cholangiocarcinoma can complicate cirrhosis, and hilar cholangiocarcinoma can complicate primary sclerosing cholangitis.

Diagnosis of intrahepatic cholangiocarcinoma requires imaging with CT or MRI, and usually a biopsy. An elevated CA 19-9 level is supportive but insufficient for diagnosis. First-line therapy for intrahepatic cholangiocarcinoma is resection. Locoregional and/or systemic chemotherapy are appropriate for patients who are not candidates for resection.

Diagnosis of hilar cholangiocarcinoma can be challenging and is made by a combination of MRCP and ERCP. During ERCP, bile-duct brushings should be obtained for cytologic examination and fluorescence in situ hybridization testing. The latter test uses DNA probes to evaluate for gain or loss of chromosomes or loci, which are often present in biliary cancer. An elevated CA 19-9 level is supportive, but repeat ERCP is often required every 2 to 3 months to make the diagnosis. First-line therapy for hilar cholangiocarcinoma is resection. Patients with obstructive jaundice may require ERCP with stent placement to allow for biliary drainage. Patients with unresectable hilar cholangiocarcinoma smaller than 3 cm in size and without extrahepatic spread can be evaluated for liver transplantation at select centers with neoadjuvant chemoradiation protocols. However, percutaneous or transluminal biopsy of hilar cholangiocarcinoma excludes a patient for liver transplantation due to the risk for tumor seeding.

The preferred treatment for distal cholangiocarcinoma is a Whipple resection.

Metastatic cholangiocarcinoma of any variety should be treated with gemcitabine-cisplatin.

The 5-year survival rate for patients with cholangiocarcinoma (excluding liver transplant recipients), including those who undergo resection, is 20% to 30%.

KEY POINTS

- Resection is first-line treatment for cholangiocarcinoma.
- Selected patients with unresectable hilar cholangiocarcinoma smaller than 3 cm in size 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% but is usually due to other factors related to comorbid diseases. Lower gastrointestinal bleeding (LGIB) occurs from the colon or anorectum. It is less common, typically less severe, and has a lower mortality rate than UGIB. Small-bowel bleeding, formerly called obscure gastrointestinal bleeding, is bleeding that does not appear to originate from the upper or lower gastrointestinal tract; it is relatively uncommon.

KEY POINT

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

Upper Gastrointestinal Bleeding

UGIB can present in various ways, including hematemesis, "coffee-ground" emesis, melena, or hematochezia. Hematemesis is vomiting of bright red blood or clots. Coffee-ground emesis is the vomiting of dark, digested blood. Melena is black, tarry stool with a distinctive odor. Hematochezia is the passage of fresh 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 only rarely causes clinically important UGIB. Therefore, in a patient with UGIB and erosive esophagitis, alternative causes for the bleeding should be excluded.

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 consists of a mucosal disruption at the gastroesophageal junction and typically forms after repeated episodes of severe vomiting or retching.

Less common causes of UGIB include Cameron erosions, Dieulafoy lesion, gastric antral vascular ectasia, aortoenteric fistula, hemosuccus pancreaticus, hemobilia, and upper gastrointestinal tumors (**Table 37**).

Evaluation

The initial step in the approach to UGIB is a risk assessment to determine the severity of UGIB. This risk assessment includes the measurement of 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 all associated with increased risk for rebleeding and death.

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

Management

Patients with altered mental status, massive hematemesis, or an increased risk for aspiration should undergo endotracheal intubation. Hemoglobin levels should be measured. A restrictive transfusion strategy is recommended and initiated when

TABLE 37. 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, and 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; associated with cirrhosis and systemic sclerosis	Acute bleeding or iron deficiency anemia	Endoscopic
Aortoenteric fistula	Direct communication between aorta and GI tract	"Herald" bleed 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 and endoscopy for malignant tumors, surgical resection for benign tumors

GI = gastrointestinal; PPI = proton pump inhibitor.

CONT. 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 transfused 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.

For variceal bleeding, resuscitative measures need to be initiated with the goal of hemodynamic stabilization. Two large-bore peripheral intravenous catheters (minimum 18 gauge) are required with initiation of crystalloid fluids, either normal saline or lactated Ringer solution, to maintain adequate blood pressure. See Disorders of the Liver for discussion of variceal bleeding, including prophylaxis.

Pre-endoscopic Care

Intravenous proton pump inhibitor (PPI) therapy initiated before endoscopy decreases high-risk endoscopic stigmata seen (**Figure 33** and **Figure 34**) but does not influence outcome. Octreotide and antibiotics should be initiated if variceal

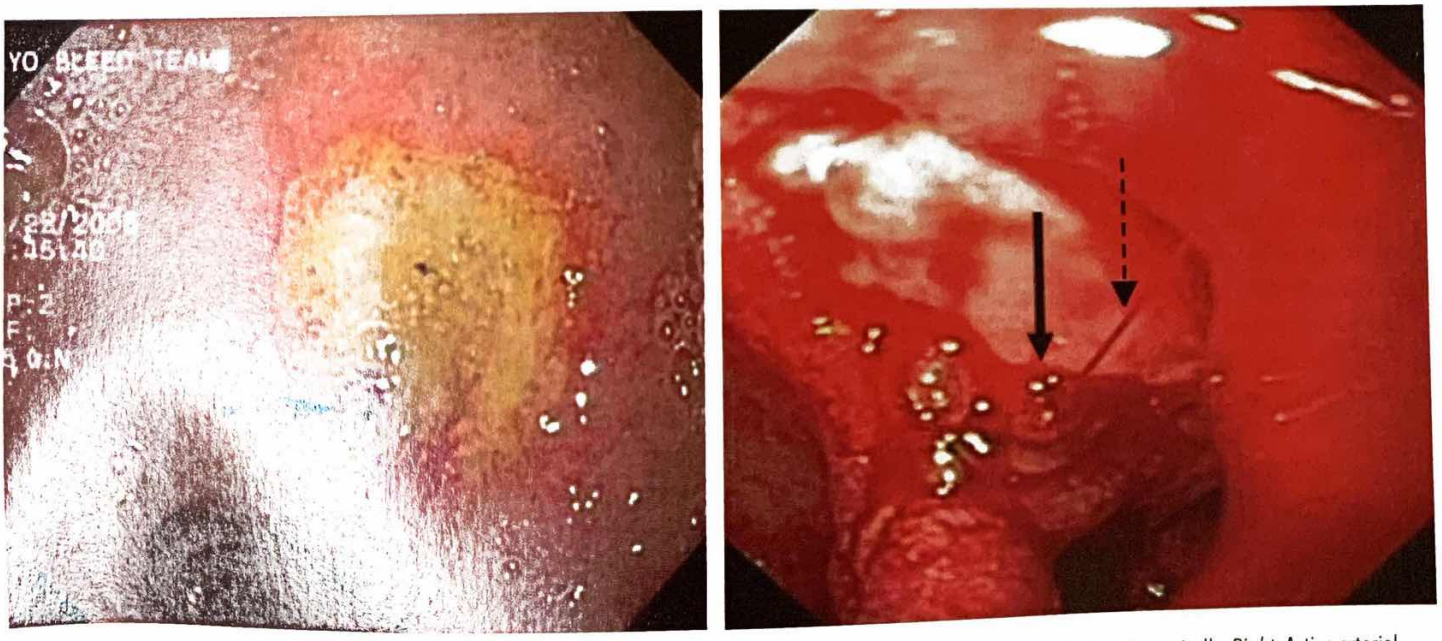

FIGURE 33. *Left*: Duodenal ulcer with nonbleeding visible vessel (*arrow*) that is at high risk for rebleeding and must be treated endoscopically. *Right*: Active arterial spurting (*dotted arrow*) from a duodenal ulcer (*solid arrow*). This lesion is at the highest risk for rebleeding and must be treated endoscopically.

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

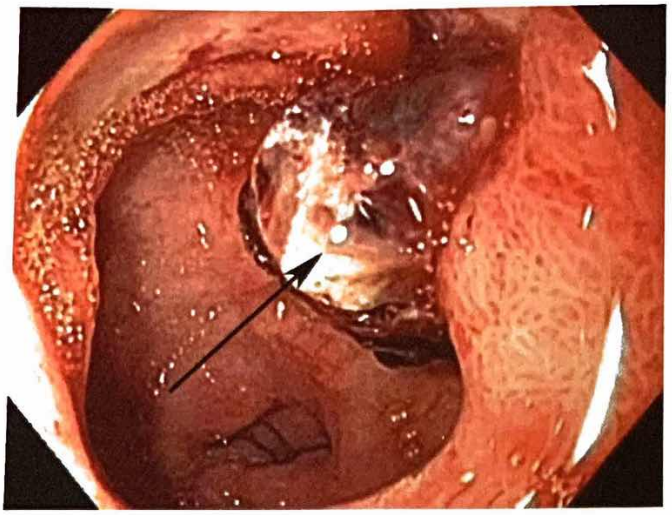

FIGURE 34. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding. This can be treated medically or by clot removal and endoscopic therapy in addition to standard medical therapy.

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

CONT.

hemorrhage is suspected. 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, not routinely. Nasogastric tube lavage is not required, as it has shown no evidence of clinical benefit.

Vitamin K and 4-factor prothrombin complex concentrate should be administered to patients on anticoagulation with a supratherapeutic INR. The risk for continued bleeding on anticoagulation therapy should be weighed against the risk associated with stopping therapy. Furthermore, endoscopy should not be delayed for anticoagulation reversal unless the INR is greater than 3.0.

Decisions regarding discontinuing antiplatelet therapy are based on whether the therapy is for primary or secondary prophylaxis. If aspirin is being taken for primary prophylaxis, then it should be discontinued because the risk for recurrent bleeding outweighs the benefit. Aspirin for secondary prophylaxis can be discontinued for 3 days but needs to be promptly resumed when hemostasis is secure. Decisions regarding discontinuing clopidogrel and other antiplatelet agents should be made in conjunction with a cardiologist.

Patients with hemodynamic instability or active bleeding (hematemesis or recurrent large-volume hematochezia) should be admitted to an ICU for resuscitation. Other patients can be admitted to a regular hospital ward. Several decision rules and predictive models have been developed to identify patients who are at low risk for recurrent or life-threatening UGIB. The modified Glasgow-Blatchford bleeding score is calculated using the 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 according to the modified Glasgow-Blatchford score 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. The possibility of aortoenteric fistula should always be considered in patients who have had previous aortic graft surgery and who 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.

Endoscopy can determine the cause of bleeding and helps to risk-stratify the patient. Lesions at high risk for recurrent bleeding that require endoscopic treatment include: actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels (see Figure 33), and ulcers with adherent clots (see Figure 34). An adherent clot should be irrigated with the intention of removing the clot; if clot removal is successful, the ulcer is then considered low-risk for rebleeding. Lesions at low risk for rebleeding (clean-based ulcers, ulcers with pigmented spots, and Mallory-Weiss tears) do not require endoscopic treatment (**Figure 35**). Most Mallory-Weiss tears (**Figure 36**) stop bleeding spontaneously. Endoscopic techniques such as injection therapy, thermal devices, and endoclips can be used for actively bleeding tears.

The initial therapy for acute esophageal variceal hemorrhage (**Figure 37**) is resuscitation in an ICU with the goal of maintaining hemodynamic stability and a hemoglobin of 7 g/dL (70 g/L). Overtransfusion can precipitate variceal rebleeding due to increased portal pressure.

The most effective approach for control of acute variceal hemorrhage is combined therapy with octreotide (somatostatin analog) and endoscopic therapy. Octreotide decreases splanchnic blood flow and lowers portal pressure; it should be initiated before endoscopic evaluation and 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%. Subsequent endoscopy with further band ligation as needed to obliterate varices should be performed every 2 to 4 weeks.

Patients who develop variceal hemorrhage are at high risk for infection, such as pneumonia and urinary tract infection, and nearly 50% of patients with cirrhosis who are hospitalized with UGIB have a bacterial infection. Rates of rebleeding and death are reduced with prophylactic antibiotics (such as ceftriaxone or quinolone). Initiation of antibiotics at the time of hospitalization is recommended in all patients with cirrhosis and gastrointestinal bleeding, and antibiotic therapy should continue for 7 days after variceal hemorrhage, even in the absence of ascites.

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 all associated with increased risk for rebleeding and death in patients with upper gastrointestinal bleeding.
- Upper endoscopy is the primary diagnostic modality for evaluating upper gastrointestinal bleeding.
- Management of an ulcer depends on the endoscopic appearance and risk for rebleeding.

H 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, higher rates of morbidity and mortality are seen in older patients and in 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 present with additional symptoms of pain, diarrhea, or change in bowel movements.

Causes

The most common cause of minor LGIB is hemorrhoidal bleeding. Hemorrhoidal bleeding is usually characterized by a small volume of bright red blood and 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, solitary rectal ulcer syndrome, rectal varices, or malignancy (**Table 38**). Fifteen percent of patients with a presumed lower gastrointestinal source of bleeding are found to have an upper gastrointestinal source.

TABLE 38. Causes of Severe Lower Gastrointestinal Bleeding

Diverticulosis
Aortoenteric fistula
Colonic or rectal varices
Dieulafoy lesions
Neoplasm
Colitis
Ischemic
Inflammatory bowel disease
Infectious
Intussusception
Meckel diverticulum
Angiodysplasia

Diverticular bleeding is arterial, usually painless, occurs in the neck or dome of a diverticulum, and stops spontaneously in 75% of cases. In patients with diverticulosis, the 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 and patients on anticoagulation therapy are at highest risk.

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

Patients with ischemic colitis usually present with severe abdominal pain, often out of proportion to physical findings. Diarrhea, abdominal pain, and hematochezia can occur with inflammatory bowel disease and infectious colitis. LGIB from a colon malignancy may be painless or associated with obstructive symptoms. Patients with cardiac disease, such as valve dysfunction or dilated cardiomyopathy, are at risk for acquired von Willebrand disease and gastrointestinal bleeding.

Evaluation

An initial patient assessment and hemodynamic resuscitation should be performed simultaneously. The timing and quality of any previous colonoscopy should be assessed, as should whether or not polypectomy or biopsies were performed. The patient's medication history, especially use and dosing of antithrombotic agents, should be assessed, as well as personal history, risk factors for liver disease, other comorbidities, and recent illness.

Management

Resuscitation goals for patients with LGIB should be normalization of blood pressure and heart rate, as well as the transfusion of packed red blood cells if needed to maintain the hemoglobin level above 7 g/dL (70 g/L), with a threshold of 9 g/dL (90 g/L) in patients with massive bleeding, or when treatment may be delayed. Platelet transfusion to maintain counts above 50,000 cells/μL (50×10^9/L) is recommended in patients with active bleeding. The decision to discontinue or reverse anticoagulant agents should balance the risk of ongoing bleeding with the risk of thromboembolic events and often requires a multidisciplinary approach.

Colonoscopy is the initial diagnostic test in the majority of patients with LGIB and should be performed within 24 hours of presentation after adequate colon preparation in patients with significant bleeding. Colonoscopy identifies a source of LGIB in two thirds of patients. Hematochezia with

CONT. hemodynamic instability may indicate a rapid UGIB source, and upper endoscopy may be indicated.

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

Angiography with embolization is frequently used to stop persistent or recurrent diverticular bleeding because endoscopic approaches are limited due to the typical location of the vessel inside a thin-walled diverticulum. Surgical consultation is usually reserved for patients who do not respond to endoscopic or radiographic measures.

The risk for rebleeding is highest in patients with diverticular bleeding (9% to 47%) and angiodysplasia bleeding (37% to 64%). For prevention of recurrent LGIB, nonaspirin NSAIDs should be avoided, particularly after diverticular or angiodysplasia bleeding. The continued use of antiplatelet or anticoagulants needs to be weighed against the risk for rebleeding. Aspirin for secondary prevention in patients with high-risk cardiovascular disease should not be discontinued. Decisions about discontinuation of dual antiplatelet therapy in patients with an acute coronary syndrome or coronary stent placement should be made in conjunction with a cardiologist. Anticoagulation use for other medical indications should be resumed as soon as possible, within at least 7 days for most patients.

KEY POINTS

- Patients with lower gastrointestinal bleeding usually present with sudden onset of hematochezia (maroon or red blood per rectum).
- Most cases of lower gastrointestinal bleeding stop spontaneously and have good outcomes; however, higher rates of morbidity and mortality are seen in older patients and in those with comorbid conditions.
- Colonoscopy identifies a source of lower gastrointestinal bleeding in two thirds of patients.

Small-Bowel Bleeding

The term *small-bowel bleeding* is preferred to *obscure gastrointestinal bleeding* because in many clinical situations the cause of the bleeding can now be identified. Patients with small-bowel bleeding often have normal results on upper endoscopy and colonoscopy. Small-bowel bleeding can be characterized as overt or occult. In patients with visible bleeding (either melena or hematochezia), it is overt. In patients who present with anemia but no gross signs of bleeding, the bleeding is considered occult. It is estimated that 5% to 10% of gastrointestinal bleeding occurs between the ligament of Treitz and the ileocecal valve; this is also known as midgastrointestinal bleeding.

Causes

The likely underlying cause of small-bowel bleeding varies with patient age (**Table 39**). Patients younger than age 40 years are likely to have bleeding due to inflammatory bowel disease, Dieulafoy lesions, neoplasia (leiomyoma, carcinoid, lymphoma, or adenocarcinoma), Meckel diverticulum, or a polyposis syndrome. Patients older than age 40 years are likely to have bleeding due to angiodysplasia, Dieulafoy lesion, neoplasia, or NSAID-related ulcers. Angiodysplasia (**Figure 38**) is the most common cause of small-bowel bleeding. It is found in 40% of cases and is often seen in elderly patients. Rare causes of bleeding include Henoch-Schönlein purpura, small-bowel varices or portal hypertensive enteropathy, amyloidosis, blue rubber bleb nevus syndrome, hematobilia, aortoenteric fistula, and hemosuccus entericus.

Evaluation

A detailed medical history and physical examination are needed to narrow the differential diagnosis to a small-bowel source. Patients should be asked about NSAID use to evaluate for NSAID-induced small-bowel ulcers, aortic aneurysm

TABLE 39. Causes of Small-Bowel Gastrointestinal Bleeding

Differential Diagnosis	Patient Age (Years)	Clinical Clues
Angiodysplasia	>60	Intermittent, usually occult bleeding; may also occur in the colon
Peutz-Jeghers syndrome	<20	Perioral pigmentation, obstructive symptoms
Meckel diverticulum	20-60	Possible abdominal pain
Hemangioma	<20	Possible cutaneous hemangiomas
Malignancy	>50	Weight loss, abdominal pain
Hereditary hemorrhagic telangiectasia	>50	Mucocutaneous telangiectasias

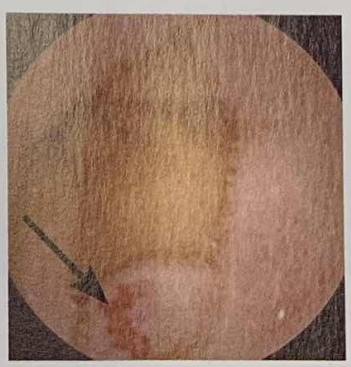

FIGURE 38. Capsule endoscopy image of angiodysplasia. The lesion (*arrow*) has a fernlike pattern and is red in color. Angiodysplasia can have no bleeding or active bleeding.