Because of late symptom development, 5-year survival for patients with cholangiocarcinoma (except liver transplant recipients), including those who undergo resection, is low (20% to 30%).

KEY POINTS

- Resection is first-line treatment for cholangiocarcinoma.
- Selected patients with unresectable perihilar cholangiocarcinoma smaller than 3 cm and without extrahepatic spread may be candidates for liver transplantation.

Gastrointestinal Bleeding

Overview

In the United States, gastrointestinal bleeding is a common gastrointestinal cause of hospitalization. Upper gastrointestinal bleeding (UGIB) is defined as bleeding from the esophagus, stomach, or duodenum. The mortality rate for patients with UGIB varies from 2% to 10%, with much of the mortality occurring in patients with significant comorbid medical conditions. Lower gastrointestinal bleeding (LGIB) occurs in the colon or anorectum. It is less common, is typically less severe, and has a lower mortality rate than UGIB. Suspected small-bowel bleeding, in which bleeding does not appear to originate from the upper or lower gastrointestinal tract following upper and lower endoscopy, accounts for less than 10% of gastrointestinal bleeding. In 25% of these patients, however, the upper or lower gastrointestinal source of bleeding was missed on initial endoscopy.

KEY POINT

- Upper gastrointestinal bleeding is more common, is more severe, and has a higher mortality rate than lower gastrointestinal bleeding.

Upper Gastrointestinal Bleeding

UGIB can present in various ways: hematemesis (vomiting of bright red blood or clots), coffee-ground emesis (vomiting of dark granular material resulting from the action of gastric acid on blood), melena (black, tarry stool with a distinctive odor), and hematochezia (passage of red blood or clots from the rectum).

Causes

Common causes of UGIB include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear. Peptic ulcer disease is the most common cause (50%), with most gastroduodenal ulcers caused by *Helicobacter pylori* or NSAID use. Erosive esophagitis is a common endoscopic finding but infrequently causes clinically important UGIB. Therefore, in a patient with significant UGIB and erosive esophagitis, alternative causes for the bleeding should be sought.

Bleeding gastroesophageal varices typically occur in the distal esophagus or proximal stomach in individuals with advanced liver disease. Bleeding risk of varices is proportional to varix size.

A Mallory-Weiss tear is a mucosal disruption at the gastroesophageal junction and typically forms after repeated episodes of severe vomiting or retching.

Less common causes of UGIB are listed in **Table 41**.

TABLE 41. Less Common Causes of Upper Gastrointestinal Bleeding

Lesion	Pathogenesis	Presentation	Treatment
Cameron erosion	Mechanical trauma to mucosal folds of hiatal hernia	Typically chronic GI bleeding presenting as iron deficiency anemia	Includes medical therapy with PPI and iron; surgical repair of hiatal hernia
Dieulafoy lesion	Dilated, aberrant submucosal vessel	Included in differential diagnosis of recurrent, often massive bleeding without clear source	Endoscopic
Gastric antral vascular ectasia	Most idiopathic; some associated with cirrhosis and systemic sclerosis	Acute bleeding or iron deficiency anemia	Endoscopic
Aortoenteric fistula	Direct communication between aorta and GI tract	"Herald" bleeding followed by massive exsanguination	Surgical
Hemosuccus pancreaticus	Erosion of pancreatic pseudocyst or tumor into a vessel with bleeding into pancreatic duct	Upper GI bleeding in setting of pancreatic disease	Mesenteric angiography with coil embolization
Hemobilia	Bleeding from the hepatobiliary tract often caused by arteriobiliary fistula from trauma or liver biopsy	Triad of jaundice, biliary colic, and GI bleeding	Angiography or surgical
Upper GI tumors	Benign or malignant neoplasms	Slow or massive hemorrhage	Palliative radiographic, endoscopic techniques, surgery
Portal hypertensive gastropathy	Portal hypertension	Usually slow/chronic blood loss; occasionally significant hemorrhage	Medical therapy (β-blocker, octreotide); rarely transjugular intrahepatic portosystemic shunting

GI = gastrointestinal; PPI = proton pump inhibitor.

Evaluation

The initial step in evaluation is risk assessment to determine severity. This assessment includes measuring vital signs and reviewing patient factors. Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are associated with increased risk for rebleeding and death. Several clinical scores (e.g., the Glasgow-Blatchford and Rockall scores) are available to help predict risk for recurrent bleeding and mortality.

Findings of stigmata of chronic liver disease suggest a possible variceal source of bleeding.

Management

Hemodynamic status should be assessed in all patients, and resuscitative measures must be initiated with the goal of hemodynamic stabilization before endoscopy. Adequate intravenous access, usually with two large-bore peripheral intravenous catheters (minimum 18-gauge), should be established. Hemoglobin levels should be measured in all patients. A restrictive transfusion strategy is recommended and initiated when the hemoglobin level is below 7 g/dL (70 g/L) in hemodynamically stable patients without preexisting cardiovascular disease. Patients with hypotension due to severe, ongoing UGIB and those with concomitant cardiovascular disease should be considered for transfusion before the hemoglobin level decreases below 7 g/dL (70 g/L) to prevent the decreases below 7 g/dL (70 g/L) that may occur with fluid resuscitation alone. Care should be taken in patients with variceal hemorrhage because overtransfusion can precipitate variceal rebleeding due to increased portal pressure. Patients with altered mental status, massive hematemesis, or increased risk for aspiration should be considered for endotracheal intubation.

Pre-Endoscopic Care

Intravenous erythromycin given before endoscopy improves gastric visualization and decreases the need for repeat endoscopy, but it should be administered only when requested by the endoscopist. Nasogastric tube lavage is not required because there is no evidence of clinical benefit.

Intravenous proton pump inhibitor (PPI) therapy initiated before endoscopy decreases high-risk endoscopic stigmata in peptic ulcer disease and may reduce the need for endoscopic therapy (**Figure 39** and **Figure 40**), but it does not influence outcomes, such as rebleeding or death.

Octreotide, a somatostatin analogue that decreases splanchnic blood flow and lowers portal pressure, should be initiated if variceal hemorrhage is suspected. Initiation of antibiotics, such as ceftriaxone or quinolone, at the time of hospitalization for gastrointestinal bleeding is recommended for all patients with cirrhosis. Nearly 50% of patients with cirrhosis who are hospitalized with UGIB have a bacterial infection, such as pneumonia and urinary tract infection, and antibiotics reduce the rates of rebleeding and death. Balloon tamponade may be necessary as a temporizing measure for management of variceal bleeding until more definitive interventions are available.

In patients receiving warfarin with significant hemorrhage, warfarin should be discontinued and anticoagulation reversed with prothrombin complex concentrate with vitamin K. Endoscopy, however, should not be delayed for anticoagulation reversal. In patients receiving direct oral anticoagulants, the anticoagulant should be discontinued on presentation,

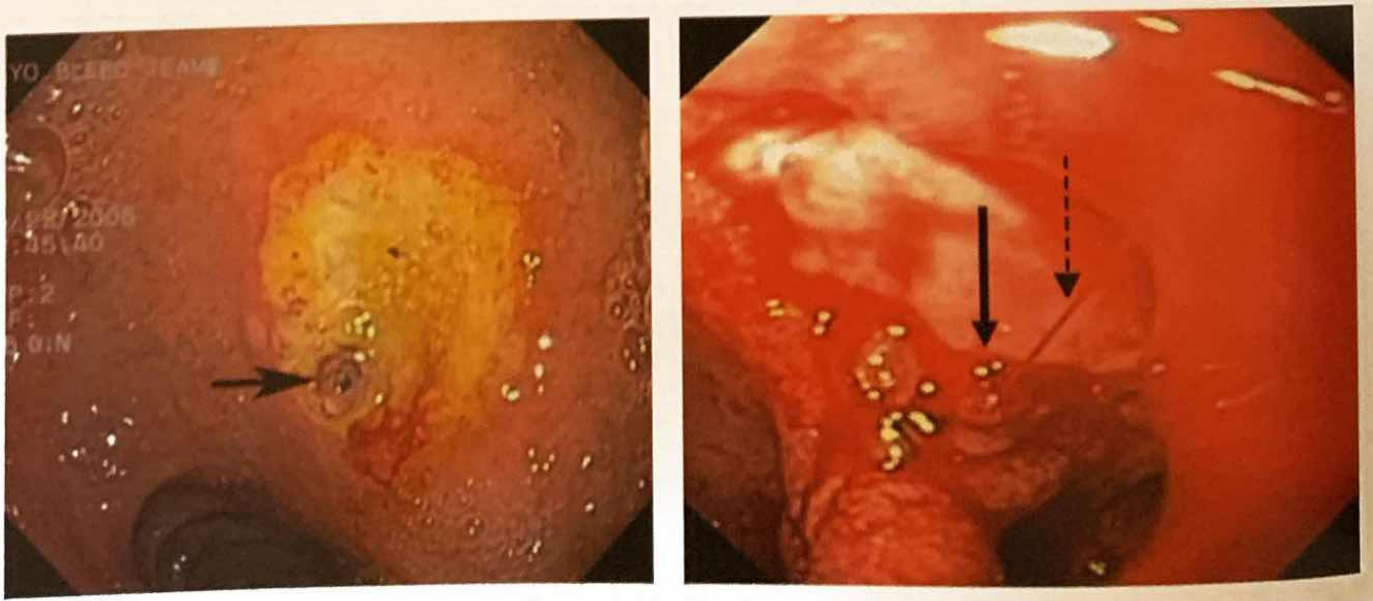

FIGURE 39. Duodenal ulcers. *Left:* Duodenal ulcer with nonbleeding visible vessel (*arrow*) that is at high risk for rebleeding and must be treated endoscopically. *Right:* Duodenal ulcer (*solid arrow*) with active arterial spurting (*dotted arrow*). This lesion is at the highest risk for rebleeding and must be treated endoscopically.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

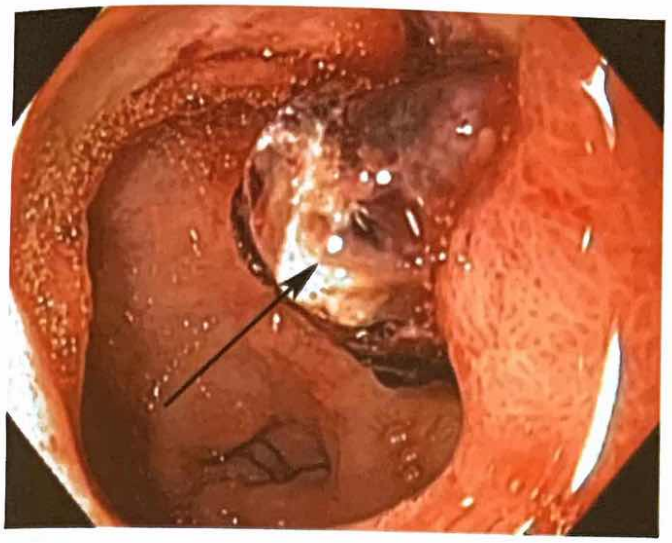

FIGURE 40. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding. This can be treated medically or by clot removal and endoscopic therapy in addition to standard medical therapy.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

and, if significant hemorrhage is present, reversal with activated prothrombin complex concentrate or the appropriate agent (idarucizumab or andexanet alfa) should be considered. See MKSAP 19 Hematology for further information on reversal of anticoagulants.

In patients with active bleeding who have platelet counts less than 50,000/μL, platelets should be transfused. Aspirin for primary prevention of cardiovascular disease should be discontinued and not restarted because the risk for recurrent bleeding outweighs the benefit. Aspirin for secondary prevention in patients with high-risk cardiovascular disease should be discontinued only if necessary. Decisions about discontinuing dual antiplatelet therapy with a P2Y12 receptor antagonist and aspirin in patients with a recent acute coronary syndrome or coronary stent placement should be made with a cardiologist. In patients with significant hemorrhage in whom the P2Y12 receptor antagonist must be discontinued, aspirin should be continued.

Patients with hemodynamic instability, active bleeding (hematemesis or recurrent large-volume hematochezia), or suspected variceal hemorrhage should be admitted to an ICU. Most other patients can be admitted to a regular hospital ward. Several decision rules and predictive models have been developed to identify patients at low risk for recurrent or life-threatening UGIB. The modified Glasgow-Blatchford bleeding score is calculated using blood urea nitrogen level, hemoglobin level, systolic blood pressure, and pulse rate. It predicts the need for clinical intervention, rebleeding, and mortality. Patients at low risk with a modified Glasgow-Blatchford score of 1 or less may be considered for early discharge or outpatient treatment.

Endoscopic Evaluation and Treatment

Upper endoscopy is the primary diagnostic modality for evaluating UGIB. For patients hospitalized with UGIB, endoscopy should be performed within 24 hours of resuscitation; in those with rapid bleeding or suspected variceal hemorrhage, it should be done more emergently.

Endoscopy can determine the cause of bleeding and helps with risk stratification. Lesions at high risk for recurrent bleeding that require endoscopic treatment include actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels (see Figure 39), and ulcers with adherent clots (see Figure 40). An adherent clot should be irrigated with the intention of removing the clot; the ulcer base is then examined to exclude an underlying arterial vessel requiring endoscopic hemostasis. Lesions at low risk for rebleeding (clean-based ulcers, ulcers with pigmented spots, and Mallory-Weiss tears) do not require endoscopic treatment (**Figure 41**). Most Mallory-Weiss tears

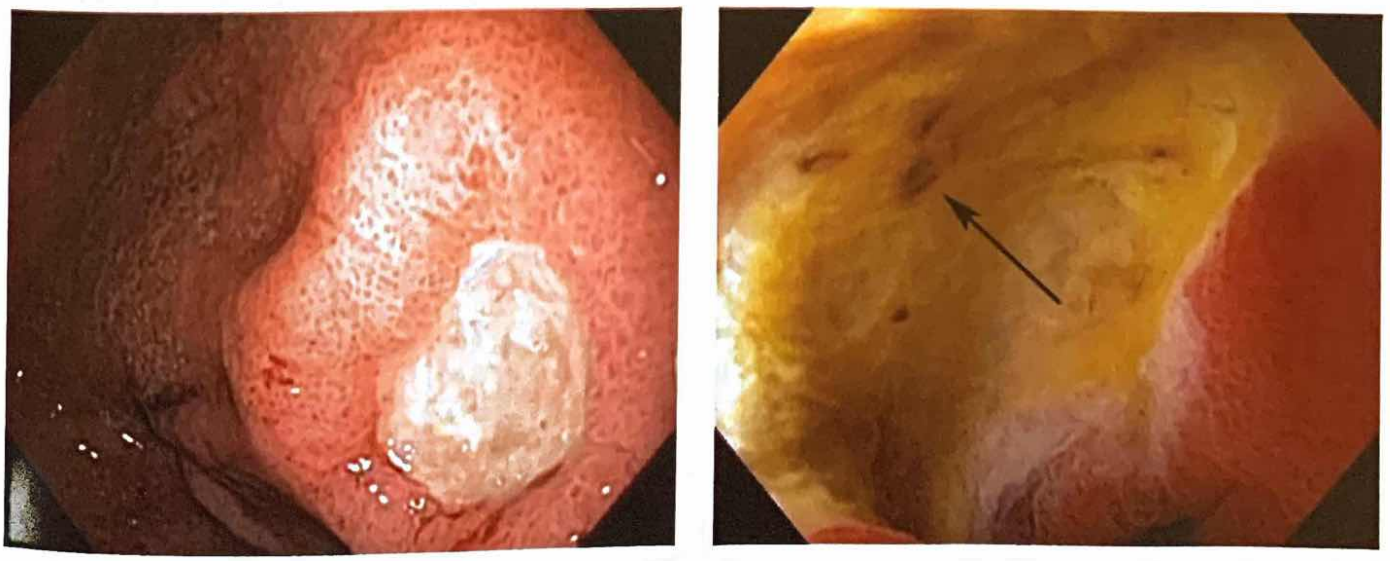

FIGURE 41. Ulcers at low risk for rebleeding, for which endoscopic therapy is not indicated. *Left:* Clean-based gastric ulcer with no blood vessels, pigmented spots/protuberances, or clots in the base. *Right:* Nonprotuberant pigmented spot (*arrow*) in a duodenal ulcer bed.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

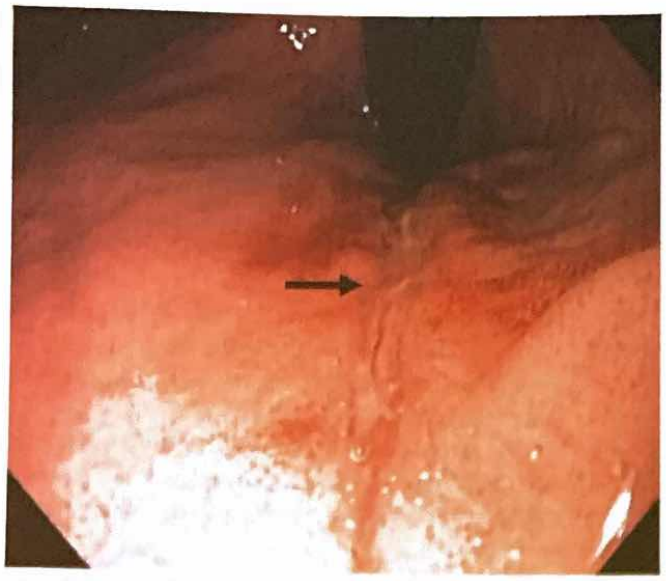

FIGURE 42. Mallory-Weiss tear. This superficial linear mucosal tear (*arrow*) is shown on endoscopic retroflexion in the proximal stomach.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

(**Figure 42**) stop bleeding spontaneously. Endoscopic techniques, such as injection therapy, thermal devices, and endoclips, can be used for actively bleeding tears.

The most effective approach for control of acute variceal hemorrhage (**Figure 43**) is combined therapy with octreotide and endoscopic therapy. Octreotide should be continued for 3 to 5 days after variceal hemorrhage. Endoscopic variceal ligation within 12 hours of presentation is the endoscopic treatment of choice for hemostasis of active variceal hemorrhage, with a success rate of 90%. In patients with bleeding gastric varices, endoscopic control may be difficult and transjugular intrahepatic portocaval shunting may be considered if bleeding persists despite octreotide.

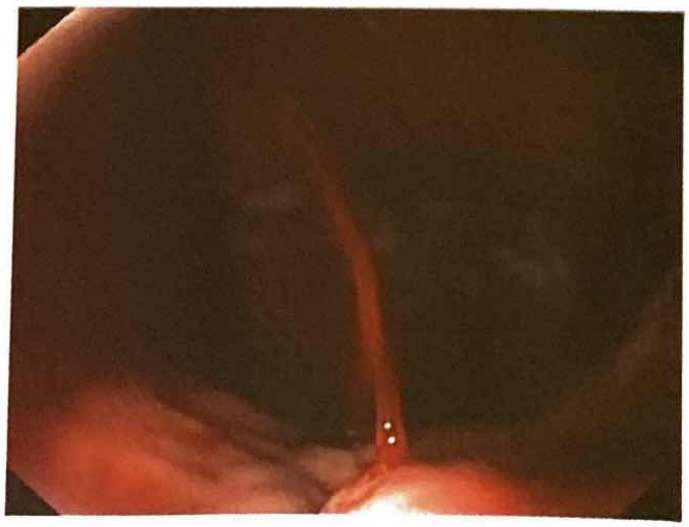

FIGURE 43. Acute esophageal variceal hemorrhage. A varix in the distal esophagus is seen spurting bright red blood.

The possibility of aortoenteric fistula should always be considered in patients who previously had aortic graft surgery and present with gastrointestinal bleeding because aortoenteric fistula is life-threatening, with a mortality rate of 50% even with surgical intervention. When there is a high degree of suspicion for an aortoenteric fistula, CT with intravenous contrast should be performed before endoscopy or other types of gastrointestinal evaluation.

Postendoscopic Care

Patients with peptic ulcer disease and low-risk stigmata can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital. Patients with high-risk lesions and those with adherent clots requiring endoscopic treatment should receive intravenous PPI therapy for 72 hours to decrease the risk for rebleeding and remain in the hospital for this interval. For high-risk lesions, twice-daily oral PPI therapy should continue for 2 weeks. Intermittent intravenous dosing is as efficacious as continuous infusion and may be preferable from a cost and logistic standpoint. For discussion of management of peptic ulcer disease, see Disorders of the Stomach and Duodenum.

Nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) should be initiated in addition to endoscopic band ligation for secondary prophylaxis of variceal hemorrhage. The dosage of β-blockers should be increased as tolerated to obtain a resting pulse rate of 55 to 60/min. Subsequent endoscopy with further band ligation as needed to obliterate varices should also be performed every 2 to 4 weeks. Patients with cirrhosis and gastrointestinal bleeding should have antibiotic therapy continued for 7 days after hemorrhage, even in the absence of ascites.

Aspirin discontinued for secondary prevention of cardiovascular disease should be restarted as soon as possible after hemostasis is achieved. In patients with a recent acute coronary syndrome or coronary stent placement in whom a P2Y12 receptor was discontinued, therapy should be reinitiated within 5 days. In patients in whom warfarin was discontinued, re-anticoagulation with low-molecular-weight heparin or unfractionated heparin should be considered within 48 hours in patients at high thrombotic risk (mechanical prosthetic heart valve in the mitral position, atrial fibrillation with prosthetic heart valve or mitral stenosis, or recent venous thromboembolism). Timing of resuming direct oral anticoagulants depends on the risk profile, but resumption generally should occur within 7 days.

For all causes of UGIB, endoscopic therapy should be repeated if bleeding recurs, but routine second-look endoscopy is not recommended. Interventional radiology or surgery is reserved for cases of rebleeding despite endoscopic treatment. For variceal bleeding, placement of a transjugular intrahepatic portocaval shunt is reserved for bleeding that is not controlled by drug and endoscopic therapy.

KEY POINTS

- The most common causes of upper gastrointestinal bleeding include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear.
- Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are associated with increased risk for rebleeding and death in patients with upper gastrointestinal bleeding.
- Octreotide should be initiated if variceal hemorrhage is suspected, and initiation of antibiotics is recommended for all patients with cirrhosis.
- Endoscopic variceal ligation within 12 hours of presentation is the endoscopic treatment of choice for hemostasis of active variceal hemorrhage.
- HVC Patients with peptic ulcer disease and low-risk stigmata can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital.
- Patients with high-risk peptic ulcer lesions and those with adherent clots requiring endoscopic treatment should receive intravenous PPI therapy for 72 hours.

Lower Gastrointestinal Bleeding

Twenty percent of all cases of gastrointestinal bleeding originate in the colon or rectum. Most cases of LGIB stop spontaneously and have good outcomes; however, morbidity and mortality are higher in older patients and those with comorbid conditions. Patients with LGIB usually present with sudden onset of hematochezia (maroon or red blood per rectum). Occasionally, bleeding from the cecum or right colon may appear black and tarry, like melena. LGIB may also present with pain, diarrhea, or change in bowel movements.

Causes

The most common cause of minor LGIB is hemorrhoidal bleeding. This is usually characterized by a small volume of bright red blood and usually does not cause hemodynamic instability or significant volume loss (see Disorders of the Small and Large Bowel for discussion of hemorrhoids). Causes of severe LGIB that may lead to clinical instability include diverticular bleeding, colonic angiodysplasia, postpolypectomy bleeding, Dieulafoy lesion, rectal varices, and malignancy (**Table 42**). Fifteen percent of patients with hematochezia, however, are found to have an upper gastrointestinal source.

TABLE 42. Causes of Severe Lower Gastrointestinal Bleeding

Bleeding Source	Pathogenesis	Presentation	Treatment
Diverticulosis	Segmental weakness of arteries coursing over the dome of the diverticulum	Painless hematochezia or self-limited massive bleeding	Endoscopic, interventional radiologic, and surgical
Aortoenteric fistula	Erosion of aortic aneurysm (primary) into GI tract or following surgical or endovascular grafting (secondary)	Minor hemorrhage (herald bleeding) or massive bleeding	Aggressive resuscitation and emergent surgical repair
Rectal varices	Portal hypertension	Episodic hematochezia or severe bleeding (rare)	Endoscopic therapy and treatment of portal hypertension
Dieulafoy lesion	Erosion of an aberrant dilated submucosal blood vessel	Recurrent hematochezia or massive bleeding	Endoscopic therapy
Neoplasm	Tumor invasion	Recurrent episodes of hematochezia or melena or iron deficiency	Radiographic or endoscopic techniques or surgery
Colonic ischemia	Colonic hypoperfusion	Abdominal pain and hematochezia	Supportive care; surgical intervention for cases of irreversible ischemia
Inflammatory bowel disease	Mucosal inflammation and ulceration	Bloody diarrhea and abdominal pain	Medical therapy for underlying disease
Infectious colitis	Mucosal invasion of infectious organism	Bloody diarrhea	Treatment of causative organism
Intussusception	Intestinal wall ischemia from underlying obstruction	Hematochezia in setting of bowel obstruction	Surgical
Meckel diverticulum	Ulceration of small bowel from ectopic gastric mucosa-produced acid	Chronic and insidious bleeding or acute massive bleeding	Surgical resection of the diverticulum
Angiodysplasia	Ectatic, dilated, thin-walled blood vessels	Chronic and insidious bleeding or acute and massive bleeding	Endoscopic; interventional radiography and surgery in refractory cases

Diverticular bleeding is arterial and stops spontaneously in 75% of cases. In patients with diverticulosis, risk for bleeding is estimated at 0.5 per 1000 person-years. For further discussion of diverticular disease, see Disorders of the Small and Large Bowel.

Angiodysplasia, also known as angiectasia or arteriovenous malformation, can occur throughout the colon but is most common in the right colon. Elderly patients, patients with end-stage kidney disease, and patients receiving anticoagulation therapy are at highest risk. Patients with cardiac disease, especially valve dysfunction, and patients with left ventricular assist devices may be at increased risk for gastrointestinal bleeding secondary to acquired von Willebrand disease.

Postpolypectomy bleeding can occur immediately after polyp removal or days or weeks later. Risk is increased in patients with polyps larger than 2 cm or polyps in the right colon and with resumption of antithrombotic therapy.

Diarrhea, abdominal pain, and hematochezia can occur with inflammatory bowel disease and infectious colitis; ischemic colitis may also present with these symptoms, although the bleeding is rarely significant. LGIB from a colon malignancy may be painless or associated with obstructive symptoms.

Evaluation

An initial patient assessment and hemodynamic resuscitation should be performed simultaneously. The timing and quality of any previous colonoscopy should be assessed, particularly for a report of polypectomy or biopsies. A careful assessment should be performed for use of antithrombotic or antiplatelet agents as well as for a personal history of or risk factors for liver disease, other comorbidities, or recent illness. Special attention should be paid to the factors that suggest an upper gastrointestinal source of hematochezia, including concomitant melena, liver disease, and hemodynamic instability.

Management

As with upper gastrointestinal bleeding, immediate attention should be paid to hemodynamic status, and resuscitative measures must be initiated with the goal of hemodynamic stabilization before endoscopy. The approach to management of hemoglobin level and platelet count are as described for UGIB, as are decisions regarding discontinuation and/or reversal of anticoagulant and antiplatelet agents.

CT angiography is the initial diagnostic test in patients who are hemodynamically unstable after initial resuscitation or have rapid ongoing bleeding, followed by immediate upper endoscopy if CT angiography does not reveal a source of bleeding. Upper endoscopy may also be a reasonable first choice in patients at risk for a rapidly bleeding upper gastrointestinal source for hematochezia.

In hemodynamically stable patients without evidence of rapid bleeding, colonoscopy is the first study of choice in patients with LGIB. It should be performed within 24 hours of presentation after adequate colon preparation, which may include rapid preparation. Colonoscopy identifies a source of LGIB in two thirds of patients.

Radiographic studies should be considered in patients who cannot tolerate colonoscopy or colon preparation or in patients in whom a source of bleeding is not identified endoscopically. Techniques include CT angiography, angiography, and, less frequently, tagged red blood cell scintigraphy.

Catheter-based angiography with embolization should be performed as soon as possible if active bleeding is noted on CT angiography. Angiographic embolization is also frequently used to stop persistent or recurrent diverticular bleeding because of the limitations of endoscopic approaches. Surgical consultation is reserved for patients who do not respond to endoscopic or interventional radiologic hemostatic measures.

The risk for rebleeding is highest in patients with diverticular bleeding (9% to 47%) and angiodysplasia bleeding (37% to 64%). To prevent recurrent LGIB, nonaspirin NSAIDs should be avoided, particularly after diverticular or angiodysplasia bleeding. Management of antiplatelet and anticoagulant medications is similar to that in patients with UGIB.

KEY POINTS

- CT angiography is the initial diagnostic test in patients who have lower gastrointestinal bleeding, are hemodynamically unstable, or have rapid ongoing bleeding, followed by immediate upper endoscopy if CT angiography does not reveal a source of bleeding.
- Catheter-based angiography with embolization should be performed as soon as possible if active bleeding is noted on CT angiography.
- In hemodynamically stable patients with lower gastrointestinal bleeding but no evidence of rapid bleeding, colonoscopy is the first study of choice and should be performed within 24 hours of presentation.

Small-Bowel Bleeding

Small-bowel bleeding occurs secondary to a gastrointestinal bleeding source between the ampulla of Vater and ileocecal valve. It can be overt, in which visible bleeding (melena or hematochezia) is present, or occult, which is characterized by anemia in the absence of gross signs of bleeding. Roughly 5% to 10% of gastrointestinal bleeding is due to a small-bowel source.

Causes

The causes of small-bowel bleeding vary with patient age (**Table 43**). Angiodysplasia (**Figure 44**) is the most common cause. Patients younger than 40 years are likely to have small-bowel bleeding due to inflammatory bowel disease, Dieulafoy lesions, neoplasia, Meckel diverticulum, or a polyposis syndrome. Patients age 40 years and older are likely to have bleeding due to angiodysplasia, Dieulafoy lesions, neoplasia, or NSAID-related ulcers. Rare causes include Henoch-Schönlein purpura, small-bowel varices or portal hypertensive enteropathy, amyloidosis, blue rubber bleb nevus syndrome, aortoenteric fistula, and radiation enteritis.