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# Optimal management of the patient presenting with small bowel bleeding

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ABSTRACT

The management of small bowel bleeding, also known as obscure gastrointestinal bleeding, has changed substantially over the past two decades due to revolutionary technological advances in small intestinal endoscopy. This clinical review will summarize the evolving definition of small bowel bleeding, how to perform a detailed initial assessment of patients with the condition, the strengths and limitations of small bowel endoscopy, and the treatment of small bowel bleeding.



## Introduction

Historically, bleeding from the gastrointestinal tract was classified as upper and lower gastrointestinal bleeding, with the latter defined as bleeding distal to the ligament of Treitz. Using this framework, small bowel bleeding was grouped with colonic bleeding despite the two often having vastly different presentations, etiologies, and managements [1,2]. Accordingly, the definition of lower gastrointestinal bleeding has evolved to only include colonic bleeding, whereas small bowel bleeding is now recognized as a separate clinical entity, often requiring specialized care [2–5]. The anatomic boundaries of small bowel bleeding is between the ligament of Treitz and the ileocecal valve, although some have advocated using the ampulla of Vater as the proximal boundary instead [1,6]. This latter definition is perhaps more clinically useful since it sets the proximal boundary as the limit of insertion during most upper endoscopies, leaving bleeding from the distal duodenum within the purvey of small bowel bleeding.

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding after non-diagnostic upper and lower endoscopies although this definition is also evolving. Most patients with OGIB have bleeding from the small intestine, although approximately 10% have sources in the upper and lower gastrointestinal tract not recognized at the initial endoscopies [7,8]. OGIB can be further classified as "*overt*" when there is visible blood or melena in the stool, or "*occult*", typically in the form of iron deficiency anemia without overt bleeding. However, since the advent of small bowel imaging, in particular capsule endoscopy, the majority of patients with OGIB have a source of bleeding identified. As such, some have recently suggested that the term "*suspected small bowel bleeding*" be used for patients meeting the old definition of OGIB and true OGIB reserved for those who have negative small bowel investigations, including capsule endoscopy [6,9]. For the purposes of this review, we use the term "OGIB" for those with bleeding and negative upper and lower endoscopies as this definition is still widely used today.

## Epidemiology and etiologies of small bowel bleeding

The true prevalence of small bowel bleeding is unknown although a commonly cited value is 5% of all cases of gastrointestinal bleeding [6,10,11]. Unfortunately, this estimate is largely based on single centre surgical case series published over 25 years ago [6,12–14]. In a more rigorous population based study of lower gastrointestinal bleeding conducted in a Health Maintenance Organization in the United States, bleeding from the small bowel was

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responsible for 4% of cases (9/219) [15]. However, even this study was published before the invention of capsule endoscopy and likely underestimates the true prevalence. Ultimately, determining the prevalence of small bowel bleeding has proven difficult due to the evolving definition of small bowel bleeding, paucity of nationally representative datasets, selection bias from tertiary care centres where small bowel endoscopies and studies tend to be performed, and varied presentation of small bowel bleeding where milder cases of occult bleeding may not be investigated beyond upper and lower endoscopy. Similarly, the natural history of small bowel bleeding is largely unknown due to the lack of large scale epidemiological studies. Although information on natural history can often be gleaned from the placebo arms of randomized clinical trials, studies within the field of small bowel bleeding have been too small to draw meaningful conclusions.

The etiologies of small bowel bleeding are distinct from elsewhere in the gastrointestinal tract. Whereas peptic ulcer disease and diverticular bleeding are the most common causes in upper and lower gastrointestinal bleeding, respectively, angioectasias predominate in the small intestine among Western countries [16–18]. Liao and colleagues conducted a systematic review and meta-analysis of 227 studies involving 22,840 small intestinal capsule endoscopies and reported angioectasias to be the most commonly found lesion when the indication was OGIB (50.0%) [18]. The terms “angioectasia” and “angiodysplasia” are synonymous clinically and in the literature, however we prefer the former terminology given there are no dysplastic features histologically. Other causes include NSAID ulcers, Crohn's disease, and malignancy (Table 1).

## Initial assessment of patients with obscure GI bleeding

Most patients with OGIB, or suspected small bowel bleeding, are hemodynamically stable and do not require urgent resuscitation [6]. This is because bleeding from the small bowel is rarely arterial in nature, with the exception of aortoenteric fistula, Dieulafoy lesion, and small bowel diverticular bleeding, all of which are important to consider but thankfully rare. Ectopic small bowel varices can also bleed severely and result in hemodynamic instability, although they too are an uncommon cause of OGIB. As such, there is usually ample time to perform a thorough history.

**Table 1**
Etiologies of small bowel bleeding.

| |
|---|
| **Vascular lesions** |
| Angioectasia |
| Dieulafoy's lesion |
| Blue rubber nevus syndrome |
| Ectopic varices |
| Aorto-enteric fistula |
| **Small bowel ulcer(s)** |
| NSAID induced |
| Crohn's disease |
| Anastomotic |
| Radiation induced |
| Ischemic enteritis |
| Ulcerative jejunitis |
| **Neoplastic** |
| Malignancy |
| Submucosal lesion with mucosal ulceration |
| Small bowel polyp(s) |
| **Other** |
| Portal hypertensive enteropathy |
| Meckel's diverticulum |
| Small bowel diverticulosis |
| Hemosuccus pancreaticus |
| Hemobilia |

The history should include a detailed assessment of bleeding symptoms, including melena, maroon coloured stool, and hematochezia. The presence of bright red blood per rectum, present only on the toilet paper, coating the stool, or seen between bowel motions in someone with preserved continence suggests rectal outlet bleeding. Although by definition all patients with OGIB should already have had a negative colonoscopy, we have found that perianal disease such as fissures or hemorrhoids can be missed. Perhaps more importantly, they may be seen but felt to be insufficient to explain the extent of anemia. The adage of “they are just hemorrhoids” fails to do justice to the size of hemorrhoidal veins compared to small bowel angioectasias, which are typically a fraction of its size. Similarly, the presence of hematemesis is an important clue. From our experience, small intestinal bleeding rarely presents with hematemesis, although we have seen isolated cases of brisk bleeding from the distal duodenum or proximal jejunum reflux back into the stomach to cause hematemesis. The presence of melena in the setting of OGIB may help localize the bleeding source. Just as melena historically pointed towards bleeding proximal to the ligament of Treitz in patients with gastrointestinal bleeding, the presence of melena in OGIB doubles the odds of finding the bleeding source within the proximal 2/3 of the small intestine, which is an important landmark for deciding between antegrade and retrograde double balloon enteroscopy [19]. At times, patients may be unsure if they have seen melena as opposed to dark brown stool. In these cases, showing a picture of melena, easily found on Google Images, may be helpful. Similarly, it may be difficult to differentiate melena from stool colour changes induced by oral iron. In these cases, holding the oral iron and supplementing with intravenous formulations will delineate the true colour of the stool, although this is rarely required.

The bleeding timeline should be accurately documented for several reasons. First, overt bleeding within 2–7 days of capsule endoscopy may increase the odds of finding a bleeding source. Study estimates vary greatly, but capsules performed near the time of overt bleeding can increase the diagnostic yield by up to eight times [20–24]. Second, OGIB of many years duration, typically as iron deficiency anemia without overt bleeding, suggests a benign cause in the right clinical setting. Bleeding severity can be assessed by hemoglobin nadir or number of blood transfusions over a period of time. This is of particular importance since the treatment of those with mild bleeding severity can often be conservative with oral iron replacement. It should be noted that a very low hemoglobin nadir which developed over many months to years may still be indicative of mild bleeding that could respond well to oral iron replacement. In those with occult OGIB, causes other than gastrointestinal bleeding should be considered, such as dietary, Celiac disease, Roux-en-Y gastric bypass, menorrhagia, epistaxis, losses during hemodialysis, or overly frequent blood donation. Lastly, a complete past medical history with particular attention to diseases associated with angioectasias (ex. congestive heart failure, chronic kidney disease, cirrhosis, aortic stenosis, systemic sclerosis), relevant medications (ex. anti-coagulatants, anti-platelet agents, NSAIDS), and family history of Osler-Weber-Rendu or polyposis syndromes, should be obtained.

A general physical exam should be performed with particular focus on the skin. Patients with Osler-Weber-Rendu may have telangiectasias on their lips, buccal mucosa, tongue, or hands (Fig. 1) [25]. In Peutz-Jegher's syndrome, hyperpigmentation of the lips is easily seen although they may also occur on the hands and feet (Fig. 2) [26]. Patients with blue rubber nevus syndrome may have cutaneous venous blebs on the skin or oral mucosa. Findings of iron deficiency anemia may include atrophic glossitis, angular cheilitis, koilonychia, and conjunctival pallor [27]. Otherwise, a general physical exam should be performed to assess for findings of aortic

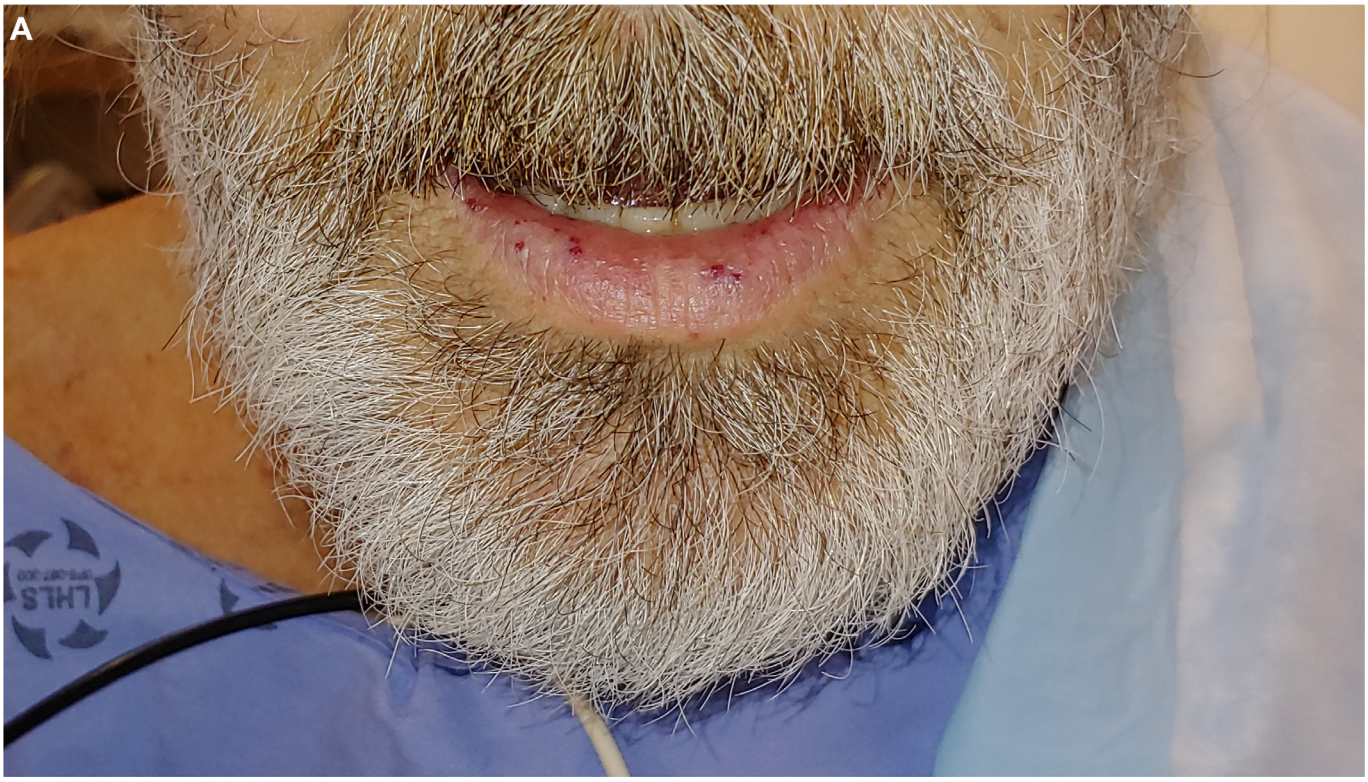



**Fig. 1.** Clinical findings of Osler-Weber-Rendu syndrome.

stenosis and cirrhosis.

A thorough review of prior investigations should be performed as a part of the initial assessment. At our centre, the Small Intestinal Endoscopy Program does not accept referrals for OGIB without accompanying upper and lower endoscopy notes and radiologic imaging if performed. This is important for several reasons. First, it allows for the review of prior upper and lower endoscopies for adequacy of assessment. For example, if bowel preparation was inadequate during the colonoscopy, it would need to be repeated before considering small bowel investigations. Second, it may identify relative contraindications for capsule endoscopy not appreciated by the referring endoscopist, such as a peptic stricture that may require dilation before performing a capsule study. Third, it may provide clues for commonly missed diagnoses in the gastrointestinal tract. For example, the presence of a large sliding hiatus hernia may indicate Cameron erosions/ulcers that may have been missed at the initial upper endoscopy, especially if it is intermittent in nature. The presence of "gastritis" may in fact be portal hypertensive gastropathy or gastric antral vascular ectasia. Hemoglobin concentration should be assessed and trended when possible, with particular attention to fluctuations due to bleeding events, and response to iron replacement and blood transfusion. Hemoglobin nadir should be assessed and the time to reach the nadir evaluated to determine the rate of blood loss. For occult OGIB, confirmation of iron deficiency should be performed whenever possible. From our experience, the prescription of iron by a physician to a patient with anemia may not indicate the presence of iron deficiency as patients are sometimes prescribed iron for undifferentiated anemia.

## Investigation

### *Capsule endoscopy and radiologic imaging*

In Western countries, the first line investigation for OGIB is capsule endoscopy [6,28]. This is primarily due to a high diagnostic yield compared to other forms of small bowel imaging. In the capsule literature, incremental yield (IY), defined as the increase in diagnostic yield between two imaging modalities, is often reported rather than sensitivity and specificity due to the lack of a gold standard [28,29]. Triester et al. conducted a systematic review and meta-analysis of 14 studies comparing capsule endoscopy to other modalities in patients with OGIB [29]. They reported a capsule endoscopy diagnostic rate of 56% versus 26% for push enteroscopy ($IY = 30\%$, $p < 0.00001$) and 42% versus 6% for small bowel barium radiography ($IY = 36\%$, $p < 0.0001$). In the radiology literature, Wang et al. conducted a meta-analysis comparing capsule endoscopy to CT enterography for OGIB and reported a higher diagnostic yield with capsule studies (53% vs. 34%, IY 19%, $p = 0.009$) [30]. The use of MR enterography/enteroclysis (MRE) for OGIB is less well studied. In a case series of 38 patients with OGIB who underwent MRE followed by capsule endoscopy and double balloon enteroscopy, the diagnostic yield of capsule endoscopy surpassed MRE (50% vs. 13.2%, $p < 0.001$) [31]. The lower diagnostic performance of radiologic imaging in general is likely due to its inability to visualize small angioectasias, which are the most common cause of OGIB [32]. For causes of OGIB other than angioectasia, such as neoplastic lesions, the diagnostic performance of the two are likely comparable [30]. In the largest systematic review and meta-analysis to date of 22,840 capsule procedures, Liao et al. reported an overall


**Fig. 1.** (*continued*).

diagnostic rate of 60.5% for OGIB with angioectasia being the most common etiology (50%) [18]. Unfortunately, the diagnostic performance of capsule endoscopy was not compared to other imaging modalities.

Unsurprisingly, capsule endoscopy is not diagnostic in all cases. It is important to understand that capsule endoscopy does not visualize the small bowel mucosa in entirety. Capsule visualization is limited by numerous factors including transit time, peristaltic activity, bowel distension, bowel preparation, shadows, and the angle or direction of the camera. Air bubbles, bile, shadows, collapsed lumen, or simply the valleys between valvulae conniventes impair visualization. Considering the miss rate for tandem colonoscopy for polyps is 22% [33], it should not be surprising that capsule endoscopy is imperfect given the overall length of the small intestine, lack of air insufflation, pump irrigation, and tip control available with colonoscopy. Attesting to this point is the fact that capsule endoscopy is only able to visualize the papilla 43.6% of the time in a series of 112 consecutive capsule patients who had prior documentation of a normal papilla on upper endoscopy [34]. Furthermore, findings on capsule endoscopy are non-specific and healthy individuals may have incidental findings. In a multi-centre randomized clinical trial evaluating the effect of NSAIDS on the small intestine, 7% of patients randomized to placebo had mucosal abnormalities visualized [35]. Accordingly, we recommend capsule endoscopy be performed only in cases of OGIB with overt blood loss or iron deficiency rather than undifferentiated anemia. Lastly, small intestinal capsule endoscopy poorly visualizes the esophagus, stomach, and colon. Although incidental findings in the upper gastrointestinal tract or cecum may be seen on capsule endoscopy, it should not be used in place of proper upper and lower endoscopies when indicated.

### *Deep enteroscopy*

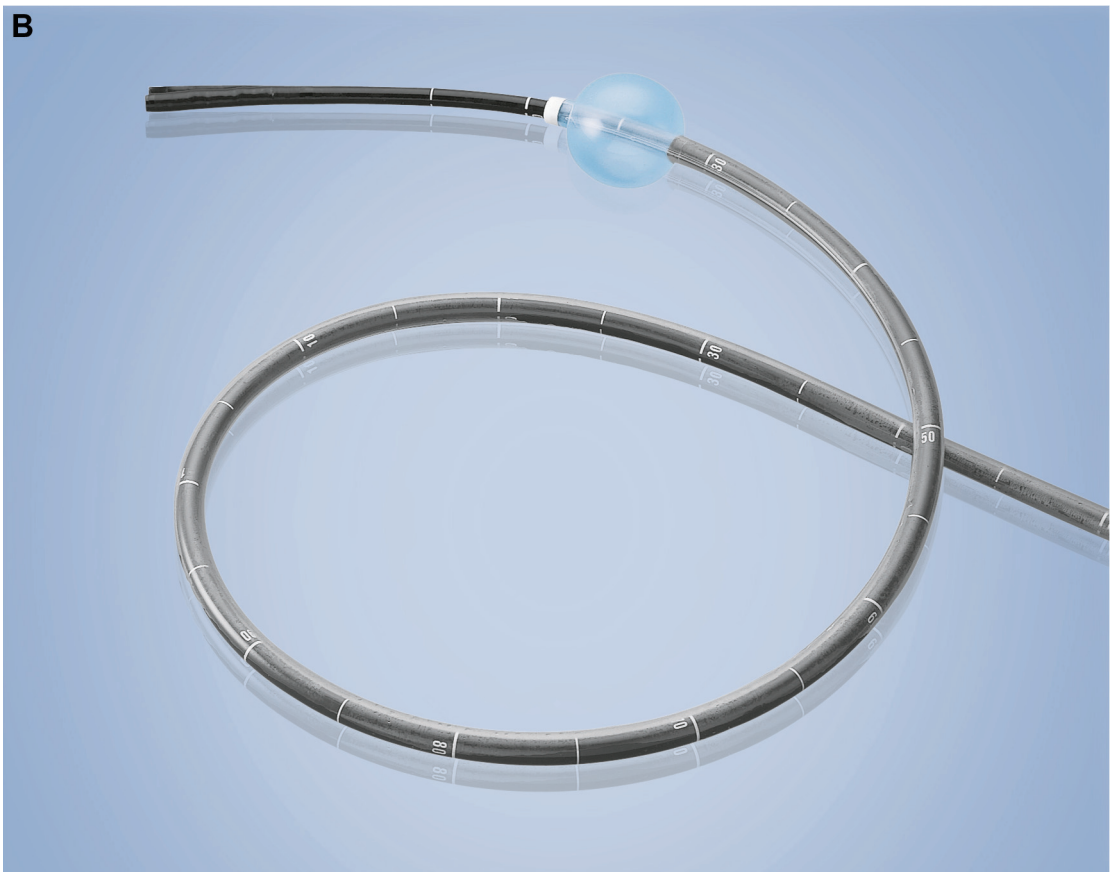
Deep enteroscopy refers to endoscopic techniques able to penetrate further into the small bowel than push enteroscopy. In general, push enteroscopy using a pediatric colonoscope is only able to visualize 45–60 cm distal to the ligament of Treitz due to looping, which is likely no further than the proximal jejunum [6]. Deep enteroscopy, including double balloon enteroscopy (DBE), single balloon enteroscopy (SBE), balloon guided enteroscopy, and spiral enteroscopy, all use various methods to anchor the enteroscope in the small bowel to permit effective loop reduction and are collectively known as device assisted enteroscopy (Fig. 2). Double balloon enteroscopy was the first to be developed and is still widely considered to be the gold standard for deep enteroscopy. Invented in 2002 by Dr. Hironori Yamamoto, DBE consist of a flexible overtube and two pressure sensitive inflatable balloons, one at the tip of the enteroscope and one on the overtube (Fujinon EN-580T, Tokyo, Japan) [36]. Through a series of push/pull maneuvers, along with


**Fig. 2.** Currently available types of device assisted enteroscopy (A=double balloon enteroscopy, B=single balloon enteroscopy, C=balloon guided enteroscopy, D=spiral enteroscopy).

inflation/deflation of each balloon in sequence, deep intubation of the small intestine, even to the cecum, is possible. Single balloon enteroscopy followed as a simplification of DBE whereby the only balloon required is on the overtube (Olympus SIF-Q180, Tokyo, Japan) [37,38]. With this technique, maximal tip deflection is used in place of the enteroscope balloon to anchor or "hook" the scope in place. Balloon guided enteroscopy differs from DBE and SBE in that a regular pediatric colonoscope can be used [39]. In this system, conventional push enteroscopy is performed until the depth of maximal insertion reached. A through the scope balloon catheter (Smart Medical Systems NaviAid AB, Ra'anana, Israel) is advanced distally, balloon inflated, and the enteroscope moved forward by a combined advancement of the pediatric colonoscope with retraction of the balloon catheter. Spiral enteroscopy (Spirus Medical, Stoughton, USA) uses a grooved overtube akin to a screw to anchor it in place. The technology was purchased by Olympus in 2011 for further development. In the interim, the overtube has limited market availability only in the United States.

The diagnostic yield of DBE overall is similar to capsule endoscopy. In a systematic review and meta-analysis of 10 studies ($n = 642$) comparing the two, the diagnostic yield of DBE was 56% compared to 62% for capsule endoscopy ($p = 0.16$). Given the comparable diagnostic yield, Western countries have adopted capsule endoscopy instead of DBE as the first line investigation for OGIB as it is less invasive and readily available. In contrast, DBE requires considerable endoscopy resources and locally, we book 2.5 h for each case. Instead, the role of DBE has become more therapeutic in nature, typically to treat angioectasias after an abnormal capsule study. In many ways, the role of capsule endoscopy and DBE is similar to the evolution seen over the past decades with MRCP and ERCP. Capsule endoscopy is purely diagnostic, as is MRCP, and DBE is primarily therapeutic, as is ERCP. In this framework, DBE may still be the first line test based on abnormal radiologic studies, and non-diagnostic capsule cases may still undergo DBE if the index of suspicion is high. However, in this latter scenario, the yield of DBE after a negative capsule study is low [40].

Double balloon enteroscopy has been compared to other forms of enteroscopy, in particular single balloon enteroscopy. To date, four randomized clinical trials have been conducted comparing the two [41–44]. However, selecting an appropriate outcome for clinical trials has proven problematic. A logical option would be complete enteroscopy, defined as visualizing the entire small bowel. This is usually achieved by performing an antegrade DBE through an oral route, tattooing the depth of maximal insertion, followed by retrograde DBE through an anal route and reaching the tattoo. Less commonly, the cecum can be reached during antegrade DBE alone. Complete enteroscopy is perhaps the holy grail of deep enteroscopy as an enteroscope that permits visualization of the entire small bowel would theoretically always be able to reach an abnormality. A well designed German multi-centre randomized clinical trial ($n = 100$ patients) compared the rate of complete enteroscopy between DBE and SBE [41]. Overall, the rate of complete enteroscopy was



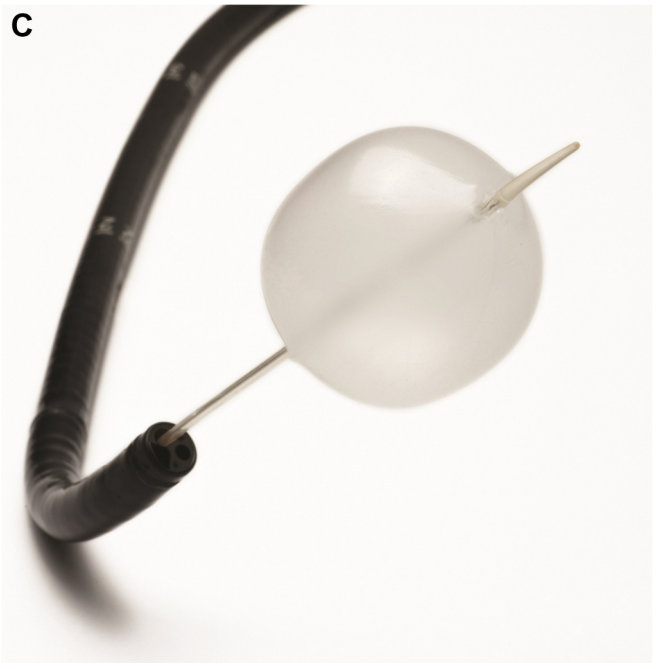




**Fig. 2.** (*continued*).

66% in those randomized to DBE compared to 22% in those who underwent SBE ($p < 0.0001$). Subsequently, Takano et al. conducted another randomized clinical trial comparing the rate of complete enteroscopy between DBE and SBE in Japan [42]. Although originally designed to recruit 118 patients, the study fulfilled the criteria for a pre-defined early stopping rule when DBE was found to be vastly superior to SBE during an interim analysis (57.1% vs. 0%, $p = 0.002$). Domagk et al. designed a European multi-centre randomized clinical trial comparing DBE to SBE [43]. Although complete enteroscopy was originally the primary outcome, a pilot study


**Fig. 2.** (*continued*).

in 20 patients showed a low rate of complete enteroscopy, resulting in an unacceptably high sample size that would be required (n = 23,000 patients). Instead, the authors selected maximal insertion depth into the small bowel as the primary outcome. The method of measurement used was based on an ex-vivo porcine model, consisting of a pig esophagus, stomach, and either 100 cm or 200 cm of small intestine fitted inside a plastic Erlangen Endo-Trainer [45]. Testing for this measurement method was conducted in 10 procedures using the ex-vivo model, validated in 25 live pigs, but not in humans [46]. With this technique, the endoscopist would guess how far into the small bowel they advanced with each reduction cycle, between 0 and 40 cm, and the total depth of insertion would be its sum. Using this measure, Domagk et al. reported similar maximal depth of insertion between the two enteroscopes (253 cm vs. 258 cm). However, given the highly subjective outcome measure coupled with unblinded outcome assessors, being the endoscopoists, the validity of these results is questionable due to the risk of conscious and unconscious bias. To overcome the challenge of accurately measuring the depth of insertion into the small intestine, Efthymiou et al. conducted another multi-centre randomized clinical trial in Australia [44]. In this trial, the endoscopists painstakingly counted the number of folds seen in the small bowel during withdrawal of the enteroscope and also measured the distance using a probe with a 5 cm mark protruding from the tip of the enteroscope and adding up the number of 5 cm segments on withdrawal. DBE had a 25% greater depth of maximal insertion when compared to SBE using the fold counting method (258.6 vs. 201.1 folds, $p = 0.046$) and a non-significant advantage using the 5 cm probe method (234.1 cm vs. 203.8 cm, $p = 0.176$). Unfortunately, the validity of this trial is threatened by the inability of the trial to reach target recruitment size. Although originally designed to recruit 300 patients, the study enrolled just a third of this number (n = 107).

Pragmatically, another outcome of interest when comparing forms of deep enteroscopy is the diagnostic and therapeutic rate. Of the four randomized clinical trials, DBE and SBE had similar diagnostic and therapeutic rates, with the exception of the trial by May et al. where DBE had a higher therapeutic yield than SBE (72% vs 48%) [41–44] These results should be interpreted cautiously given the outcomes, “diagnostic procedure” and “therapeutic procedure”, are dichotomous in nature and treated simply as “yes/no”. As such, there is no differentiation between finding/treating 1 or 10 angioectasias. However, this may not have much clinical significance if the area of abnormality is within the proximal to mid jejunum, where the ability of DBE to reach deeper may not matter. At our centre, we perform both DBE and SBE. Generally, we use SBE for lesions located in the proximal to mid jejunum and DBE for anything more distal or if complete enteroscopy is desired.

### *Intraoperative enteroscopy*

Intraoperative enteroscopy (IOE) is usually performed through an oral route, through an enterotomy, or via an anal route [47,48]. With this technique, a pediatric colonoscope or enteroscope is fed into the small intestine and advanced by the surgeon, either manually during a laparotomy or with the aid of graspers during a laparoscopy. Even during a laparotomy, it can be difficult to thread the pediatric colonoscope or enteroscope all the way through to the cecum and an enterotomy may be required to visualize the most distal portions.

Careful coordination between the endoscopist and surgeon is necessary for this procedure. Unlike conventional endoscopy, the scope is driven by two people during IOE, with the endoscopist controlling the handle and dials and the surgeon advancing the tip. Care should be exercised to avoid over distending the gastrointestinal tract to avoid excessive looping in the stomach as well as over distension of the small intestine, which may make closure of the abdomen more difficult for the surgeon. Use of carbon dioxide is desirable and a clamp may be placed in the mid small bowel by the surgeon to avoid distension of the distal small intestine until the enteroscope has reached that segment. Evisceration of the small bowel out of the abdomen in conjunction with lighting in the operating theater can result in undesired transillumination of the small bowel that appears semi-translucent, making abnormalities more difficult to see. Dimming the lights along with placement of sterile towels over the small bowel can minimize this problem. Slow, methodical advancement of the scope is then performed until the abnormality is found, no further advancement can be made, or the cecum is reached.

With the advent of capsule endoscopy and deep enteroscopy,

the role of IOE has diminished. In a small but important prospective case series, 47 consecutive patients with OGIB underwent capsule endoscopy followed by IOE. The diagnostic rate was 74.5% with capsule endoscopy and 72.3% with IOE. Perhaps more importantly, one patient died from peritonitis after laparotomy, equating to a 2.1% mortality rate. The risk of IOE are generally due to the laparotomy and its complications include serosal laceration, prolonged ileus, abscess, peritonitis, perforation from lysis of adhesions, and a mortality rate up to 6% [47]. At our centre, IOE is now rarely required given capsule endoscopy has comparable diagnostic yield and DBE generally able to reach any abnormalities seen on the capsule study. However, hemodynamically unstable small bowel bleeding or requirement for lysis of adhesions may still lead to an IOE.

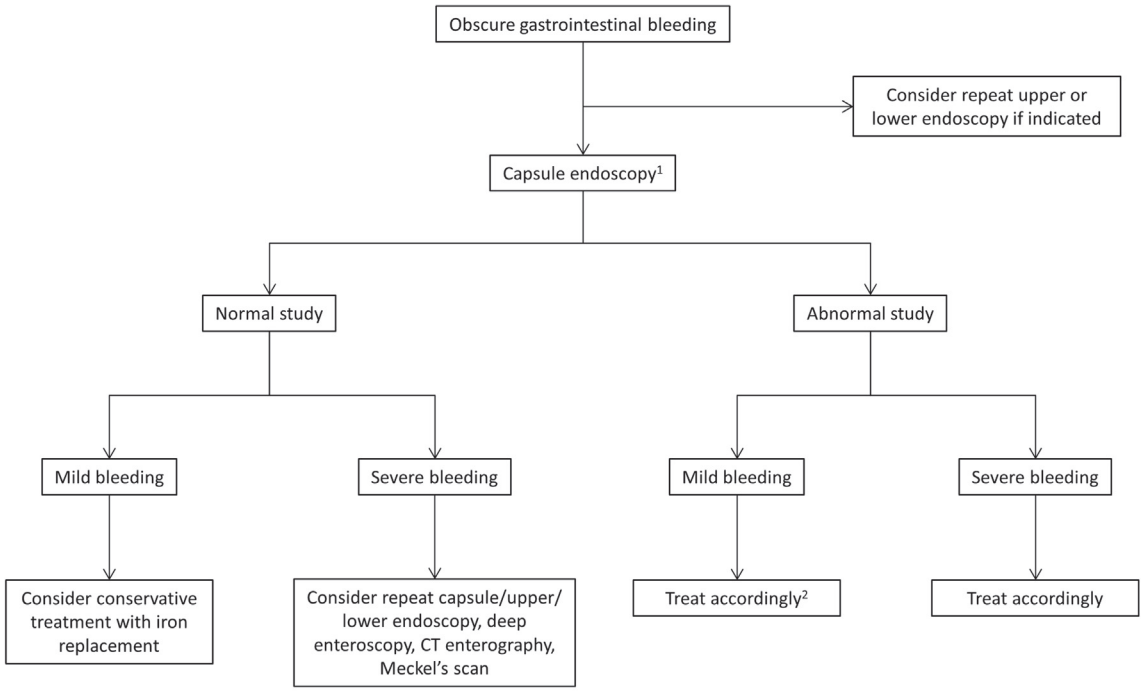
## Management of obscure gastrointestinal bleeding

### *Management algorithm*

The management of OGIB should take into account the imperfect diagnostic yield of all existing forms of small bowel imaging. A proposed general algorithm we use in our Small Intestinal Endoscopy Program is provided although this should not replace sound clinical judgement (Fig. 3). The first line test for OGIB is capsule endoscopy, primarily due to its high diagnostic yield and ability to visualize the entire small bowel. However, a CT enterography may be considered if capsule endoscopy is unavailable. In general, CTE has a lower diagnostic yield than capsule endoscopy due to difficulty in visualizing angioectasias although they are likely comparable for excluding small bowel neoplasms, which are rare but important to exclude [30]. MR enterography could be considered if there is concern regarding ionizing radiation, although CT enterography has been better studied for OGIB. If the capsule is normal and the patient has mild bleeding, conservative therapy with iron replacement may be suitable. We consider OGIB to be severe if it is refractory to appropriate iron replacement resulting in recurrent blood transfusions. For those treated conservatively, the patient and referring doctor should be made aware that OGIB is often a chronic condition and regular hemoglobin and iron panel checks should be performed to prevent dangerous drops in the hemoglobin concentration, especially if iron replacement therapy is eventually withdrawn. In those with severe bleeding and a normal capsule study, consideration should be given to repeating capsule endoscopy, upper and/or lower endoscopy, CT enterography, or deep enteroscopy. In the appropriate scenarios, consideration can be given to exclude hemobilia or hemosuccus pancreaticus as well. Alternatively, if the first line capsule study is abnormal, the findings should be treated accordingly. However, if the bleeding is mild and due to benign angioectasias, conservative treatment with iron replacement may still be appropriate.

### *Endoscopic therapy*

The endoscopic management of OGIB has largely focused on the treatment of angioectasias, given it is the most common etiology. Unfortunately, there is a paucity of high quality data on the effectiveness of endoscopic eradication of small intestinal angioectasias and the limited data available has shown only modest success in reducing blood loss and transfusion requirement [6,11,49]. In a case series of 101 patients who underwent DBE for OGIB, of which 40 had endoscopic treatment for angioectasias, only 50% of patients had no bleeding at 30 months. Unfortunately, endoscopic eradication of small bowel angioectasias may not produce a “cure” for several reasons. First, the angioectasia(s) visualized on capsule




[1]Consider CT enterography as an alternative if capsule endoscopy is unavailable
[2]Consider conservative treatment with iron replacement for angioectasias

**Fig. 3.** Management algorithm for hemodynamically stable suspected small bowel bleeding.

endoscopy and targeted by deep enteroscopy may not be the bleeding culprit. In fact, there is no way of knowing which is the bleeding culprit unless there is active bleeding at the time of the procedure. Second, even if the bleeding culprit was treated, it may recur. Third, patients may have multiple bleeding culprits. Fourth, new angioectasias may simply develop in the future. Anecdotally, from our experience, we are able to achieve hemostasis in carefully selected patients who undergo deep enteroscopy although some require multiple sessions.

The endoscopic techniques and tools used to treat small bowel angioectasias have been extrapolated from its use to treat vascular lesions in the upper gastrointestinal tract. Argon plasma coagulation is the most commonly used modality although bipolar probe and hemostatic clips can also be used, largely drive by endoscopist preference, local availability, and expert opinion [6,11].

*Medical therapy*

Other than oral or intravenous iron, medical therapy for small bowel angioectasias is generally considered supplemental to endoscopic therapy, largely due to poor efficacy, limited evidence, or toxicity. Hormonal therapy was considered in the 1990s due to its supposed effect on reducing bleeding time, although this has largely been abandoned due to lack of efficacy [6,49]. Octreotide has been used on the premise it may reduce angiogenesis and reduce splanchnic blood flow. In a 2014 meta-analysis, octreotide analogues were associated with an odds ratio of 14.5 ($p < 0.001$) for bleeding cessation, although based only on 4 low quality studies with a total of just 74 patients. Thalidomide has also been tried on the basis of anti-angiogenesis effects mediated by vascular endothelial growth factor (VEGF). In a small open-label randomized clinical trial of 55 patients with mostly small intestinal angioectasias, those randomized to thalidomide were less likely to be blood transfusion dependent at 12 months compared to those treated with iron (10.7% vs. 48.2%, $p = 0.002$). Those randomized to thalidomide had vastly more adverse events than iron (71.4% vs. 33.3%), albeit none were serious adverse events. Although promising, the results require replication on a larger scale before routine use can be endorsed. We will use thalidomide in limited scenarios, typically for repeated recurrences after multiple sessions of endoscopic therapy and with the aid of a hematologist to prescribe thalidomide with regulatory approval for off-label use in Canada.

*Patients with brisk obscure gastrointestinal bleeding*

The aforementioned management strategy for OGIB has largely focused on patients with stable OGIB, which represent the vast majority. For those with brisk bleeding, a different approach is required. Pragmatically, hemodynamically unstable gastrointestinal bleeding is rarely diagnosed as OGIB since the definition requires both an upper and lower endoscopy be formed, with the latter being inappropriate in an unstable patient. Instead, those who present with unstable brisk bleeding should be managed accordingly, with resuscitation followed by upper endoscopy to exclude brisk upper gastrointestinal bleeding that may respond to endoscopic therapy, CT angiogram and/or angiography, and the early involvement of a general surgeon.

For those with subacute small bowel bleeding, small bowel endoscopic investigations may be more appropriate. From our experience, these patients are typically hemodynamically stable inpatients with ongoing melena or hematochezia, negative upper and lower endoscopies, but ongoing blood loss requiring 1–2 units of blood a day. In these patients, a capsule study would be appropriate. The study itself may show only fresh blood in the small intestine but even the location of blood accumulation guides whether an oral or anal route should be pursed with deep enteroscopy. Alternatively, a red blood cell scan or CT angiography may be suitable, whereas they are usually negative when used in the outpatient OGIB setting. Therapeutic intervention is dependent on the cause of bleeding but we prefer endoscopic treatment when possible. Angiography and embolization carries a risk for small bowel ischemia, more so than in the upper gastrointestinal tract where there is more vascular redundancy, and may result in the need for an emergent laparotomy for small intestinal ischemia [50].

## Summary

Obscure gastrointestinal bleeding, or suspected small bowel bleeding, is a challenging condition that requires a thorough review of the patient, prior investigations, and an understanding of the strengths and limitations of existing technologies to image the small bowel. Most patients can be managed conservatively with iron replacement although careful selection of those who have severe bleeding for deep enteroscopy can lead to successful results.

## Practice points

- In Western nations, angioectasias are the most common cause of small bowel bleeding
- Capsule endoscopy, where available, is the first line test for small bowel bleeding due to a high diagnostic yield
- Treatment of small bowel bleeding depends on bleeding severity and whether the bleeding etiology is benign or neoplastic

## Research agenda

- The epidemiology and natural history of suspected small bowel bleeding is unknown due to the lack of nationally representative datasets
- The efficacy of endoscopic treatment of small bowel angioectasias is unknown due to the lack of large multi-centre randomized clinical trials
- Future research in both areas will help clinicians decide which patient will benefit from endoscopic treatment versus conservative management

## Conflicts of interest

None.

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