Upper Gastrointestinal Bleeding: Etiologies and Management

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Learning Objectives: On completion of this article, you should be able to (1) state common and uncommon etiologies of upper gastrointestinal bleeding, (2) organize patients with upper gastrointestinal bleeding into low-risk and high-risk categories, and (3) recall the management of patients with upper gastrointestinal bleeding.

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Abstract

Upper gastrointestinal bleeding is a medical condition routinely encountered in clinical practice. Overt upper gastrointestinal bleeding usually presents as melena or hematemesis but can also present as hematochezia in cases of brisk bleeding. The initial evaluation of a patient with suspected upper gastrointestinal bleeding begins with assessment of hemodynamic status, identification of potential risk factors, and appropriate triage of level of care. After resuscitation measures, endoscopic evaluation can be performed to diagnose and potentially treat the source of bleeding. Risk factors that increase the propensity for recurrent bleeding should be identified and addressed.

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Upper gastrointestinal bleeding (UGIB) is a common medical condition with various etiologies and presentations. It is defined as blood loss originating proximal to the ligament of Treitz, in the esophagus, stomach, or duodenum. The most common manifestation of UGIB is melena or hematemesis. However, UGIB should also be suspected in hemodynamically unstable patients who present with hematochezia. The severity of UGIB is defined by the patient's hemodynamic status and packed red

blood cell transfusion requirements. Although patients who remain hemodynamically stable may be managed appropriately in the outpatient setting, severe UGIB requires close monitoring in the intensive care unit with early upper endoscopy. This review discusses the various etiologies of UGIB and provides a stepwise approach to its management.

EPIDEMIOLOGY

In the United States, there are approximately 350,000 hospital admissions for UGIB annually.[1] The incidence of hospitalizations generally increases with age and is more common in men than in women.[2] The 3 most common causes of UGIB are peptic ulcer disease (PUD), esophagogastric varices, and erosive esophagitis. The patient history and physical examination can often provide clues as to the specific etiology of the bleed.

DIFFERENTIAL DIAGNOSIS

Common and uncommon etiologies of UGIB are presented in Table 1.

Peptic Ulcer Disease

The most common cause of UGIB is PUD. Ulceration results when mucosal defense mechanisms in the upper gastrointestinal tract are overwhelmed by endogenous (acid, pepsin, bile) or exogenous factors. The 2 most common causes of PUD are nonsteroidal anti-inflammatory drug (NSAID) use and *Helicobacter pylori* infection, both of which may present with gastric or duodenal ulceration. Duodenal ulceration is more common in patients with antral-predominant *H pylori* gastritis, where destruction of somatostatin-producing D cells leads to increased gastrin and acid load to the duodenum. Other, less common causes of PUD include physiologic stress, acid hypersecretion (ie, gastrinoma), and malignancy. Stress-induced ulceration is most likely to be seen in severely ill patients in the intensive care unit, with long-term mechanical ventilation and coagulopathy as the predominant risk factors.[3]

Patients with PUD may complain of gnawing epigastric pain. Classically, patients with gastric ulcers have pain that worsens with food consumption, and those with duodenal ulcers report decreased pain with food intake. Peptic ulcers can also present without pain regardless of the underlying etiology.

TABLE 1. Etiologies of Upper Gastrointestinal Bleeding

Esophagus	Esophageal varices Erosive esophagitis Infectious esophagitis Pill-induced esophagitis Esophageal malignancy Mallory-Weiss tear Black esophagus (ischemia)
Stomach	Peptic ulcer Gastric varices Gastric malignancy Portal hypertensive gastropathy Gastric antral vascular ectasia Dieulafoy lesion
Small bowel (proximal to ligament of Treitz)	Duodenal ulcer Duodenal malignancy
Miscellaneous	Hemobilia Hemosuccus pancreaticus Aortoenteric fistula Iatrogenic

Esophagogastric Varices

Esophagogastric variceal bleeding is the second most common cause of UGIB and should always be considered in patients with a history of cirrhosis with portal hypertension. Approximately half the patients with cirrhosis have gastroesophageal varices as a consequence of an elevated hepatic venous pressure gradient (>10-12 mm Hg).[4] However, it is important to consider that approximately 60% of UGIB cases in patients with cirrhosis are unrelated to portal hypertension.[5] The severity of the underlying cirrhosis (Child-Pugh score) is directly related to the probability that the patient will have varices. Patients with variceal bleeding may present with melena, hematemesis, or hematochezia, depending on the severity of the bleed. The physical examination should focus on identifying stigmata of chronic liver disease suggestive of portal hypertension (ie, ascites, caput medusae, spider angiomata).

Esophagitis

Esophagitis accounts for approximately 10% of UGIB cases. Severe gastroesophageal reflux

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disease and alcohol abuse are the 2 most common risk factors for erosive esophagitis complicated by bleeding. Other causes of esophagitis associated with bleeding include pill esophagitis and infectious esophagitis.[6] Although rare, ischemia may lead to esophageal necrosis (black esophagus) and should be suspected in a patient with a history of hemodynamic instability preceding UGIB. In patients with UGIB secondary to esophagitis, hematemesis is more common than melena.[7] The presence of associated odynophagia and dysphagia will depend on the chronicity and severity of the underlying condition.

Other Causes

There is a wide array of other causes of UGIB that are less common than the etiologies discussed previously herein, many of which include vascular etiologies. Arteriovenous malformations are often found on routine endoscopy and are typically innocuous. However, larger arteriovenous malformations can result in clinically significant UGIB.[8] Nonvariceal causes of UGIB in patients with underlying liver disease include gastric antral vascular ectasias, a relatively uncommon pathology that causes red streaking and bleeding extending from the pylorus to the antrum, and portal hypertensive gastropathy, in patients with concomitant portal hypertension. Dieulafoy lesions typically occur in the stomach and represent a submucosal artery that erodes and provokes intermittent and potentially life-threatening bleeding. Mallory-Weiss tears are longitudinal lacerations of the distal esophageal/proximal gastric mucosa that typically present as hematemesis after excessive retching. Esophageal, gastric, and duodenal malignancies can also lead to UGIB, although these are a relatively uncommon cause of an acute bleed.

Aortoenteric fistulas are a rare, yet lethal cause of UGIB. Aortoenteric fistulas can occur as a late complication of abdominal aortic surgery or vascular reconstruction,[9,10] with the duodenum as the most common site of involvement.[10] The classic presentation involves a "herald bleed" usually manifesting as an episode of hematemesis or hematochezia, followed by a grace period of several days, with subsequent massive bleeding and cardiovascular collapse.[9] Other symptoms can include abdominal or back pain, fever, and sepsis.[10]

INITIAL EVALUATION AND RISK STRATIFICATION

The initial evaluation of a patient with suspected UGIB begins with a thorough history and physical examination. The chronicity, onset, description, and intensity of symptoms should be elicited because these may help clinicians understand the severity of the bleed. In particular, patients should be asked about previous episodes of UGIB because a similar lesion may be involved. The history should include a comprehensive review of patient medications, a medical history, and a social history focused on alcohol, tobacco, and substance use. All patients should be asked about intake of NSAIDs, anticoagulants, antiplatelet agents, and selective serotonin reuptake inhibitors because these medications increase the risk of bleeding. The goal of the patient history is to identify risk factors that may point to an underlying etiology of the UGIB. For example, a patient with daily NSAID use for osteoarthritis presenting with UGIB may have PUD, whereas a patient with alcohol abuse and cirrhosis may have esophageal varices.

The physical examination should begin with an assessment of patient appearance and vital signs. Resting tachycardia is often the first sign of hypovolemia. Additional signs of blood loss include hypotension (orthostatic then supine), tachypnea, decreased urine output, and central nervous system symptoms (confusion and lethargy).[11] A complete abdominal and rectal examination should be performed with assessment of bowel sounds, tenderness with palpation, peritoneal signs, and presence or absence of melena or bright red blood in the rectal vault. Severe UGIB is defined by evidence of hemodynamic compromise requiring aggressive volume resuscitation along with a decrease in hemoglobin level of at least 2 g/dL (to convert to g/L, multiply by 10) from baseline or a hemoglobin level less than 8 g/dL, often requiring packed red blood cell transfusion.[12]

All patients should undergo a complete blood cell count, electrolyte panel, liver function

tests, and coagulation studies. Other laboratory studies should be obtained as guided by patient history and physical examination findings. The hemoglobin level may initially be falsely normal and represent the baseline value because it takes several hours to reflect blood loss. Therefore, the hemoglobin value at presentation should not be used as the sole predictor of bleeding severity because it can be initially normal even in cases of severe bleeding. Serial hemoglobin levels should be obtained while the patient is being monitored. Acute UGIB typically presents as normocytic anemia, whereas chronic UGIB is usually microcytic. Evidence of thrombocytopenia or coagulopathy (in the absence of oral anticoagulants) should alert the provider to the possibility of cirrhosis and portal hypertension.

Factors that increase the likelihood of UGIB include a patient history of melena (likelihood ratio [LR], 5.1-5.9), melena on examination (LR, 25), nasogastric lavage with blood or coffee ground contents (LR, 9.6), and a ratio of blood urea nitrogen to creatinine greater than 30 (LR, 7.5).[12]

Patients presenting with UGIB should be stratified based on all factors in their clinical presentation. Patients considered high risk are those who present with hemodynamic instability oftentimes in the setting of profound anemia requiring aggressive supportive care and monitoring in the intensive care unit. Several published scoring systems (ie, Glasgow-Blatchford) may help guide risk stratification but are not meant to replace the clinical evaluation. The vital signs of patients presenting with UGIB should be monitored closely for signs of hemodynamic instability, including evidence of tachycardia and orthostatic hypotension.

PRE-ENDOSCOPY MANAGEMENT

Hospitalized patients with UGIB should have 2 large-caliber peripheral intravenous (IV) catheters in place. Endotracheal intubation should be considered for patients at high risk for aspiration, such as those with ongoing hematemesis or altered mental status. Early correction of hemodynamics, hematocrit level, and coagulopathy with aggressive fluid resuscitation should be performed because this substantially decreases mortality.[13] Blood transfusion should be considered for most patients when the hemoglobin level is less than 7 g/dL, although a higher transfusion threshold may be necessary for patients with unstable coronary artery disease or active, ongoing bleeding.[14] Platelet transfusion should be administered to patients with active bleeding and a platelet count less than $50{,}000\times10^3/\mu L$ (to convert to $\times10^9$/L, multiply by 1). In cases in which urgent endoscopy is warranted, endotherapy can be performed safely with an international normalized ratio less than 2.5.[15] The decision to stop or reverse anticoagulation should weigh the risks of thromboembolism against ongoing bleeding. In patients with life-threatening UGIB taking warfarin, warfarin should be held and 4-factor prothrombin complex should be administered.

Patients with severe UGIB should be initiated on high-dose IV proton pump inhibitor (PPI) therapy on presentation because this reduces the need for endoscopic intervention at the time of endoscopy. Intermittent PPI twice daily can be used and is comparable with a bolus plus continuous-infusion PPI regimen.[16] Although prokinetic agents such as erythromycin do not improve clinical outcomes, they may be administered 30 minutes before endoscopy to improve endoscopic visualization and decrease the need for repeated endoscopy.[17] Octreotide should be administered to patients with acute variceal bleeding because it improves the efficacy of endoscopic therapy in achieving initial and 5-day hemostasis, although it does not affect mortality.[18] Administration of antibiotic drugs (ie, ceftriaxone) to patients with cirrhosis presenting with acute UGIB regardless of the underlying etiology is associated with improved survival and decreased rebleeding.[19] The use of NSAIDs should be discontinued. Antiplatelet agents and anticoagulants should be held in patients with severe UGIB if safe based on the indication for the medication. For example, antiplatelet agents would likely be continued in patients with recent (<3 months) coronary ischemia or drug-eluting coronary stent placement.

Patients with suspected aortoenteric fistulas should undergo urgent computed tomography of the abdomen with IV contrast,

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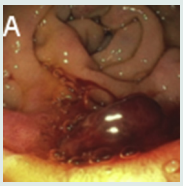
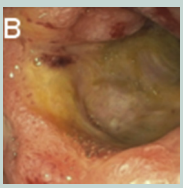
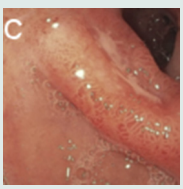
TABLE 2. Forrest Classification for Describing Endoscopic Findings in Patients With Bleeding Ulcers and Predicting Risk of Rebleeding[a]

Endoscopy				After endoscopy		
Forrest classification			Therapy	Rebleeding (%)	PPI	Diet
	I	Active bleeding				
	Ia	Spurting bleed	Yes	55	IV[b]	Clear liquid[c]
	Ib	Oozing bleed				
	II	Stigmata of bleeding				
	IIa	Visible vessel	Yes	43	IV	Clear liquid
	IIb	Adherent clot	Yes/No	22	IV	Clear liquid
	IIc	Flat pigmented spot	No	10	Oral	Regular diet
	III	Clean ulcer base	No	5	Oral	Regular diet

[a]IV = intravenous; PPI = proton pump inhibitor.
[b]Intravenous PPI therapy twice daily should be continued for 72 hours after endoscopic management before transitioning to oral PPI once daily.
[c]Clear liquid diet should be started immediately after the endoscopic procedure and then advanced as tolerated.

given its widespread availability and efficiency.[20] The sensitivity and specificity of computed tomography for diagnosis of aortoenteric fistulas are variable and range from 40% to 90% and from 33% to 100%, respectively.[20] An upper endoscopy may still be performed in these patients as a diagnostic procedure to exclude other sources of bleeding.

ENDOSCOPIC INTERVENTION

Patients with UGIB should undergo an esophagoduodenoscopy because this can be diagnostic and therapeutic. For most patients, an esophagoduodenoscopy should be performed within 24 hours of hospital admission, after they have received appropriate resuscitation as outlined previously herein.[17] However, urgent endoscopy, ideally within 12 hours, should be performed in patients with high-risk clinical features.[17] Moreover, endoscopy within 12 hours is the standard of care for patients with suspected variceal bleeding.

The Forrest classification can be used to describe endoscopic findings in patients with PUD (Table 2).[21] A clean-based ulcer is associated with a 5% risk of rebleeding, whereas ulcers with stigmata of recent bleeding are associated with a 10% to 43% risk. An active bleeding ulcer has the highest risk of rebleeding, estimated to be 55%.[17] Consequently, endoscopic therapy is offered to patients who present with an active bleeding ulcer and those with strong stigmata of recent bleeding.[17] No endoscopic therapy is usually required in patients with an ulcer that contains a flat pigmented spot or a clean-based ulcer.[17]

Endoscopic therapy of an ulcer with high-risk stigmata of bleeding usually involves epinephrine injection to promote vasoconstriction and pressure tamponade combined

with either bipolar electrocoagulation or hemoclip placement. Argon plasma coagulation is a noncontact ablative therapy that may be used for superficial vascular lesions.[22]

POST-ENDOSCOPY MANAGEMENT

After endoscopic evaluation, patients may be considered to have a low risk of rebleeding if they have stable vital signs, a normal hemoglobin level, no comorbidities, and an endoscopic lesion that is not at high risk for rebleeding. Intravenous PPI therapy twice daily should be continued for 72 hours after endoscopic management of patients who have an ulcer with active bleeding or high-risk stigmata of recent bleeding.[17] These patients should be started on a clear liquid diet after the procedure, and their diet should be advanced as tolerated. In contrast, patients who have ulcers with a low risk of rebleeding can be transitioned to oral PPI once daily and initiated on a regular diet.[17] Repeated outpatient endoscopy is not routinely performed but may be indicated in cases of idiopathic gastric ulcers to rule out malignancy and in cases of severe esophagitis to confirm healing and exclude Barrett esophagus.[17] Idiopathic duodenal ulcers do not routinely require repeated endoscopy to ensure healing. For patients with refractory bleeding despite a second therapeutic endoscopy, surgery or interventional radiology embolization may be required.[17]

In patients with PUD secondary to *H pylori* infection, *H pylori* should be treated and eradication should be confirmed using a urea breath test or stool antigen test.[23] Eradication confirmation testing should be performed at least 4 weeks after the completion of antibiotic drug therapy, and patients should be off acid suppression therapy to minimize the risk of false-negative results. In patients with NSAID-associated ulcers, NSAIDs should be discontinued if possible or, if necessary, switched to a cyclooxygenase-2 selective inhibitor, in addition to daily PPI therapy.[17] In patients with aspirin-associated ulcers, aspirin should be discontinued if used for primary prevention but resumed within 3 to 7 days in conjunction with daily PPI if used for secondary prevention.[17] Last, in patients with idiopathic ulcers, daily PPI therapy should be continued indefinitely because the risk of recurrent ulcer bleeding and mortality in these patients is higher compared with that of patients with ulcers with an identifiable cause.[17,24]

CONCLUSION

Upper gastrointestinal bleeding should be suspected in patients presenting with melena or hematemesis and in hemodynamically unstable patients presenting with hematochezia. The most common causes of UGIB include PUD, esophagogastric varices, and esophagitis. The patient's clinical presentation, including hemodynamic status and transfusion requirements, is used to determine level of care and timing of endoscopy. After resuscitation measures, endoscopic evaluation can be performed to diagnose and potentially treat the source of bleeding. Risk factors that increase propensity for recurrent bleeding should be identified and addressed.

Abbreviations and Acronyms: **IV** = intravenous; **LR** = likelihood ratio; **NSAID** = nonsteroidal anti-inflammatory drug; **PPI** = proton pump inhibitor; **PUD** = peptic ulcer disease; **UGIB** = upper gastrointestinal bleeding

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