIDs, the NSAIDs should be discontinued if possible. If NSAIDs are required, the most appropriate strategy to prevent recurrent bleeding ulcers is a cyclooxygenase-2 (COX-2) selective inhibitor plus a PPI. The annual incidence of recurrent ulcer bleeding with either a COX-2 selective inhibitor or a PPI plus traditional NSAID alone is approximately 10%, whereas the use of the combination significantly reduces risk.¹⁸ Patients with bleeding ulcers unrelated to *H pylori* or NSAIDs should remain on full-dose antisecretory therapy indefinitely.

Mallory-Weiss tears

Mallory-Weiss tears are diagnosed in approximately 5% to 15% of patients with UGIB. Mallory Weiss tears occur at the gastroesophageal junction, primarily on the gastric side. Vomiting, retching, or coughing is classically reported before hematemesis, especially in a patient who is alcoholic. Bleeding stops spontaneously in most patients and rarely recurs (0% to 7%). Endoscopic therapy is indicated only if the Mallory-Weiss tear is seen to be actively bleeding at endoscopy.

Esophageal varices and portal hypertension

Esophageal varices account for approximately 5% to 30% of cases of UGIB, and the proportion varies widely, depending on the population served. Patients with variceal hemorrhage have higher rates of recurrent bleeding and death than patients with the other common sources of UGIB. Endoscopic therapy has been documented to significantly reduce further bleeding and mortality in randomized controlled trials. Endoscopic therapy is used in the acute setting, when patients present with bleeding and is also repeated at regular intervals (eg, 1 to 2 weeks) to eradicate varices. Once varices are eradicated, patients return periodically (eg, 3- to 12-month intervals) to identify and treat recurrent varices. "Rubber-band" ligation has supplanted sclerotherapy for endoscopic treatment of esophageal varices, because it has less recurrent bleeding, has a lower mortality rate, has fewer local complications, and requires fewer treatment sessions to eradicate varices.¹⁹

Octreotide (50 µg bolus and 50 µg/h IV infusion for 2 to 5 days) improves the control of acute bleeding when used in combination with endoscopic therapy.²⁰ Antibiotic therapy (eg, quinolones) is also recommended for patients with cirrhosis with UGIB, because randomized controlled trials demonstrate a significant decrease in bacterial infections and mortality.²⁰ Long-term treatment with nonselective beta blockers is also recommended, in combination with endoscopic ligation therapy, to decrease recurrent bleeding from esophageal varices.²⁰

Patients with persistent or recurrent bleeding despite endoscopic and medical therapy require more invasive therapy. Transjugular intrahepatic portosystemic shunt (TIPS) decreases recurrent bleeding more effectively than endoscopic therapy, although hepatic encephalopathy is more common and the mortality rates are comparable. Most patients with TIPS have shunt stenosis within 1 to 2 years and require reintervention to maintain shunt patency, although the use of coated stents appears to markedly decrease shunt dysfunction, at least in the first year. A randomized comparison of TIPS and distal splenorenal shunt in Child-Pugh class A or B cirrhosis with

refractory variceal bleeding revealed no significant difference in recurrent bleeding, encephalopathy, or survival but a much higher rate of reintervention with TIPS (82% vs 11%).²¹ Thus, patients with milder, well-compensated cirrhosis should require fewer reinterventions with decompressive surgery, although the higher risks of surgery at the time of the initial procedure must also be considered.

Patients with portal hypertension also may develop bleeding from gastric varices, although this is less common than bleeding from esophageal varices. Unfortunately, standard endoscopic therapy with ligation is relatively ineffective at preventing further bleeding. Endoscopic therapy with tissue adhesives is more effective, but this therapy is not approved for variceal treatment in the United States and is rarely used here. Therefore, in the United States, patients with bleeding gastric varices typically are treated with TIPS. The possibility of splenic vein thrombosis (most commonly from pancreatic disease) should always be considered in patients with gastric varices but no esophageal varices. If present, this can be cured with splenectomy. Portal hypertensive gastropathy is commonly identified at endoscopy in patients with cirrhosis but rarely causes major overt UGIB.

Hemorrhagic and erosive gastropathy

Hemorrhagic and erosive gastropathy, often incorrectly labeled as "gastritis," refers to subepithelial hemorrhages and erosions. These lesions are restricted to the mucosa, where no large blood vessels are present and, therefore, do not cause major bleeding.

The most common causes are NSAID use, alcohol intake, and stress. Half of patients regularly taking traditional NSAIDs develop erosions, and up to 20% of patients who are alcoholic and are actively drinking and with symptoms of UGIB have subepithelial hemorrhages or erosions. The discontinuation of the offending agents and the use of antisecretory therapy are recommended in patients with bleeding.

Stress-related injury occurs in extremely sick patients: eg, major trauma, extensive burns, major intracranial disease, and severe medical illness (ie, ventilator dependence, coagulopathy). Major bleeding from stress injury probably requires progression of an erosion to an ulcer. Preventive therapy should only be used in high-risk patients (eg, mechanical ventilation). Strong evidence supports the use of IV H₂-receptor antagonist therapy. This therapy is more effective than sucralfate but not superior to a PPI immediate-release suspension via nasogastric tube.^{22,23}

Other causes of UGIB

A great number of other lesions also may cause UGIB. These include erosive esophagitis, neoplasms, vascular lesions (eg, hereditary hemorrhagic telangiectasias [Osler-Weber-Rendu syndrom], gastric antral vascular ectasia ["watermelon stomach"], Dieulafoy's lesion [in which an aberrant vessel in the mucosa bleeds from a pinpoint mucosal defect]), prolapse gastropathy (prolapse of the proximal stomach into the esophagus, with retching, especially in patients with alcoholism), erosive duodenitis, aortoenteric fistulas, and hemobilia and hemosuccus pancreaticus (bleeding into the duodenum from the bile duct or pancreatic duct).

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