

Chronic Gastrointestinal Bleeding of Obscure Origin: Diagnosis and Management

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Chronic gastrointestinal bleeding leading to iron deficiency anemia continues to be a major clinical problem in general as well as subspecialty practice. In adult men and women in the western hemisphere, severe iron deficiency is almost always caused by gastrointestinal bleeding. In approximately 5% of all patients with gastrointestinal hemorrhaging and anemia, standard evaluation with esophagogastroduodenoscopy (EGD) and colonoscopy will not reveal a specific bleeding site.¹⁻³ The source of bleeding in these patients is most often the small intestine.

The cause of bleeding in the small intestine, unless massive, is often difficult to determine. Besides being an unusual site of bleeding (and so not routinely considered), the small intestine is relatively less accessible than are the stomach and colon.⁴ The diagnostic accuracy of customary techniques (eg, barium enema studies, endoscopic intubation, nuclear medicine scans, angiography) is limited by the small intestine's length, its free intraperitoneal location, its vigorous contractility, and its overlying loops. Moreover, bleeding in the small intestine is sometimes slow or intermittent, thus further limiting the usefulness of any diagnostic tool.

Because of the frequent inability to localize a bleeding site, patients with bleeding in the small intestine can experience prolonged blood loss or recurrent episodes of melena or maroon stool before receiving a specific diagnosis. For example, cancer of the small intestine—an uncommon cause of acute and chronic gastrointestinal bleeding—is notoriously difficult to diagnose and thus often advanced at the time of definitive treatment.⁴⁻⁸ This and other rare causes of gastrointestinal blood loss can be overlooked by unsus-

pecting physicians if an adequate work-up (**Figure 1**) is not performed.

This review will attempt to present useful information about the etiology, clinical evaluation, and treatment of patients with bleeding in the small intestine. As such, it should assist primary care physicians in providing appropriate work-up, management, and referral of these patients.

PREVALENCE

As mentioned previously, the small intestine, especially beyond the duodenal bulb, is an uncommon site of hemorrhage. According to published estimates, the site of gastrointestinal bleeding is located between the second portion of the duodenum and the ileocecal valve in only 3% to 5% of patients with gastrointestinal bleeding.¹⁻³ Nevertheless, bleeding, whether occult or massive, may be the only sign of a potentially fatal pathology in the small intestine. For this reason, any patient with obscure gastrointestinal bleeding should undergo a thorough evaluation so that a diagnosis can be reached without excessive delay. That such evaluations are not routinely performed is suggested by the

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Figure 1. Algorithm showing recommended work-up of obscure gastrointestinal bleeding. EGD = esophagogastrroduodenoscopy; GI = gastrointestinal.

fact that survival from primary cancers of the small intestine has not improved during the last 4 decades, primarily because of delayed diagnoses.

ETIOLOGY

Bleeding in the small intestine can result from several causes, each of which has its own bleeding pattern. The most common causes will be discussed in the following paragraphs.

Angiodysplasia

Angiodysplasia classically has been described as occurring in the right colon.¹⁻³ However, its characteristic vascular lesions also have been identified in the stomach and small intestine, although far less commonly than in the colon. Angiodysplasia is the most common cause of bleeding in the small intestine, accounting for 70% to 80% of cases. However, it is estimated that fewer than 10% of all patients with intestinal angiodysplasia eventually bleed. When bleeding does occur, it can be either brisk and evident or occult. According to a published report, melena was the presenting sign in 64% of 102 patients with bleeding caused by angiodysplasia of the small intestine, whereas occult blood in the stool was detected in only 36%.⁹

Little is known about the origin of angiodysplasia of the small intestine. The vascular lesions usually are detected on either enteroscopy or intraoperative endoscopy; angiography rarely leads to detection of vascular lesions in the small intestine. The natural history of angiodysplasia associated with bleeding also is not well characterized. Spontaneous cessation of bleeding has been reported in 44% of patients with angiodysplasia of the small intestine during a mean follow-up of period of 13.1 months.^{9,10} Moreover, once vascular lesions have bled, their tendency to rebleed cannot be fully known. Although physicians are eager to treat these lesions, as many as 50% might not rebleed. Finally, prophylactic therapy is not recommended for angiodysplasia found incidentally.^{1,2}

Tumors of the Small Intestine

Tumors are the second most common cause of bleeding in the small intestine. As previously suggested, these tumors often are not diagnosed early in their course. A study found that the total number of tests per patient with a tumor of the small intestine averaged 2.3 and that the average time from onset of symptoms to resection was 30.2 weeks.⁵ Tumors of the small intestine account for only 6% of all gastrointestinal tumors and 5% to 10% of all cases of hemorrhage of the small intestine⁶; often, bleeding is the only symp-

tom. More than half of these tumors are benign. Benign tumors more commonly present with acute gastrointestinal hemorrhage but are often asymptomatic, whereas malignant tumors more commonly present with abdominal pain and weight loss.

Leiomyomas and leiomyosarcomas are the most common tumors of the small intestine that bleed. Adenocarcinomas, carcinoids, and lymphomas are associated with more gradual but also more chronic blood loss. Adenocarcinomas (and adenomatous polyps) most frequently are found in the proximal small intestine, with 90% of lesions located in the duodenum and the first 20 cm of the jejunum. Lymphomas, on the other hand, tend to be distally located.

Other Causes

Other causes of bleeding in the small intestine include Crohn's disease, Meckel's diverticulum, Zollinger-Ellison syndrome, infections, use of certain drugs, vasculitis, radiation enteritis,¹ jejunal diverticulosis,¹¹ and pancreatic pseudocysts.¹

Crohn's disease is the most common ulcerative disease of the small intestine that can cause bleeding. Nevertheless, gross bleeding is unusual in Crohn's disease, occurring in only 4% to 10% of patients with the condition.¹ The diagnosis is virtually always made on a radiographic series of the small intestine.

Meckel's diverticulum occurs in 2% of the population. Located approximately 100 cm from the ileocecal valve,¹² this anomaly occurs more frequently in men than in women and is the cause of bleeding in two thirds of men younger than age 30 years who have bleeding in the small intestine. The bleeding is usually brisk. Although preoperative diagnosis is uncommon, technetium-99m pertechnetate scanning can diagnose Meckel's diverticulum.

Zollinger-Ellison syndrome can also cause bleeding ulcerations of the small intestine in the second, third and fourth parts of the duodenum, as well as in the jejunum. Infections, including tuberculosis, syphilis, typhoid, and histoplasmosis, similarly can result in bleeding in the small intestine. In addition, use of nonsteroidal anti-inflammatory drugs, potassium, 6-mercaptopurine, and other medications can cause ulcerations and bleeding in the small intestine. Other etiologies include vasculitis (associated with, eg, polyarteritis nodosa, systemic lupus erythematosus, rheumatoid arthritis, hypersensitivity), radiation enteritis, jejunal diverticula,^{1,13} and pancreatic pseudocyst.¹⁴

CLINICAL EVALUATION

Patients with gastrointestinal hemorrhage usually

undergo standard examinations such as EGD and colonoscopy. If these tests do not identify a source of the bleeding, the small intestine is assumed to be the source of blood loss. Several studies are available to help locate the precise source within the small intestine.

Radiographic Series of the Small Intestine

A radiographic series of the small intestine with enteroclysis is usually the initial study performed in a patient who is not actively bleeding. Standard radiographs by themselves are likely to result in a relatively low yield of positive findings when patients have bleeding of obscure origin.¹⁵ Although Crohn's disease and large ulcerations of the small intestine can readily be diagnosed by standard radiographs, only 5% of such radiographic examinations will detect the bleeding site in the small intestine.¹⁶⁻¹⁸ Enteroclysis, however, can increase the yield of such radiography to 10%.¹⁶⁻¹⁸ In this procedure a tube is positioned in the duodenum and barium mixed with air, water, or methylcellulose is instilled. The radiographs subsequently obtained are comparable to the double-contrast radiographs obtained on barium enema studies of the colon. This modality is unable to diagnose angiodysplasia but can help in the diagnosis of Meckel's diverticulum, Crohn's disease, adenocarcinoma, metastatic melanoma, leiomyoma, and leiomyosarcoma.¹⁶

Radioisotope Scans

Radioisotope scans can be diagnostic when bleeding is distal to the ligament of Treitz. Erythrocytes labeled with technetium-99m are prepared in vivo (or prepared in vitro and then injected into the circulation). As little as 5 mL of intraluminal blood will yield positive results.¹² These cells have a half-life of about 24 hours and, therefore, sequential scans may be performed to increase the probability of identifying the bleeding site. Technetium-99m pertechnetate can be used to detect Meckel's diverticulum (reported sensitivity, approximately 75 to 100%¹⁹) or leiomyomas (because of their vascularity). Because of their ready availability, low cost, and absence of complications, such scans are universally accepted and often are a prerequisite to angiography.

Angiography

Angiography can detect bleeding occurring at a rate of at least 0.5 mL/min and can localize a site of bleeding in 50% to 72% of patients with massive gastrointestinal hemorrhage.^{19,20} The yield drops to 25% to 50% in patients without active bleeding. A radiologist can attempt embolization of the responsible lesions in order to stop the bleeding. In addition to identifying

active bleeding sites, angiography can be used to diagnose lesions (eg, angiodysplasia, tumors) of the small intestine that are not bleeding. Angiography has been reported to show a tumor blush in 86% of tumorous lesions in the small intestine.²¹

Exploratory Surgery

Exploratory surgery often is considered in patients with recurrent gastrointestinal bleeding. However, there is a low success rate for surgical exploration when unaccompanied by other evaluations such as intraoperative endoscopy. As an illustration of how uncommon it is to approach patients with gastrointestinal bleeding of obscure origin with surgical exploration only, the only estimates of the yield of the procedure come from reports in the 1960s.²² If one excludes diagnoses readily made by endoscopy (eg, peptic ulcer disease), the yield of exploration alone falls to about 10%.

Endoscopy

Endoscopy of the small intestine can be accomplished in several ways. The usual techniques of EGD and colonoscopy with intubation of the ileocecal valve provide visualization of the most proximal and distal ends of the intestines. Routine EGD generally reaches the junction of the second and third portions of the duodenum.

Push enteroscopy. In the procedure referred to as *push enteroscopy*, a long endoscope is passed beyond the ligament of Treitz. The newer push enteroscopes allow intubation of the jejunum, to about 200 to 225 cm. Reported diagnostic yields of this procedure have ranged from 15% to 38%.^{1,23-30} Angiodysplasia was the most common finding, accounting for 80% of diagnoses. Push enteroscopy not only is diagnostic but also can be therapeutic, allowing fulguration of bleeding sites and polypectomy.¹³ This technique also allows detection of a significant number of lesions which are missed on EGD.^{31,32}

Sonde enteroscopy. Sonde enteroscopy (ie, small intestine enteroscopy), the only possible way to examine the entire small intestine, entails the passage of a long flexible fiberoptic instrument through the intestine by peristalsis. A balloon at the tip of the instrument is carried forward by peristalsis, and the endoscopic examination is performed during its withdrawal. In contrast to push enteroscopy, this technique has no therapeutic capability and no tip deflection. Thus, visualization is not total, with only approximately 50% to 70% of the mucosa of the small intestine observed during a standard examination.¹⁸ The ileum is reached in 75% of examinations, and only 10% reach the ileocecal

valve.¹⁸ Other limitations of this procedure are its sparse availability and tedious nature. Recent studies have shown a diagnostic yield of approximately 40% in patients with obscure gastrointestinal bleeding who undergo push enteroscopy and sonde enteroscopy.²³

Intraoperative enteroscopy. In light of the many limitations of sonde enteroscopy, intraoperative enteroscopy remains the most common form of endoscopic examination of the entire small intestine, especially in difficult cases. Published investigations have reported variable success with this type of enteroscopy.^{31,33,34} Various specific techniques have been described that are successful in determining the site of bleeding in 58 to 100% of patients.^{1,31} A study recently reported a diagnostic yield of 58% for patients with gastrointestinal bleeding of obscure origin who underwent intraoperative enteroscopy, with a cecal intubation rate of 93%.³¹ However, the authors also reported a high operative morbidity (30%).

MANAGEMENT

Management of chronic gastrointestinal bleeding of obscure origin continues to perplex clinicians. Treatable conditions (eg, surgically resectable tumors, vasculitis, Crohn's disease) should be managed definitively. Treatment of angiodysplasia continues to be controversial.^{1,35} Fulgration of the associated vascular lesions is most likely necessary only for actively bleeding lesions. Combination hormonal therapy has been tried, with variable success,³⁵ and might be effective in selected cases. Although gastrointestinal bleeding can have a negative effect on patients' quality of life, given the need for repeated transfusions and hospitalizations, it is seldom associated with high mortality or life-threatening bleeding.

SUMMARY POINTS

- In approximately 5% of patients with chronic gastrointestinal bleeding, the precise site of bleeding will not be determined with EGD and colonoscopy. These patients should undergo aggressive evaluation, with intensive study of the small intestine.
- The 2 most common etiologies of obscure gastrointestinal bleeding include angiodysplasia and tumors of the small intestine.
- Radiographic techniques are not very sensitive in identifying angiodysplasia, the most common cause of bleeding in the small intestine.
- Push enteroscopy is becoming more widely available as a diagnostic modality in patients with suspected bleeding in the small intestine. Because sonde enteroscopy (or complete enteroscopy of the

small intestine) is not always feasible, surgical exploration with intraoperative enteroscopy is a possible alternative.

- Management of chronic gastrointestinal bleeding of obscure origin continues to be controversial. Possible treatment modalities include fulgration of vascular lesions as well as combination hormonal therapy. **HP**

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