Obscure gastrointestinal bleeding

This is one of a series of statements discussing the utilization of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this guideline, a MEDLINE literature search was performed, and additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts.

Guidelines for appropriate utilization of endoscopy are based on a critical review of the available data and expert consensus. Further controlled clinical studies are needed to clarify aspects of this statement, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations.

BACKGROUND

Obscure GI bleeding (OGIB) has been defined as bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation, including colonoscopy and/or upper endoscopy (EGD). There are little data on the natural history of this disorder, including prognosis and clinical outcomes. As a result, there is no single cost-effective approach to the management of these patients. It has been estimated that approximately 5% of GI bleeding occurs between the ligament of Treitz and the ileocecal valve. Angiodysplasia of the small bowel account for 30% to 40% of GI bleeding and are the most common source in older patients. Between the ages of 30 and 50, tumors such as leiomyomas, carcinoid tumors, lymphomas, and adenocarcinomas predominate. Younger patients most commonly bleed from Meckel’s diverticula-associated ulceration. Non-steroid anti-inflammatory drug (NSAID) enteropathy has been associated with erosions, ulcers, and strictures of the small bowel and, therefore, can be a potential cause of OGIB. Less common causes of OGIB include hemosuccus pancreaticus, Strongyloides stercoralis infection, pelvic radiotherapy, pseudoxanthoma elasticum, and Dieulafoy’s lesions.

Obscure GI bleeding can be divided into that which is occult in manifestation and that which is overt. Occult OGIB is manifested by recurrent iron-deficiency anemia (IDA) and/or recurrent positive fecal occult blood test results. Overt OGIB presents as gross or visible recurrent bleeding with melena or hematochezia. Repeat studies of the upper and lower GI tract should be performed before evaluation of the small bowel because of the significant miss rate on initial endoscopy. Commonly missed lesions in the upper tract include Cameron’s erosions in large hiatal hernias, peptic ulcer disease, and angiodysplasia. Colonoscopy with ileoscopy should be performed in cases of OGIB to rule out missed lesions in the colon as well as an occult ileal process. Lesions most often missed in the colon include angiodysplasia and neoplasms.

DIAGNOSTIC TESTS

Upper endoscopy

EGD is indicated for the initial evaluation of a suspected upper GI source of bleeding. A repeat examination may yield a source even when the initial EGD was negative. One study suggested that up to 64% of lesions identified with a push enteroscope were within reach of a standard endoscope. Conditions that might increase the yield of repeat EGD include large hiatal hernias and a history of NSAID use. If GI bleeding has not been documented clearly in the presence of IDA, one must consider a small bowel biopsy to evaluate for celiac sprue at the time of EGD, although studies are mixed on the yield of small bowel biopsy in IDA.

Push enteroscopy

Push enteroscopy (PE), whereby a long endoscope is inserted into the jejunum through the mouth, is used to evaluate a larger segment of the small intestine, particularly in the setting of OGIB. The diagnostic yield is approximately 40% to 65%. An advantage of PE is that it allows not only for diagnosis but also for therapeutic intervention. Lesions may be biopsied, and bleeding can be treated with electrocoagulation. A prospective study compared PE with EGD after a normal colonoscopy for evaluation of IDA. It was found that PE increased the diagnostic yield from 41% to 67% and was associated with a lower cost. A retrospective study
noted positive findings in 78% and an improvement in clinical outcomes, based on hospitalization days and transfusions.\(^{22}\) One study also found PE superior to small bowel follow-through (SBFT) for OGIB.\(^{23}\) Studies suggest that PE changes management in 40% to 73% of patients.\(^{14,15}\) For occult OGIB, a retrospective study in 83 patients noted a diagnostic yield of 59%.\(^{24}\) Angiodysplasia was the most common lesion identified and was treated with bipolar electrocoagulation, when possible, and/or hormonal therapy. Long-term outcome in this study (mean follow-up, 12.2 months) was considered to be “good” in only 50%. However, PE may be effective in improving clinical outcomes by reducing the transfusion requirements and improving quality of life.\(^{25}\)

Sonde enteroscopy consists of a long endoscope measuring 270 to 400 cm, which advances through the small intestine by using normal peristalsis.\(^{26}\) This technically challenging procedure is not used often because of the considerable time it takes to perform the procedure and inability to perform therapy or biopsy if a lesion is found.

**Capsule endoscopy**

Wireless video capsule endoscopy (CE) is a new technology that enables endoscopic evaluation of the small intestine.\(^{27,28}\) The capsule, measuring 26.4 mm long and 11 mm in diameter, is ingested after an 8-hour fast and progresses through the small intestine propelled by peristalsis. The capsule is composed of a lens, a light source, a complementary metal-oxide semiconductor chip (image acquisition), a battery, and a transmitter. Images are transmitted two per second to a recording device worn on a belt and then downloaded to a computer workstation where they are viewed by using proprietary software.\(^{29}\) This new technology has the potential to identify a source of bleeding in patients with OGIB and/or IDA.\(^{30,31}\) Several early studies have shown that this technology is useful in the evaluation of OGIB and may have a higher diagnostic yield in the small intestine compared with PE and SBFT.\(^{32-37}\) There also are data to suggest that CE is complementary to PE, since a significant number of lesions are missed in the esophagus and stomach.\(^{32}\) By using CE, a potential source of bleeding will be found in about half of patients with negative evaluations, including PE. Limitations of CE include its inability to provide therapy or to locate precisely the site of a lesion. The capsule may become entrapped, requiring surgical removal and should be used with caution in patients with potentially obstructing lesions, strictures, dysphagia,\(^{38}\) or prior major abdominal surgery. A pre-CE small bowel contrast study has been advocated to rule out an obstructing lesion although whether this will decrease CE complications is unclear.\(^{39}\) Further studies are needed to clarify CE’s role in OGIB and to determine its impact on clinical outcomes.

**Radiology**

**Radiographic contrast studies of the small bowel.** Small bowel follow-through has been used to screen the small intestine for a potential bleeding source. A previous study comparing SBFT with PE suggested that the yield of PE was superior.\(^{23}\) The yield of SBFT in the evaluation of OGIB ranges from 0% to 5.6%.\(^{40,41}\)

Enteroclysis allows more detailed visualization of the small bowel than does SBFT. This is accomplished by the passage of a naso-enteric tube into the proximal small bowel, followed by the installation of contrast material.\(^{42}\) One retrospective study in 128 patients with OGIB found an overall yield of 21% in identifying confirmed or highly probable lesions.\(^{43}\) Tumors involving the small bowel were found in 13%. Another study suggested a lower yield,\(^{44}\) although the yield improved in a subset of patients with unequivocally normal EGD and colonoscopy. Most studies suggest that enteroclysis has a higher diagnostic yield compared with SBFT.\(^{45,46}\) The sensitivity for enteroclysis to detect angiodysplasia is low.\(^{43}\) In patients with a negative PE, enteroclysis identifies a bleeding source in 8%.\(^{47}\) Significant patient discomfort may limit the clinical applicability of this procedure.

**Nuclear scans.** Radioisotope bleeding scans may be helpful in cases of overt OGIB if the bleeding rate is in the range of 0.1 to 0.4 mL/min. The technetium Tc 99m-labeled red blood cell scan is used most commonly. This is most often used in the actively bleeding patient where no source has been identified on routine EGD and colonoscopy. These scans can aid in localization of bleeding that can then be verified either endoscopically or angiographically, or can guide curative surgery. Early blush appears to be more accurate than delayed positivity, at least in lower GI hemorrhage.\(^{48}\) Although relatively sensitive, nuclear medicine scans can only identify a general area of bleeding and are limited in terms of directing treatment. In one study evaluating technetium-labeled red blood cell scintigraphy, the test failed to localize hemorrhage in 85% of cases and did not adequately screen patients for angiography.\(^{49}\) In the appropriate setting, Meckel’s scanning also is a useful test for OGIB. It uses technetium Tc 99m-pertechnetate and has a sensitivity of 75% to 100%.\(^{50}\) However, a positive scan only suggests the presence of gastric mucosa and not a definitive bleeding source.

**Angiography.** Angiography also may be helpful in the evaluation of overt OGIB, if the bleeding rate is
greater than 0.5 mL/min. Bleeding is manifested as active extravasation into the lumen of the bowel. Unfortunately, little data are available in OGIB. Although technically less sensitive than nuclear scans, it has the potential for being more effective at localizing the bleeding site. In a study of visceral angiography involving 36 patients, a diagnostic yield of 44% was noted. There were no false positives, but there were three false negatives. Also, there is evidence to suggest that if the initial angiogram is negative, a repeat study may be of benefit. Angiography is often used as a localization technique for embolization or before surgery. In patients who are going to surgery, preoperative selective angiographic catheter placement, in conjunction with intra-operative methylene blue dye injection, may be useful to allow more precise localization of the bleeding so that a minimal segment of small bowel can be resected. Angiography also has the potential to identify non-bleeding angiodysplasia and/or tumors.

Helical CT angiography is a newer technique where the abdominal aorta is catheterized, followed by intra-arterial injections of contrast medium. The site of hemorrhage is identified by extravasation of contrast medium, resulting in a hyper-dense area in the intestinal lumen. One study involving 13 patients compared helical CT angiography with conventional angiography and found CT angiography to be easier and faster for localizing OGIB and to be useful as a guide to subsequent selective conventional angiography.

Provocative testing

To avoid false-negative studies, some investigators have advocated the use of vasodilators (tolazoline, nitroglycerin), anticoagulants (heparin), and/or fibrinolytics (urokinase, streptokinase) to induce bleeding while bleeding scans or angiography are performed. While some investigators have reported an increased diagnostic yield, others have found a more limited benefit and have questioned the cost-effectiveness and safety of this approach.

Surgery

Intra-operative enteroscopy. Intra-operative enteroscopy (IOE) during laparotomy is typically used as a last resort in patients with OGIB requiring multiple transfusions and/or repeated hospitalizations. Endoscopic evaluation has been performed orally, rectally, or through enterostomies at the time of laparotomy. No controlled trials exist comparing this procedure with other procedures for OGIB, but it appears to be safe and effective. An earlier study involving 44 patients showed that IOE found a source of bleeding in 70%, although the therapeutic efficacy was only 41%. One study suggested a success rate of 82% when used in conjunction with other localization techniques. A retrospective study evaluating 12 patients found that the terminal ileum was reached in 93% of patients, with an overall diagnostic yield of 58%. More recently, a study in 25 patients found that IOE detected a lesion in 16 of 20 patients in whom the cause of bleeding was unknown before surgery. The bleeding rate was 30% at a mean follow-up of 19 months.

Diagnostic approach

In patients with occult OGIB and no lesions found on repeat EGD and colonoscopy, who have recurrent anemia despite iron supplementation, it is reasonable to proceed with further evaluation of the small intestine. Options include capsule endoscopy, push enteroscopy, or barium radiography (SBFT or enteroclysis). The choice among these tests and the order in which they should be performed has not been determined. If these tests are negative, then the benefit of further evaluation must be weighed against the potential risks. If the clinical situation warrants further evaluation because of frequent hospitalizations and transfusions, then one must consider angiography and/or intra-operative enteroscopy.

In the case of overt OGIB, if the patient is not actively bleeding at the time of evaluation, one should proceed as described above for occult OGIB. If the patient is actively bleeding, it is reasonable to proceed with repeat EGD, PE, and/or colonoscopy. If negative, one must consider a nuclear scan, angiography, and/or CE based on the rate of bleeding and availability of these tests. A Meckel’s scan should be considered, particularly in younger patients. If bleeding continues, then repeat angiography should be considered as well as IOE.

Therapeutic approach

Therapy for OGIB depends on the etiology. If a tumor is identified, surgical resection is indicated. Angiodysplasia is effectively treated with electocautery or argon plasma coagulation if it is localized and within reach of the endoscope. There is evidence to suggest that this treatment does have a positive impact on clinical outcome, by decreasing blood loss and blood transfusions. If angiodysplasia is identified diffusely throughout the GI tract, medical therapy including adequate iron supplementation (oral or parenteral), blood transfusion, or hormonal therapy is preferred. Prospective longitudinal observational studies had suggested that combination estrogen/progesterone therapy may be beneficial. However, a recent multicenter randomized
trial found no benefit for hormonal therapy. Octreotide has shown some benefit, but has not been extensively studied.

**SUMMARY**

For the following points: (A), prospective controlled trials; (B), observational studies; (C), expert opinion.

- OGIB comprises approximately 5% of all patients with GI bleeding, with the majority of lesions located in the small intestine. (B)
- Common small intestine lesions include angiodysplasia, tumors, NSAID enteropathy, and Meckel’s diverticulum-associated ulcers. (B)
- Obscure GI bleeding can either be occult, manifesting as IDA, or overt, manifesting as hema-
tochezia or melena. (C)
- Once upper and lower GI lesions have been excluded by carefully performed repeated EGD and colonoscopy to the terminal ileum, examination of the small intestine is warranted. (C)
- Diagnostic tests include PE, CE, barium studies (SBFT or enteroclysis), nuclear medicine testing, angiography, and IOE. (B) While large published comparative trials are lacking, PE has been shown to be superior to EGD and SBFT, and CE is similarly superior to SBFT and possibly to PE as well. (A)
- Choice among tests has yet to be established and will be dictated by the clinical scenario, availabil-
ity, and local expertise. (C)
- Intra-operative enteroscopy is reserved for patients with refractory severe recurrent bleeding, transfusion dependency, or those in whom a lesion is identified that cannot be treated by using PE or colonoscopy with ileoscopy. (C)
- Once a diagnosis is established, appropriate medical and/or surgical therapy must be individualized. (C)

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