The role of endoscopy in the management of obscure GI bleeding

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, we performed a search of the medical literature by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines were drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations are based on reviewed studies and are graded on the strength of the supporting evidence (Table 1). The strength of individual recommendations is based both upon the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as “we suggest,” whereas stronger recommendations are typically stated as “we recommend.”

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient’s condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

BACKGROUND

Obscure GI bleeding (OGIB) is defined as occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including colonoscopy and EGD. Overt OGIB is defined as visible GI bleeding (eg, melena or hematochezia) and can be categorized further as active (ie, evidence of ongoing bleeding) versus inactive bleeding. Although there are no standard criteria for defining occult OGIB, for the purposes of this document, OGIB is designated as occult when there is no evidence of gross bleeding (eg, unexplained iron deficiency anemia suspected to be caused by GI blood loss).

Approximately 5% of GI bleeding occurs between the ligament of Treitz and the ileocecal valve. Angiectasias of the small bowel account for 30% to 40% of OGIB and are the most common source in older patients. Nonsteroidal anti-inflammatory drug enteropathy and inflammatory bowel disease have been associated with erosions, ulcers, and strictures of the small bowel and therefore are also causes of OGIB. Other causes include tumors, which are considered the most common source of OGIB in patients <50 years old (eg, leiomyomas, carcinoid tumors, lymphomas, and adenocarcinomas). Meckel’s diverticular–associated ulceration (especially in younger patients), radiation enteropathy, Dieulafoy’s lesions, hemオスCUS pancreaticus, and small-bowel varices.

OGIB may occur anywhere throughout the GI tract. Prior to evaluation of the small bowel, upper and lower GI tract endoscopies are often repeated in patients with OGIB because substantial initial endoscopic miss rates have been reported. Newer endoscopic evaluation techniques for the small bowel include video capsule endoscopy (VCE) and deep enteroscopy. The diagnostic yield and therapeutic capabilities of these technologies have been compared with the conventional approaches of push enteroscopy (PE), intraoperative enteroscopy, and radiologic methods and show promise in producing superior yields. However, the most cost-effective approach to the management of patients with OGIB has not been fully determined. This guideline is an update of a prior ASGE document on the management of OGIB. In this guideline, we describe the performance characteristics of various endoscopic and nonendoscopic tests available to evaluate patients with OGIB, followed by a suggested diagnostic approach.

DIAGNOSTIC TESTS FOR THE EVALUATION OF OGIB

EGD and colonoscopy

EGD is indicated for the initial evaluation of a suspected upper GI source of bleeding. Early endoscopic intervention has been associated with lower hospital cost; however, optimal timing after an episode of bleeding and the impact of early endoscopy on diagnostic yield have not been rigorously studied. Repeat examination may yield a source even when the initial EGD is negative. For example, in studies of patients with OGIB that used small-bowel technologies, sus-
Table 1. GRADE system for rating the quality of evidence for guidelines

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Definition</th>
<th>Symbol</th>
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<tbody>
<tr>
<td>High quality</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
<td>☢☢☢☢</td>
</tr>
<tr>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
<td>☢☢☢</td>
</tr>
<tr>
<td>Low quality</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
<td>☢☢</td>
</tr>
<tr>
<td>Very low quality</td>
<td>Any estimate of effect is very uncertain.</td>
<td>☢</td>
</tr>
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patients with iron deficiency anemia found that 35% of second VCE studies showed positive or suspected findings, and 10% resulted in changed management.

Deep enteroscopy

Deep enteroscopy encompasses both BAE (ie, single and double balloon systems) and spiral enteroscopy. Total enteroscopy may be achieved through a combination of antegrade and retrograde approaches. A detailed discussion of BAE can be found in an ASGE Technology Evaluation Status report.

In multiple large studies of patients with OGIB who underwent BAE, the diagnostic yield ranged from 43% to 81%. Treatment success rates of between 43% and 84% have been reported. Few studies have evaluated a combined antegrade and retrograde approach. Multiple studies have been conducted to compare BAE with PE and VCE. In one controlled, prospective trial of 52 patients with OGIB, BAE was superior to PE in length of small bowel visualized (230 cm vs 80 cm, \( P < .0001 \)) and diagnostic yield (63% vs 44%, \( P < .0001 \)).

A meta-analysis of 11 studies comparing the yield of VCE and BAE, including 375 patients with small-bowel disease, reported comparable diagnostic yields (60% vs 57%, respectively). The pooled yield for angiectasias in the 350 patients with OGIB was identical, with 24% for both VCE and BAE. A more recent retrospective study of 162 patients with OGIB also suggested no significant difference in overall diagnostic yield between VCE (54%) and BAE (64%). Similar results were found in another meta-analysis. In this study, a subanalysis of 191 patients undergoing only antegrade or retrograde BAE indicated a significantly higher yield of VCE vs BAE (62% vs 50%, \( P < .05 \)). However, when both antegrade and retrograde BAEs were performed in 24 patients, the yield of BAE was higher than that of VCE (88% vs 46%, \( P < .01 \)). Finally, in a retrospective study investigating the role of BAE prior to intraoperative endoscopy for those in whom BAE identified a source (53/56 patients), subsequent intraoperative endoscopy was negative in only one patient.

A modeled cost-minimization analysis of the management of occult OGIB proposed BAE as the most cost-effective initial test after standard endoscopy if the goal is treatment or definitive diagnosis. Another model suggested that initial BAE was a cost-effective approach for patients with OGIB who likely have angiectasias in the small bowel accessible with a single antegrade approach. Spiral enteroscopy, in which a specialized spiral overtube is placed over a pediatric colonoscope, has been recently described. However, comparative studies regarding existing deep enteroscopy techniques are lacking.

Radiographic contrast studies of the small bowel

Until recently, small-bowel follow-through was routinely used to screen the small intestine for a potential bleeding source. The yield of small-bowel follow-through in the evaluation of OGIB is extremely low (0%-5.6%). and a comparison of small-bowel follow-through and PE in 40 patients demonstrated a superior yield of PE (2.5% vs 35%, respectively). Enteroctasis allows more detailed visualization of the small bowel, with utility in detection of inflammatory bowel disease and neoplasm in patients with OGIB. However, enteroclysis has not been shown to be useful in the detection of angiectasias, and it identifies a bleeding source in only 8% of patients with negative PE. In patients with active bleeding, the use of contrast material may complicate subsequent evaluation with endoscopy or other radiologic imaging tests. Both small-bowel follow-through and enteroclysis should be considered of limited value in the evaluation of GI bleeding.

Nuclear scans

Radioisotope bleeding scans may be helpful in cases of overt OGIB if the bleeding rate is at least 0.1 to 0.4 mL/minute. The technetium 99m-labeled red blood cell scan is used most commonly in the actively bleeding patient in which no source has been identified on EGD or colonoscopy. These scans can aid in the localization of bleeding that can then be verified with repeat endoscopy, angiography, or surgery. An early blush appears to be more accurate than delayed positivity in lower GI hemorrhage. Although sensitive, nuclear medicine scans can identify only a general area of bleeding and are very limited in terms of directing treatment. Results from studies of technetium-labeled red blood cell scintigraphy vary widely and may reflect differences in patient selection and timing of the study in relation to clinical presentation. In one study of 103 patients with OGIB, scintigraphy failed to localize hemorrhage in 85% of cases and was a poor predictor of a positive angiographic study. In another retrospective study of 92 patients with OGIB, 25% had a definitive bleeding source found and confirmed with further diagnostic procedures. In pediatric patients and young adults, Meckel's scanning is a useful test for overt OGIB, with a sensitivity ranging between 50% and 91% for ectopic gastric mucosa.

Angiography

Angiography also may be helpful in the evaluation of overt OGIB if the bleeding rate is >0.5 mL/minute. Although technically less sensitive than nuclear scans, it is more effective at localizing the bleeding site. There are limited data on the diagnostic yield of angiography in OGIB. Reported yields range from 27% to 77% in lower GI bleeding. There is some evidence that if the initial angiogram is negative, a repeat study may be of benefit. Angiography carries the potential for therapy, including superselective mesenteric embolization.

CT imaging

CT enterography is a noninvasive imaging technique that uses neutral intraluminal and intravenous contrast to
evaluate the small bowel and has been particularly useful in enhancement of the small-intestine wall in inflammatory bowel disease. Recent improvements from single phase (for inflammatory bowel disease) to multiphasic imaging allow detection of a vascular blush, which is important for recognition of small vascular lesions. Initial experience with 64-section, multiphase CT enterography at one center reported successful identification of a bleeding source in 45% of 22 outpatients with OGIB, including 3 lesions that were missed on VCE. In a study of 26 patients with massive GI bleeding, a multiple-detector CT had an accuracy of 89% and positive predictive value of 95%. The location of lesions corresponded exactly to that of active bleeding on angiograms in all patients.

CT angiography visualizes extravasation of contrast medium into the intestinal lumen in order to identify the source of OGIB. In one study of 18 patients, CT angiography was found to be easier and faster for localizing OGIB than conventional angiography and useful as a guide to subsequent selective conventional angiography.

**Intraoperative enteroscopy**

Intraoperative enteroscopy during laparotomy or laparoscopy is typically used as a last resort in patients with OGIB requiring multiple transfusions and/or repeated hospitalizations. Endoscopic evaluation can be performed orally, rectally, or through enterotomies at the time of surgery. This procedure appears to be safe and effective, although there are no controlled trials comparing intraoperative enteroscopy with other therapeutic procedures for OGIB. Early studies, before the advent of BAE and VCE, have shown diagnostic yields of intraoperative enteroscopy in GI bleeding to be between 58% and 82%. The role of intraoperative enteroscopy in coordination with VCE was evaluated in a recent study of 18 patients with OGIB. In the 15 patients with lesions on VCE, intraoperative enteroscopy yielded treatment in 13 (87%), whereas in the 3 negative VCE studies, the intraoperative enteroscopy result was normal, suggesting an important directive role for VCE.

**DIAGNOSTIC APPROACH TO PATIENTS WITH OGIB**

The diagnostic approach to patients with OGIB depends upon clinical factors, such as the age of the patient, quality of the prior endoscopic evaluation, and the overt or occult status of the bleeding. Clinical clues, such as nasogastric tube aspirates and the nature of the bleeding (eg, melena vs hematochezia) can help direct the choice of endoscopic tests. In addition, local availability of procedures, patient preferences, physician expertise, risks, and costs are also important determinants of management. Resuscitation is key to the management of all patients with GI bleeding. Patients on antithrombotic therapy should be managed according to recent ASGE guidelines. A suggested algorithm for management is shown in Figures 1 and 2.

**Overt OGIB**

**Active overt OGIB.** If the clinical presentation is compatible with upper GI bleeding (eg, hematemesis or blood in the nasogastric tube aspirate), then urgent EGD should be performed. Otherwise, recommended diagnostic options include PE, repeat colonoscopy, VCE, and tagged red blood cell scintigraphy. Other options include deep enteroscopy, CT enterography, or CT angiography. Because these tests are complementary, a combination may be required. Furthermore, in patients with surgically altered anatomy in whom portions of the GI tract are bypassed (eg, Roux-en-Y gastrojejunostomy), deep enteroscopy is the preferred endoscopic modality to assess the excluded luminal segment, because other approaches cannot reach these areas. For those patients who present with massive bleeding, endoscopy with therapeutic capability (eg, PE or colonoscopy) or referral for angiography are recommended. If these tests are negative, then management as described for inactive overt OGIB is suggested.

**Inactive overt OGIB.** For those patients with a history of recent overt OGIB who now have no evidence of ongoing bleeding (eg, normal-appearing stools), recommended diagnostic options include VCE, deep enteroscopy, PE, and/or colonoscopy. Because these tests are complementary, a combination may be required. Other options include CT enterography or CT angiography. If these tests are negative, and bleeding recurs, then provocative testing (as described later) or intraoperative enteroscopy may be appropriate.

**Occult OGIB**

In patients with occult OGIB, options include repeat endoscopy (ie, EGD and colonoscopy) and evaluation of the small bowel. In some situations, a trial of empiric iron supplementation prior to further diagnostic work-up may be appropriate. EGD should be considered when an upper GI lesion is suspected, such as in patients with risk factors for mucosal disease caused by nonsteroidal anti-inflammatory drug use, or if details of the prior EGD are uncertain. Repeat colonoscopy should be considered when the quality of the bowel preparation on the initial examination was suboptimal or when other questions about the quality of the examination exist. Additionally, when there is clinical suspicion for missed colonic lesions, repeat colonoscopy also may be performed.

To evaluate the small bowel for occult OGIB, VCE is recommended as the first diagnostic test if no contraindications exist. Other options for small-bowel examination include deep enteroscopy or PE. Barium radiography studies, such as small-bowel follow-through and enteroclysis, and cross-sectional imaging, such as single-phase
CT enterography, have low diagnostic yields. Several authors have suggested initial VCE followed by therapeutic BAE, if positive, as the best strategy for increased yield and improved treatment success.\textsuperscript{91-94} If VCE is performed, and a culprit lesion is found, appropriate endoscopic, angiographic, medical, or surgical intervention should be instituted. If VCE is negative, the patient’s clinical status should dictate the next step. Stable patients may be observed without further evaluation. For patients who need further work-up or have recurrent bleeding, a selection of diagnostic modalities exists. Patients who did not have a second-look endoscopy may, at this point, benefit from repeat EGD and/or colonoscopy. A repeat VCE also may be informative, particularly in patients whose presentations change from occult to overt bleeding or those with decreases in hemoglobin levels of $\geq 4$ g/dL.\textsuperscript{44}

**Provocative testing**

To avoid false-negative studies, vasodilators (eg, tolazoline or nitroglycerin), anticoagulants (eg, heparin), and/or fibrinolitics (eg, urokinase or streptokinase) have been used to induce bleeding during bleeding scans, angiography, or endoscopic studies for the evaluation of OGIB.\textsuperscript{95-98} Although some investigators have reported an increased diagnostic yield,\textsuperscript{95} others have found a more limited benefit\textsuperscript{96} and have questioned the cost-effectiveness and safety of this approach.\textsuperscript{97} To determine the effect on predictive value, a study of 18 patients with OGIB found that heparinization improved the diagnostic yield of angiography from 33\% to 67\% with no reported complications.\textsuperscript{98} There is currently insufficient evidence to support or refute the effectiveness and safety of provocative testing in the evaluation of OGIB.

**THERAPEUTIC APPROACH TO PATIENTS WITH OGIB**

Therapy for OGIB depends on the etiology of the bleeding. Lesions found within the reach of a standard endoscope can be treated with appropriate therapy such as electrocautery, argon plasma coagulation, injection therapy, mechanical hemostasis (eg, hemoclips or bands), or a combination of these techniques. More distal vascular lesions, such as angiectasias, may be approached for therapy via PE or deep enteroscopy, depending upon location. There is evidence that treatment has a positive impact on clinical outcome, by decreasing blood loss and need

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**Figure 1.** Suggested diagnostic approach to overt obscure GI bleeding. Dashed arrows indicate less-preferred options. Positive test results should direct specific therapy. Because diagnostic tests can be complementary, more than one test may be needed, and the first-line test may be based upon institutional expertise and availability. PE, push enteroscopy; OGIB, obscure GI bleeding.
Masses or tumors likely require surgical intervention or intraoperative enteroscopy, and management of massive bleeding should be coordinated with surgery and interventional radiology. Oral or intravenous iron supplementation or transfusions may be required in some patients. Hormonal therapy for angiectasias is controversial but has largely been abandoned because of lack of beneficial effect. Long-acting octreotide has shown some benefit in eliminating the need for chronic blood loss from angiectasias, but this has not been extensively studied.

**RECOMMENDATIONS**

1. After appropriate resuscitation, we recommend emergent endoscopy or angiography in patients with massive OGIB. 

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Figure 2. Suggested diagnostic approach to occult obscure GI bleeding. Dashed arrows indicate less-preferred options. Positive test results should direct specific therapy. Because diagnostic tests can be complementary, more than one test may be needed, and the first-line test may be based upon institutional expertise and availability. *Hb*, hemoglobin.
2. We recommend urgent EGD in patients with active overt OGIB and a clinical presentation suggestive of upper GI bleeding. For those with signs or symptoms of lower GI bleeding, we suggest repeating colonoscopy. Otherwise, recommended diagnostic options include PE, VCE, and tagged red blood cell scintigraphy.

3. For those patients with inactive overt OGIB, we suggest VCE, deep enteroscopy, PE, and/or colonoscopy.

4. In patients with occult OGIB and a high clinical suspicion for an upper GI lesion, we suggest repeating EGD before small-bowel evaluation. For those with a suspected lower GI lesion, we suggest repeating colonoscopy prior to small-bowel evaluation. In the absence of localizing signs or symptoms, we recommend small-bowel evaluation.

5. We recommend VCE as the first-line diagnostic tool for evaluation of the small bowel in patients with OGIB.

6. We suggest that in select circumstances (e.g., where there is a high level of suspicion of small-bowel angiectasias or in patients with surgically altered anatomy), deep enteroscopy may be considered as the initial small-bowel diagnostic procedure in patients with OGIB.

7. We recommend that patients with occult OGIB and a negative VCE evaluation who remain clinically stable be treated with iron therapy if evidence of iron deficiency is present.

8. We suggest that, in patients with negative VCEs and continued bleeding, repeat VCE be considered, particularly if the clinical state changes from obscure to overt bleeding or if the hemoglobin level drops by $\geq 4$ g/dL.

9. We suggest that small-bowel follow-through and enterolysis have a limited role in the evaluation of OGIB, given their low yields for identifying lesions.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; BAE, balloon-assisted enteroscopy; OGIB, obscure GI bleeding; PE, push enteroscopy; VCE, video capsule endoscopy.

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