OCCULT gastrointestinal bleeding typically refers to bleeding that is not apparent to the patient. The potential for occult bleeding is emphasized by the finding that for melena to be produced consistently, 150 to 200 ml of blood must be present in the stomach. Moreover, patients with gastroduodenal blood loss of 100 ml per day may have stools that appear normal. Thus, occult bleeding is usually identified only by tests that detect fecal blood or, if bleeding is sufficient, when it becomes manifest as iron deficiency. Occult gastrointestinal bleeding can also refer to bleeding that is clinically evident but from an obscure source. Obscure gastrointestinal bleeding is the least common form of occult gastrointestinal bleeding but represents a tremendous diagnostic and therapeutic challenge. This article reviews important concepts in the evaluation and care of patients with each type of occult gastrointestinal bleeding.

Fecal Occult-Blood Tests

Guaiac-based fecal occult-blood tests make use of the pseudoperoxidase activity of hemoglobin. Guaiac turns blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as hydrogen peroxide. Several different guaiac-based tests are available, the characteristics of which vary considerably. For example, of the two most commonly used tests, Hemoccult II and Hemoccult II Sensa (SmithKline Diagnostics, Palo Alto, Calif.), the latter is much more sensitive than the former for detecting fecal heme.

The likelihood that a guaiac-based test will be positive is generally proportional to the quantity of fecal heme, which in turn is related to the size and location of the bleeding lesion (Fig. 1). Guaiac-based tests are generally best at detecting large, more distal lesions. However, many factors contribute to the variation in the effectiveness of guaiac-based tests for the detection of fecal blood. The inconsistency of fecal occult-blood tests in detecting fecal blood is emphasized by the finding that fecal hemoglobin levels must exceed 10 mg per gram of stool (10 ml of daily blood loss) for Hemoccult II tests to be positive 50 percent of the time, but stools containing hemoglobin levels of less than 1 mg per gram can result in positive tests. Such data have raised questions about the accuracy of guaiac-based tests for detecting colonic lesions.

Many variables influence guaiac-based tests, including dietary factors (Table 1). For this reason, it is important to consider (and modify) diet when performing guaiac-based tests. In addition, fecal rehydration markedly raises the sensitivity of guaiac-based tests but reduces specificity. Many believe that oral iron causes positive results on guaiac-based tests. Although the dark-green or black appearance of iron in stool can be confused with the blue typical of a positive guaiac-based test, iron administered orally does not cause positive guaiac reactions. Antacids and anti-diarrheal drugs containing bismuth also render the stool dark and may confound the reading of guaiac-based tests.

Immunochromatographic tests, which use antibodies directed against human globin epitopes, detect colonic blood with great sensitivity (at a level of as little as 0.3 ml of blood added to stool) and do not detect
small quantities of blood from the upper gastrointestinal tract (Fig. 1). Thus, they have a theoretical advantage over guaiac-based tests in terms of localizing bleeding to the colon. Unfortunately, the tests are limited by loss of globin antigenicity at room temperature and require processing in a laboratory. Newer slide tests may help circumvent these problems.

The heme–porphyrin test, HemoQuant (Mayo Medical Laboratories, Rochester, Minn.), measures hemoglobin-derived porphyrin spectrofluorometrically and allows exact measurement of total hemoglobin in stools. Moreover, substances that may interfere with or cause false positive guaiac-based tests (for example, vegetable peroxidases) do not affect the test. Unfortunately, the need for laboratory processing and the high false positive rate of this test have limited its clinical application.

**Differential Diagnosis and Approach to Evaluation**

Although many variables influence the results of fecal occult-blood tests, including variables that cause false positive results and those that cause false negatives, once it is determined that a patient has a positive test, the clinical focus is generally first on colonic

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**Figure 1. Sites of Gastrointestinal Bleeding, Intraluminal Metabolism of Hemoglobin, and Accuracy of Fecal Occult-Blood Tests.**

In the upper gastrointestinal tract, hemoglobin is cleaved to form heme and globin by gastric pepsin proteases, pancreatic proteases, or both types of proteases in the proximal small intestine. Some intraluminal heme (generally less than 15 percent) is reabsorbed in the small intestine. A portion of heme that is not absorbed and is converted to porphyrins and iron through poorly understood mechanisms has been termed the “intestinal converted fraction” of heme. This fraction is not detected by guaiac-based tests but is detected by the heme–porphyrin assay (e.g., HemoQuant), which measures both heme and porphyrins and is therefore a highly accurate indicator of bleeding, regardless of the level. Globin in the upper gastrointestinal tract is digested by pepsin and pancreatic and intestinal proteases and is thus not detected by immunochemical fecal occult-blood tests. The biology of intraluminal hemoglobin degradation suggests that a guaiac-based test combined with an immunochemical test could help differentiate occult bleeding in the upper gastrointestinal tract from that in the lower gastrointestinal tract. The red cells indicate the sites of blood loss.
imaging. The choice of imaging mode — colonoscopy or air-contrast barium enema — is controversial. Flexible sigmoidoscopy is mandatory for patients undergoing air-contrast barium enema to evaluate the rectosigmoid colon fully. Some studies have found that air-contrast barium enema accurately detects colon cancer and large adenomas, but most studies have found air-contrast barium enema to be less accurate than colonoscopy. Both tests can miss important neoplastic lesions. In addition, other factors are important when choosing an evaluation strategy; not only is the accuracy of the test an issue, but cost, acceptance by the patient, and complication rates differ between the two methods. On the basis of the available data, colonoscopy is recommended for the evaluation of the colon in patients with fecal occult blood; however, the use of air-contrast barium enema with flexible sigmoidoscopy may be an acceptable alternative. Computed tomographic studies of the colon (virtual colonoscopy) could eventually play a part in colonic evaluation but clinical experience is limited. Further studies are required to assess colonic-imaging techniques in patients with fecal occult blood.

Many gastrointestinal lesions can bleed and cause a positive fecal occult-blood test (Table 2); indeed, patients with fecal occult blood detected by guaiac-based tests may have serious disease of the upper gastrointestinal tract. Upper endoscopic examinations detected abnormalities in 25 to 41 percent of patients with fecal occult blood, many of whom were asymptomatic. Although this finding is surprising given the intraluminal metabolism of hemoglobin (Fig. 1), currently available guaiac-based tests detect small amounts of blood in the upper gastrointestinal tract, and many upper gastrointestinal tract lesions bleed to produce positive results on guaiac-based tests. The highly sensitive Hemoccult II Sensa test is substantially more likely to detect bleed in the upper gastrointestinal tract than is the Hemoccult II test. Therefore, the upper gastrointestinal tract must be considered as a potential source of bleeding in patients with normal results on colonoscopy, especially when highly sensitive guaiac-based tests are positive.

In the patient with a positive guaiac-based fecal occult-blood test and a negative colonoscopic examination, symptoms of upper gastrointestinal disorders (severe reflux, dyspepsia, and abdominal pain), weight loss, and iron deficiency should be assessed. If such signs and symptoms are present, the upper gastrointestinal tract should be studied. Whether asymptomatic patients should undergo evaluation of the upper gastrointestinal tract has not yet been determined.

Appropriate evaluation of patients with fecal occult blood detected by digital rectal examination is controversial, because obtaining stool by this means may lead to false positive tests. False positive tests may, in theory, result from anorectal trauma induced by the gloved finger during digital rectal examination. In addition, patients generally have not had dietary modification implemented at the time of digital rectal examination. However, in both symptomatic and asymptomatic patients with fecal occult blood detected by digital rectal examination, the number of new lesions identified by gastrointestinal evaluation is substantial. Thus, evaluation of these patients is indicated and, if symptoms are present, the investigation should be focused on the site or sites of the symptoms.

Occult gastrointestinal bleeding is often attributed to therapy with anticoagulants or aspirin. However, fecal blood levels in patients treated with anticoagulants or low-dose aspirin are normal or only minimally elevated, respectively. Neither warfarin nor low-dose aspirin alone appears to cause positive

<table>
<thead>
<tr>
<th>TABLE 2. DIFFERENTIAL DIAGNOSIS OF OCCULT GASTROINTESTINAL BLEEDING.</th>
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<tbody>
<tr>
<td>Mass lesions</td>
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<tr>
<td>Carcinoma (any site)‡</td>
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<tr>
<td>Large (&gt;1.5 cm) adenoma (any site)</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Erosive esophagitis‡</td>
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<tr>
<td>Ulcer (any site)‡</td>
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<tr>
<td>Cameron lesions‡</td>
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<tr>
<td>Erosive gastritis</td>
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<tr>
<td>Celiac disease</td>
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<tr>
<td>Ulcerative colitis</td>
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<td>Crohn’s disease</td>
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<tr>
<td>Colitis (nonspecific)</td>
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<tr>
<td>Idiopathic cecal ulcer</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td>Vascular ectasia (any site)†</td>
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<tr>
<td>Portal hypertensive gastropathy or colopathy</td>
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<tr>
<td>Watermelon stomach</td>
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<tr>
<td>Varices (any site)</td>
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<tr>
<td>Hemangioma</td>
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<tr>
<td>Dieulafoy’s vascular malformation§</td>
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<td>Infectious diseases</td>
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<tr>
<td>Hookworm</td>
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<tr>
<td>Whiplash</td>
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<tr>
<td>Strongyloidias</td>
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<tr>
<td>Ascariasis</td>
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<tr>
<td>Tuberculous enterocolitis</td>
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<tr>
<td>Amebias</td>
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<tr>
<td>Superficial bleeding</td>
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<tr>
<td>Hemoptysis</td>
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<tr>
<td>Oropharyngeal bleeding (including epistaxis)</td>
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<tr>
<td>Other causes</td>
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<tr>
<td>Hemosuccus pancreaticus</td>
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<tr>
<td>Hemobilia</td>
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<tr>
<td>Hemophilia</td>
</tr>
<tr>
<td>Long-distance running</td>
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<tr>
<td>Factitious cause</td>
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</tbody>
</table>

*Potential lesions leading to all forms of occult gastrointestinal bleeding are listed here. Some lesions that may lead to recurrent obscure bleeding are not listed.
†These abnormalities are the most common.
‡These are linear erosions within a hiatus hernia.
§This is a large superficial artery underlying a small mucosal defect.
guaiac-based fecal occult-blood tests. In a prospective study evaluating the gastrointestinal tract in patients taking anticoagulants who had positive guaiac-based fecal occult-blood tests, 15 of 16 patients had new lesions, 20 percent of which were malignant. In addition, there was no difference in the frequency of lesions between patients receiving warfarin and those receiving standard heparin. Thus, positive fecal occult-blood tests should not be attributed solely to anticoagulant therapy — whether with therapeutic or prophylactic warfarin, heparin (including low-dose heparin), or aspirin — but, rather, should lead to formal evaluation.

In patients with fecal occult blood (or any occult gastrointestinal bleeding), too high a degree of anticoagulation diminishes the yield of a gastrointestinal tract evaluation. In those with intrinsic coagulopathy (hemophilia or von Willebrand’s disease), particularly if bleeding is chronic, abnormalities of the gastrointestinal tract are also less likely to be identified; nevertheless, in both clinical scenarios, gastrointestinal evaluation must be given serious consideration.

**Treatment and Outcome**

The care of patients with fecal occult blood is based on the abnormalities identified. Likewise, outcomes are directly related to specific findings. Since nonsteroidal antiinflammatory drugs may lead to gastrointestinal injury, these should be discontinued if possible. Particularly problematic are vascular ectasias, which are often multiple and bleed chronically. (The medical management of vascular ectasias is discussed below.) The prognosis of patients with positive fecal occult-blood tests but no identifiable gastrointestinal disorder is generally favorable.

**ANEMIA DUE TO IRON DEFICIENCY**

In the United States, 5 to 11 percent of women and 1 to 4 percent of men have iron deficiency, and approximately 5 percent and 2 percent of women and men, respectively, have iron-deficiency anemia. In women, iron-deficiency anemia — a result of chronic iron loss (Fig. 2) — is most common during the reproductive years, because of menstrual and pregnancy-associated iron losses. Among other patients,
however, iron-deficiency anemia has been associated with chronic occult gastrointestinal bleeding.40

Differential Diagnosis and Approach to Evaluation

Because a diagnosis of iron-deficiency anemia necessitates extensive and often costly evaluation, the diagnosis must be established carefully. Although the gold standard is bone marrow biopsy, iron deficiency is most often indicated by a serum ferritin level of less than 45 µg per liter; iron-deficiency anemia is most often diagnosed on the basis of a similarly low ferritin level plus a hemoglobin level of less than 12 g per deciliter for women and less than 13 g per deciliter for men.41 Iron deficiency without anemia also requires further investigation, because it may be associated with serious abnormalities of the gastrointestinal tract.42,43

Cancers of the right side of the colon have traditionally been considered a leading cause of occult bleeding leading to iron-deficiency anemia, although practically any lesion in the gastrointestinal tract can bleed in an occult fashion (Table 2). Several cross-sectional studies have documented prominent abnormalities of the upper gastrointestinal tract. In studies of 381 patients with iron-deficiency anemia, lesions of the gastrointestinal tract consistent with chronic blood loss were identified in the following locations: the esophagus, stomach, or duodenum (in the form of severe esophagitis, presumably mediated by reflux, and ulcers) (41 percent), the small intestine (3 percent), and the colon (in the form of colon cancer and large adenoma) (22 percent).44-47 In this group of patients, 34 percent had no identifiable lesion consistent with blood loss, and only 5 percent had disease identified in both upper and lower gastrointestinal tracts.

Focused evaluation of the gastrointestinal tract should be considered in patients with iron-deficiency anemia. Gastrointestinal symptoms help direct the workup, although symptoms may not localize the disease.45,46 If epigastric pain, a change in stool caliber, and reflux symptoms are present, the initial investigation should be directed toward these symptoms, especially if the onset was recent. Because multiple lesions are rare, the identification of an abnormality clearly consistent with bleeding, such as a mass lesion, large ulceration, or severe inflammation, generally makes further evaluation unnecessary. In the absence of gastrointestinal symptoms, particularly in elderly patients, evaluation should begin with the colon and, if the colonic evaluation is negative, proceed to the upper gastrointestinal tract.

Large mass lesions, ulcerative gastrointestinal lesions, and even erosive gastritis associated with Helicobacter pylori infection commonly lead to serious occult blood loss (up to 60 ml per day).3,5,49 However, trivial lesions such as mild inflammation and small adenomas do not bleed substantially.3,10 Furthermore, not all patients with iron-deficiency anemia and gastrointestinal lesions have elevated levels of hemoglobin in gastrointestinal-lavage fluid.50 Thus, it is unlikely that every identified gastrointestinal tract lesion is associated with occult bleeding; caution is therefore urged in attributing iron-deficiency anemia to trivial lesions.

The role of gastrointestinal evaluation in premenopausal women with iron-deficiency anemia is not yet settled. A recent retrospective study found that 23 of 186 premenopausal women with iron-deficiency anemia (12 percent) had serious gastrointestinal tract abnormalities, including lesions of the upper gastrointestinal tract (12 patients) and the lower gastrointestinal tract (11 patients).48 Surprisingly, gastric cancer was the most common lesion of the upper gastrointestinal tract (five patients) and colon cancer the most prevalent colonic lesion (six patients). Of 15 variables examined, the only clinical features predictive of a detectable lesion were severe anemia (hemoglobin, <10 g per deciliter), abdominal symptoms, weight loss, and a positive fecal occult-blood test. Although the design of the study limits its generalizability, it shows that evaluation can lead to important diagnoses. Because iron-deficiency anemia is extremely common in premenopausal women, the management strategy is of critical importance. Currently, the best strategy is to individualize management. Patients with gastrointestinal symptoms (abdominal pain, dyspepsia, or severe reflux), weight loss, fecal occult blood, a family history of gastrointestinal cancer, or severe anemia should undergo gastrointestinal tract evaluation. Furthermore, the threshold for evaluation of patients older than 40 or 45 years should be lower than for younger women. For asymptomatic patients or those with abnormal menses, evaluation of the gastrointestinal tract is most appropriate when the severity of iron deficiency is disproportionate to the menstrual blood loss.

Both endoscopic evaluations (esophagogastroduodenoscopy and colonoscopy) and radiographic tests (air-contrast barium enema and upper gastrointestinal series) have been used to evaluate the gastrointestinal tract in patients with iron-deficiency anemia. Radiographic studies are generally effective for detecting mass lesions and large ulcerating lesions.51 However, they are not as sensitive for detecting vascular ectasias and mucosal lesions (esophagitis or colitis) as are endoscopic procedures. Therefore, endoscopic investigation is likely to be the most cost-effective approach and is recommended.

The small bowel should be considered as a potential site of bleeding in patients with iron-deficiency anemia and negative results on examinations of the colon and upper gastrointestinal tract. For example, celiac disease, a classic disorder of the small bowel, can lead to malabsorption of iron as well as to occult bleeding,52,53 especially in patients of northern Euro-
pean descent. Radiographic examination of the small bowel (either by small-bowel follow-through or by enteroclysis with barium instilled under pressure) is of limited value in patients with iron-deficiency anemia.\textsuperscript{43,47} In contrast, endoscopy of the small intestine (enteroscopy) is more sensitive for detecting mucosal lesions and possibly mass lesions; it has identified abnormalities in 6 to 27 percent of patients with iron-deficiency anemia.\textsuperscript{54,55} However, available data do not support the routine use of enteroscopy (or enteroclysis) in the initial evaluation of all patients with iron-deficiency anemia. Rather, investigation of the small bowel should be reserved for patients with negative studies of the colon and upper gastrointestinal tract but with persistent gastrointestinal symptoms or those for whom a short trial of iron therapy has failed. The role of routine biopsy of the small intestine in patients with negative evaluations of the upper and lower gastrointestinal tracts to investigate whether celiac disease is present is controversial, but the use of biopsy is reasonable in groups with a high underlying prevalence of celiac disease.

Some patients with iron-deficiency anemia have no identifiable abnormality of the gastrointestinal tract. Possible explanations for the iron-deficiency anemia include nongastrointestinal (especially oropharyngeal) blood loss, a misdiagnosis of the type of anemia, nutritional deficiency, and lesions that were not identified (especially vascular ectasias). Indeed, in a recent study, 35 percent of the patients with a negative workup had a source of bleeding that was subsequently identified by upper gastrointestinal endoscopy.\textsuperscript{55} In another study, approximately 20 percent of patients with iron-deficiency anemia were found to have gastric achlorhydria and atrophy, a finding that suggests that atrophic gastritis may contribute to the malabsorption of iron.\textsuperscript{40}

**Treatment and Outcome**

Iron therapy should be instituted for all patients once the diagnosis of iron-deficiency anemia has been confirmed. Oral ferrous sulfate is recommended because it is inexpensive and effective. Parenteral iron therapy is used only for patients with severe malabsorption or intolerance of all oral iron supplements (because of potential anaphylactic reactions to intravenous compounds). The prognosis for patients with iron-deficiency anemia and lesions amenable to medical therapy (duodenal ulcer, esophagitis, or adenoma) is excellent. Likewise, the prognosis for patients with normal results on evaluation of the gastrointestinal tract is favorable; very few of these patients are found to have serious gastrointestinal lesions during follow-up. The majority of patients respond to standard oral iron therapy\textsuperscript{43,47,57}; for patients who do not respond, the diagnosis of iron-deficiency anemia should be reevaluated. When unexplained iron-deficiency anemia persists, consideration should be given to careful reexamination of the colon, the esophagus (for linear esophageal ulceration, or Cameron lesions, within hiatus hernia), the stomach (for atrophic gastritis and other abnormalities), and the small bowel (including biopsy for celiac disease).
Enteroscopy is evolving, but it will probably be limited to and is not widely available. The role of Sonde enteroscopy is uncomfortable, does not permit therapy, requires a highly specialized endoscope. Sonde enteroscopy involves placement of a long, small-caliber endoscope into the proximal small bowel; subsequent peristalsis carries the endoscope to the distal small intestine. Although this procedure permits visualization of almost the entire small bowel, it requires a highly specialized endoscope. Sonde enteroscopy is uncomfortable, does not permit therapy, and is not widely available. The role of Sonde enteroscopy is evolving, but it will probably be limited to use in patients whose examination by push enteroscopy was negative and who have serious coexisting conditions that preclude intraoperative enteroscopy. Intraoperative enteroscopy permits the visualization of the small intestine through the use of an endoscope (or standard colonoscope) that is advanced through the small bowel during laparotomy. It has been reported to detect abnormalities in up to 70 to 100 percent of patients although this high rate of detection has not been duplicated in the experience of all clinicians.

Treatment and Outcome

Vascular ectasias of the small bowel are the most common source of bleeding in patients with obscure gastrointestinal bleeding. Endoscopic and surgical therapy is most successful in those with large, focal vascular ectasias. Because vascular ectasias are often diffuse (limiting endoscopic and surgical intervention), hormonal therapy with compounds of estrogen and progesterone has been tried as a medical alternative. Although positive experiences with such pharmacologic therapy have been reported, controlled trials have failed to show an advantage. Nevertheless, for patients with severe, recurrent bleeding from vascular ectasias, mixed hormonal therapy should be considered.

Specific treatment for patients with obscure bleeding, as for patients with fecal occult-blood loss and iron-deficiency anemia, varies according to the abnormality identified. Enteroscopy, which often reveals putative bleeding lesions, has not always led to improved outcomes. Enteroscopic cauterization of vascular ectasias can lead to a reduction in blood-transfusion requirements. Unfortunately, in only about 50 percent of patients treated at the time of intraoperative enteroscopy will bleeding stop, so this intervention is not ideal. Thus, further work is required to help determine which lesions respond best to endoscopic and surgical intervention. Finally, the care of patients with obscure gastrointestinal bleeding requires an experienced and highly dedicated team of care givers and endoscopic and imaging experts.

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