49 Obscure GI Bleed: How to Investigate?

Abstract: Obscure gastrointestinal bleeding (OGIB) has been defined as bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation. The diagnosis of OGIB is often a clinical challenge potentially leading to substantial workup and invasive testing. After a negative UGI endoscopy and colonoscopy, the small bowel is usually considered the source of bleeding. Approximately 5% of gastrointestinal(GI) bleeding occurs between the ligament of Treitz and the ileocecal value. Obscure GI bleeding can be characterized as overt (melena, hematochezia, hematemesis) or occult (iron deficiency anemia (IDA) and/or recurrent positive fecal occult blood test positive). Common small intestine lesions include angiodysplasia, tumors, NSAID-enteropathy, and Meckel's diverticulum-associated ulcers. Diagnostic tests include push entroscopy (PE),double Ballon Enteroscopy (DBE),capsule endoscopy (CE), barium studies (small bowel follow though or enteroclysis), nuclear medicine testing, angiography and intraoperative endoscopy (IOE). Diagnostic yield of CE was superior to push enteroscopy, small bowel radiography, CT-entroclysis, mesentric angiography and small bowel MRI, is even better with DBE. Choice among tests has yet to be established and will be dictated by the clinical scenario, availability, and local expertise.

BACKGROUND

Obscure gastrointestinal 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 gastrointestinal (UGI) endoscopy.[1] The diagnosis of OGIB is often a clinical challenge potentially leading to substantial workup and invasive testing.[2] After a negative UGI endoscopy and colonoscopy, the small bowel is usually considered the source of bleeding. 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 gastrointestinal (GI) bleeding occurs between the ligament of Treitz and the ileocecal value.[3] Angiodysplasia of the small bowel account for 30 to 40%.[4] Of GI bleeding and are the most common source in older patients.[5] 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.[6] Nonsteroid 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.[7,8] Less common causes of OGIB include hemosuccus pancreaticus,[9] *Strongyloides stercoralis* infection,[10] pelvic radiotherapy,[11] pseudoxanthoma elasticum,[12] and Dieulafoy's lesions.[13]

Obscure GI bleeding can be characterized as overt (melena, hematochezia, hematemesis) or occult (iron deficiency anemia (IDA) and/or recurrent positive fecal occult blood test positive). 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 lesion in the upper tract include Cameron's erosions in large hiatal hernias, peptic ulcer disease, and angiodysplasia. Colonoscopy with ileoscopy should be performed in case 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 Gastrointestinal Endoscopy

Upper GI endoscopy 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 UGI endoscopy was negative.[14-17] One study suggested that up to 64% of lesions identified with a push enteroscope were within reach of a standard endoscope.[14] Conditions that might increase the yield of repeat UGI endoscopy include large hiatal hernias and a history of NSAID use.[15] 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 UGI, although studies are mixed on the yield of small bowel biopsy in IDA.[18,19]

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.[20] The diagnostic yield is approximately 40 to 65%.[14,17,21] 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. Studies suggest that PE changes management in 40 to 73% of patients.[15-16] PE may be effective in improving clinical outcomes by reducing the transfusion requirements and improving quality of life.[22]

Sonde enteroscopy consists of a long endoscope measuring 270 to 400 cm, which advance through the small intestine by using normal peristalsis.[23] 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 (Fig. 1)

Wireless video capsule endoscopy (CE) is a new technology that enables endoscopic evaluation of the small intestine.[24,25] The widespread acceptability and utility of CE in OGIB is evident from the fact that the number of publication in peer reviewed journals have steadily increased since the first publication in 2000.[25] 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.[26] This new technology has the potential to identify a source of bleeding in patients with OGIB and/or IDA.[27,28] Several studies have now shown that capsule endoscopy (CE) is superior to small bowel barium radiography, enteroclysis, and push enteroscopy in detecting the source of OGIB.[29-36] Two recent meta-analysis of prospective studies have demonstarted an additional 30% yield of CE over these modalities for clinically significant findings, in patients with OGIB.[37,38] However, its superiority over angiographic modalities remains to be fully investigated. Recently, several studies have compared CE with Double Balloon Enteroscopy (DBE). The detection rate of potential bleeding source was significantly better with CE than DBE.[39] However these two procedures should be considered complimentary and not competitve. The usefulness of repeat CE in OGIB has been reported. In a retrospective study, repeat CE in patient with OGIB ahowed additional finding in 75% patients.[40] However this data needs further validation with prospective studies. In two recent studies, the yield of CE in

iron deficiency anemia using strict diagnostic criteria varied from 57 to 80%.[41,42] The overall positive diagnostic yield of CE in OGIB is around 50%. Subgroup analysis show that the diagnostic yield is much higher, reaching 92.3% in patients with onging overt GI bleeding compared with 44.2% in obscure occult bleeding and 12.9% in past OGIB. The ICCE consensus meeting on OGIB recommended that CE should be performed early (preferably within 2 wk) in the workup of patients with OGIB.[43] 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,[44] or prior major abdominal surgery.

Double Balloon Enteroscopy (DBE) (Fig. 2)

DBE is a novel endoscopic technique that allows for visualization of the entire small bowel facilitating diagnosis, tissue acquisition, and therapeutic interventions of abnormalities detected which were previously inaccessible to existing endoscopic technology. Diagnostic yield for DBE is 60-80% in OGIB, evaluating the role of DBE in various small bowel diseases.[45-47] Compared with CE, DBE has several advantages including improved visualization through the capability to insufflate air and irrigate and suction any obscuring mucus/material, a focused examination of any abnormality visualized, obtaining tissue samples, and therapeutic intervention. The use of devices such as argon plasma coagulation, snare electrocautery, and even retrieval of retained capsules with DBE have been reported.[46-48] In a recent prospective study comparing CE with DBE in 35 patients with OGIB the diagnostic detection rate was 80% using CE and 60% using DBE.[48] However, DBE made it possible to effectively treat 50% of patients with OGIB by argon plasma coagulation. Matsumoto et al. compared CE and DBE in patient with OGIB and polyposis.[49] Unlike CE, DBE allows therapeutic interventions. DBE has the promising potential of replacing conventional intraoperative enteroscopy for patients with OGIB who are often difficult and challenging to manage given the frequently unclear etiology of bleeding. Its role in the diagnostic algorithm for OGIB remains to be determined and will be based on the ready availability of this unique technology, operator expertise, studies confirming or refuting the effectiveness of this technology, and cost effective analysis.

Radiology

Small bowel follow-through (SBFT) has been used to screen the small intestine for a potential bleeding source. Enteroclysis allows more detailed visualization of the small bowel than does SBFT. This is accomplished by the passage of a nasoenteric tube into the proximal small bowel, followed by the installation of contrast material. Most studies suggest that enteroclysis has a higher diagnostic yield compare with SBFT.[50-51] The sensitivity for enteroclysis to detect angiodysplasia is low.[52] In patients with a negative PE, enteroclysis identifies a bleeding source in 8%.[53]

Nuclear Scan

Radioisotope bleeding scans may be helpful in case 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 UGI and colonoscopy. 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%.[54] 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. Although technically less sensitive than nuclear scans, it has the potential for being more effective at localization the bleeding site.[55] Also, there is evidence to suggest that if the initial angiogram is negative, a repeat study may be of benefit.[56] In patients who are going to surgery, preoperative selective angiographic catheter placement, in conjunction with intraoperative 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.[57]

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.[58]

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,[59] other have found a more limited benefit [60] and have questioned the cost effectiveness and safety of this approach.[61]

Surgery

Intraoperative enteroscopy (IOE) during laparotomy is typically used as a last resort in patients with OGIB requiring multiple transfusions and/or repeated hospitalizations.[62] Endoscopic evaluation has been performed orally, rectally, or through entrostomies 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.[63] 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.[64]

Diagnostic Approach (Fig. 3)

In patients with occult OGIB and no lesions found on repeat UGI 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 entroscopy, 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 considered angiography and/or intraoperative 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 UGI, PE, and/or colonoscopy. If negative, one must consider a nuclear scan, angiography, DBE 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 depend on the etiology. If a tumor is identified, surgical resection is indicated. Angiodysplasia is effectively treated with electrocautery or argon plasma coagulation if it is

localized and within reach of the endoscope.[65-66] 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.[67-68] However, a recent multicenter randomized trial found no benefit for hormonal therapy.[69] Octreotide has shown some benefit, but has not been exten-sively studied.[70]

SUMMARY

1. OGIB comprises approximately 5% of all patients with GI bleeding, with the majority of lesions located in the small intestine.
2. Obscure GI bleeding can either be occult, manifesting as IDA, or overt, manifesting as hematochezia or melena.
3. Common small intestine lesions include angiodysplasia, tumors, NSAID enteropathy, and Meckel's diverticulum-associated ulcers.
4. Once upper and lower GI lesion have been excluded by carefully performed repeated UGI and colonoscopy to the terminal ileum, examination of the small intestine is warranted.
5. Diagnostic tests includes PE, DBE, CE, barium studies (SBFT or enteroclysis), nuclear medicine testing, angiography, and IOE. While large published comparative trials are lacking, diagnostic yield of CE was superior to push entroscopy, small bowel radiography, CT-Entroclysis, mesentric angiography and small bowel MRI, is even better with DBE. However, these two procedures should be considered complimently and not competitive.
6. Choice among tests has yet to be established and will be dictated by the clinical scenario, availability, and local expertise.
7. Intraoperative 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/DBE or colonoscopy with ileoscopy.
8. Once a diagnosis is established, appropriate medical and/or surgical therapy must be individualized.

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Multiple Choice Questions

1. **Among cases of gastrointestinal bleeding OGIB comprises:**
   A. 5%
   B. 10%
   C. 15%
   D. 20%
2. **Most common site of OGIB:**
   A. Stomach and duodenum
   B. Small bowel
   C. Large bowel
   D. All above
3. **Common small intestine leisons includes:**
   A. Angiodysplasia
   B. Tumors
   C. NSIAD enteropathy
   D. Meckels diverticule asso. ulcerations
   E. All above
4. **Diagnostic tests for OGIB:**
   A. Enteroscopy (Push/balloon)
   B. Capsule endoscopy
   C. Enteroclysis
   D. Radio-nuclear study/angiography
   E. All above
5. **Best method to evaluate small bowel:**
   A. Capsule endoscopy
   B. Double balloon enteroscopy
   C. Enteroclysis
   D. Radio-nuclear study
   E. Angiography
6. **Overall positive yield of capsule endoscopy in OGIB:**
   A. 40%
   B. 50%
   C. 60%
   D. 70%