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## Evaluation and outcomes of patients with obscure gastrointestinal bleeding

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### Abstract

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding or presence of iron deficiency anaemia after evaluation with a negative bidirectional endoscopy. OGIB accounts for 5% of gastrointestinal bleeding and presents a diagnostic challenge. Current modalities available for the investigation of OGIB include capsule endoscopy, balloon assisted enteroscopy, spiral enteroscopy and computed tomography enterography. These modalities overcome the limitations of previous techniques. Following a negative bidirectional endoscopy, capsule endoscopy and double balloon enteroscopy remain the cornerstone of investigation in OGIB given their high diagnostic yield. Long-term outcome data in patients with OGIB is limited, but is most promising for capsule endoscopy. This article reviews the current literature and provides an overview of the clinical evaluation of patients with OGIB, available diagnostic and therapeutic modalities and long-term clinical outcomes.

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**Key words:** Obscure gastrointestinal bleeding; Capsule

endoscopy; Double balloon enteroscopy; Outcomes; Anaemia

**Core tip:** This article examines the role of current diagnostic modalities for the investigation of obscure gastrointestinal bleeding (OGIB) and outcomes in patients undergoing these investigations. Capsule endoscopy and double balloon enteroscopy remain the cornerstone of diagnostic and therapeutic management. The diagnostic and therapeutic capabilities of certain modalities are influenced by the nature of bleeding in OGIB. Long-term outcome data in patients with OGIB is limited but is most promising for capsule endoscopy.

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### INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding or presence of iron deficiency anaemia (IDA) after negative evaluation with oesophagogastroduodenoscopy (OGD) and colonoscopy<sup>[1]</sup>. OGIB can be categorised further into overt or occult obscure gastrointestinal (GI) bleeding. Overt GI bleeding refers to patients with clinically evident bleeding (haematemesis, melaena or haematochezia) whereas occult GI bleeding occurs in the setting of persistent IDA or a positive faecal occult blood test.

OGIB accounts for approximately 5% of GI bleeding. In more than 80% of cases, the bleeding arises from the small bowel distal to the Ampulla of Vater and proximal to the ileocaecal valve rendering it relatively inaccessible to traditional endoscopy<sup>[2-4]</sup>. Patients with OGIB

**Table 1 Aetiology of obscure gastrointestinal bleeding**

Vascular	Inflammatory	Neoplastic	Extraluminal	Rare causes
Angioectasias	Inflammatory bowel disease	Carcinoid	Haemobilia	Hereditary Haemorrhagic Telangiectasias
Dieulafoy's Lesion	Peptic ulcer disease	Gastrointestinal stromal tumour	Aortoenteric fistula	Von Willebrand disease
Gastric antral vascular ectasia	Oesophagitis	Adenocarcinoma	Haemosuccus pancreaticus	Amyloidosis
Portal hypertensive gastropathy	Cameron erosions	Metastases (melanoma)		Henoch Schonlein Purpura
Varices	Meckel's diverticulum	Lymphoma		
Radiation enteritis	NSAID related gastropathy/enteropathy	Ampullary carcinoma		
Haemorrhoids				

NSAID: Non-steroidal anti-inflammatory drugs.

undergo more investigations, have longer duration of hospitalisation, require more blood transfusions and generate higher healthcare expenditures than patients with upper or lower gastrointestinal bleeding<sup>[1]</sup>. This is largely due to difficulty accessing the small bowel endoscopically which presents a diagnostic challenge<sup>[4]</sup>.

Current modalities to investigate for OGIB include both endoscopic and radiological techniques. The role of radiological modalities in the evaluation of OGIB has declined substantially as a result of their low diagnostic yield<sup>[2]</sup>. In this article, we review the clinical evaluation and outcomes of patients presenting with OGIB.

## EVALUATION OF OGIB

The clinical history may suggest the possible cause and location of OGIB but it is rarely diagnostic. Endoscopic evaluation remains the cornerstone of diagnosis and management in OGIB<sup>[5]</sup>. A careful history is key and should include the nature (occult or overt) and clinical presentation of GI bleeding (haematemesis, melaena, haematochezia). Further history regarding other gastrointestinal symptoms (weight loss, obstructive symptoms), medications (anticoagulants, non-steroidal anti-inflammatory drugs), comorbidities (haematological disease, valvular heart disease), prior surgeries (abdominal aortic aneurysm repair, bowel surgery), and family history (inflammatory bowel disease, malignancies, familial telangiectasias) may give clues to the underlying cause<sup>[6]</sup>. While haematemesis reliably localises the bleeding proximal to the ligament of Treitz, stool colour is a less reliable indicator as it is dependent upon intestinal transit time. Elderly patients, patients with valvular heart disease, renal disease or connective tissue disease are at high risk of vascular lesions. Use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of small bowel ulceration<sup>[7]</sup>. Physical examination may be useful in detecting systemic syndromes such as hereditary haemorrhagic telangiectasias or Coeliac disease<sup>[6]</sup>.

The most common causes of OGIB vary according to age (Table 1). In patients younger than 40 years of age, small intestinal tumours, Crohn's disease, Meckel's diverticulum, polyposis syndromes and angiodysplasias pre-

dominate, whereas patients older than 40 years of age are more likely to bleed from vascular causes (*e.g.*, angiodysplasias) and NSAID enteropathy<sup>[8,9]</sup>. Causes of OGIB are mainly vascular in the Western population and ulcerations or erosions in the Asian population<sup>[10]</sup>. Patients who present with IDA without gastrointestinal symptoms, may have gastrointestinal diseases that cause iron malabsorption such as Coeliac disease, atrophic gastritis and Helicobacter Pylori gastritis<sup>[11]</sup>.

Availability of procedures, patient preferences, physician expertise, costs and risks are important determinants of investigation and management<sup>[12]</sup>.

## CAPSULE ENDOSCOPY

Capsule endoscopy (CE) has revolutionised the ability to image the small bowel. It is commonly used as a first-line diagnostic tool for investigation of OGIB<sup>[1]</sup>. This is due to its non-invasiveness, patient tolerance, high negative predictive value (80%-100%) and high diagnostic yield<sup>[3,13,14]</sup>. CE enables direct visualisation of the small bowel mucosa and has a high sensitivity for detecting flat lesions, such as angiodysplasias, ulcers and arteriovenous malformations which are not easily detectable on radiological modalities<sup>[15]</sup>.

The reported diagnostic yield in literature ranges from 58.4% to 86.8%<sup>[9,14,16-21]</sup>. The wide range is attributable to different definitions of a positive finding on CE. The diagnostic yield is not affected by age, rendering it a useful test across all age groups<sup>[22]</sup>. However, it is affected by patient factors including ongoing bleeding, low haemoglobin and ongoing transfusion requirements<sup>[23]</sup>.

Pennazio *et al.*<sup>[16]</sup> reported that the diagnostic yield of CE was significantly higher in patients with ongoing overt OGIB (92.3%), intermediate in patients with occult OGIB (44.2%) and lowest in patients with previous overt OGIB (12.9%). In the overt OGIB group, the diagnostic yield was inversely proportional to the length of time since the last bleeding episode, as delay in the use of CE allows for healing of the bleeding site<sup>[24]</sup>. CE thus has its highest diagnostic yield in patients with ongoing and overt bleeding<sup>[16,25]</sup>.

CE has been shown to be superior to other modalities

including computed tomography, and small bowel barium studies<sup>[26-29]</sup>. When compared to push enteroscopy (PE), two meta-analyses have confirmed the superiority of CE, one of which demonstrated a diagnostic yield 30% higher than PE<sup>[29,30]</sup>.

When comparing CE with double balloon enteroscopy (DBE), the literature is inconsistent due to small sample sizes<sup>[6]</sup>. Teshima *et al.*<sup>[31]</sup>'s meta-analysis comparing CE and DBE in OGIB revealed a similar diagnostic yield (62% *vs* 56%), a finding supported by 2 other meta-analyses<sup>[31-33]</sup>. CE has a higher diagnostic yield than either antegrade or retrograde DBE alone (OR = 1.61, 95%CI: 1.07-2.43) but not when both approaches are used together (OR = 0.12, 95%CI: 0.03-0.52). This highlights the importance of a total enteroscopy in patients with a high clinical suspicion of small bowel pathology<sup>[33]</sup>. However, the completion rate of DBE is highly variable (16%-86%)<sup>[34,35]</sup>.

CE has other distinct advantages since it allows the patient to remain ambulatory and requires minimal preparation without sedation<sup>[36]</sup>. Its main limitation is that it is solely a diagnostic tool lacking therapeutic capacity and the ability to obtain histology<sup>[37,38]</sup>. It has limited effectiveness in detecting small bowel submucosal tumours, with a false-negative rate up to 19%<sup>[39,40]</sup>. Other limitations include the inability to precisely locate the bleeding lesions and a small (but significant) risk of capsule retention (0.75% to 5.8%)<sup>[3,41,42]</sup>.

## ENTEROSCOPY

### PE

PE can visualise the proximal small bowel up to 100cm distal to the ligament of Trietz<sup>[6]</sup>. It has diagnostic and therapeutic (biopsy, electrocautery, injection, polypectomy) capabilities<sup>[4]</sup>. An important advantage of PE is that it facilitates a second look for missed lesions within reach of an OGD which is seen in 25%-40% of cases<sup>[43,44]</sup>.

The reported diagnostic yield is between 3%-70%<sup>[2,45-47]</sup>. The main limitation is its inability to reach lesions beyond the middle jejunum, patient discomfort and its time-consuming nature<sup>[4,48]</sup>. Complications are rare and include pancreatitis and mucosal injuries<sup>[43]</sup>. It has largely been replaced by CE for diagnosis and DBE for small bowel endoscopic treatment. Its role mainly lies in the treatment of proximal small bowel lesions found on CE<sup>[6]</sup>.

### Double balloon enteroscopy

Double balloon enteroscopy facilitates examination of the entire small bowel<sup>[4]</sup>. It is considered the gold standard for therapeutic intervention of many small bowel disorders in OGIB<sup>[49]</sup>. The diagnostic yield and treatment success of DBE for OGIB in published literature ranges from 60%-81% and 43%-84% respectively<sup>[10,50-60]</sup>. The variation in diagnostic yield is a result of differences in DBE timing, inclusion criteria and definitions of a significant finding<sup>[61]</sup>. Like CE, DBE has a higher diagnostic

yield in patients with overt-ongoing OGIB than overt previous and occult OGIB, suggesting that the time interval between the last bleeding episode and the DBE examination is a key factor in diagnosing the causative lesion in OGIB<sup>[10]</sup>.

The approach of a targeted DBE (after a prior CE) has been shown to increase both its diagnostic (73%-93%) and therapeutic yield (53%-73%)<sup>[38,62,63]</sup>. DBE can change or improve the diagnosis in a significant number of patients in whom CE is performed beforehand. In a study by Kaffes *et al.*<sup>[38]</sup>, DBE after CE clarified or made a new diagnosis in 20% of patients. A CE guided DBE is likely to diminish the need for total enteroscopy in most patients, as demonstrated by Gay *et al.*<sup>[62]</sup> who showed a high positive predictive value for CE to correctly predict the DBE approach. The targeted approach is also useful in confirming indeterminate findings from CE. Hence, it is strongly suggested that CE is the initial screening modality in OGIB and that these two investigations should be viewed as complementary<sup>[20,64]</sup>.

Not surprisingly, when compared with PE, a controlled prospective trial on patients with suspected small bowel bleeding, confirmed that antegrade DBE is significantly superior to PE in regards to the detection of pathological lesions (63% *vs* 44%) and the length of small bowel visualised (230 cm *vs* 80 cm)<sup>[65]</sup>.

DBE is restricted by its limited availability, prolonged procedural times and sedation requirements<sup>[37]</sup>. The complication rate is 0.8% for diagnostic procedures and up to 4% for therapeutics such as polypectomy, electrocautery or dilatation<sup>[6]</sup>. Complications include bleeding, ileus, intestinal perforation, pancreatitis or those related to sedation<sup>[49]</sup>. For these reasons, DBE is a second-line investigation in OGIB, reserved for patients with a positive CE who require therapeutic intervention or biopsy<sup>[2]</sup>.

Current guidelines recommend CE as the preferred initial modality in OGIB given its diagnostic yield, outcome data, safety and non-invasive nature. DBE should be viewed as a complementary procedure. It plays an important therapeutic role following diagnostic CE and diagnostic role following negative CE in patients with ongoing bleeding or high suspicion of small bowel pathology. Other scenarios for initial use of DBE are where CE is not available or affordable and in patients with overt OGIB who may benefit from early DBE<sup>[64]</sup>. More prospective randomised controlled clinical studies are required to determine the most efficient and cost effective use of CE and DBE<sup>[61]</sup>.

### Spiral enteroscopy

Spiral enteroscopy utilises a spiral shaped overtube with a raised helix at the distal end. It allows for advancement and withdrawal of the enteroscope through the small bowel by using clockwise and anticlockwise movements respectively<sup>[6]</sup>. It offers the same diagnostic and therapeutic capabilities as DBE. Initial studies comparing DBE and spiral enteroscopy have suggested that the two procedures have similar diagnostic yields<sup>[66-68]</sup>. Further studies

comparing spiral enteroscopy to other modalities such as CE and DBE are required.

### Intraoperative enteroscopy

Intraoperative enteroscopy (IOE) was previously considered the gold standard of small intestinal imaging. It has the highest sensitivity in detecting bleeding small bowel lesions with a diagnostic yield of 80%-100%<sup>[69,70]</sup>. This is at the expense of extreme invasiveness making this modality a last resort in the investigation OGIB<sup>[4]</sup>. Indications of IOE include when small bowel lesions cannot be managed by angiographic embolisation or endoscopic treatment or when surgery is required<sup>[70]</sup>.

## REPEAT UPPER AND LOWER ENDOSCOPY

Bleeding sources within reach of upper and lower endoscopy may be missed as a result of small size, atypical location, inadequate endoscopy investigation, slow or intermittent bleeding, or compromised visualisation (due to presence of blood or poor colonic preparation)<sup>[6]</sup>.

Numerous studies demonstrate that a significant proportion of patients with negative initial investigations have a bleeding source on repeat OGD in 35%-75% or repeat colonoscopy in 6% of cases<sup>[45,71-76]</sup>. Thus a re-look endoscopy may be recommended as a cost-effective first step before further evaluation<sup>[7]</sup>. Factors associated with increased yield on repeat OGD include large hiatus hernias, history of NSAID use, and haematemesis<sup>[45]</sup>.

Common missed lesions include colonic angiodysplasias, peptic ulcers, Cameron's lesions, gastric antral vascular ectasia and radiation proctitis<sup>[49]</sup>.

The American Gastroenterological Association recommend repeating OGD and colonoscopy if there is suspicion of an overlooked lesion before proceeding to CE or DBE<sup>[2]</sup>. Repeat OGD and/or colonoscopy should also be considered if suboptimal equipment was used or in the setting of inadequate mucosal visualisation secondary to poor bowel preparation<sup>[49]</sup>.

## COMPUTED TOMOGRAPHY ENTEROGRAPHY

Computed tomography enterography (CTE) is a readily available, non-invasive, operator independent method for visualising the small bowel. It can detect extraluminal pathology which is not possible with CE. The overall sensitivity of CTE is low (50%), however it is effective for detecting small bowel tumours (sensitivity exceeding 90%)<sup>[77-79]</sup>. The diagnostic yield of CE following negative CTE is high, 57% in one study<sup>[25]</sup>. Small bowel ulcers are the most commonly missed lesions with CTE which are readily detected by CE<sup>[11]</sup>. However, in patients less than 40 years of age where small bowel tumours are the most common cause of OGIB, CTE should be strongly considered given the aforementioned false negative rate of

CE for detecting small bowel neoplasms<sup>[80,81]</sup>.

## OUTCOMES

### Capsule endoscopy

Although many studies demonstrate a high diagnostic yield of CE for detecting a cause of OGIB, its impact on patient outcomes is more important<sup>[82]</sup>. With regards to rebleeding rates, Endo *et al*<sup>[18]</sup> found that among patients with significant CE findings, the rebleeding rate at a mean of 11.6 mo follow up of the patients who underwent therapeutic intervention was significantly lower than that of those without intervention (9.5% *vs* 40.0%,  $P = 0.046$ ). This is supported by other studies<sup>[83,84]</sup>. Hence, aggressive intervention of patients with significant CE findings reduces risk of rebleeding. Patients with insignificant findings (erosions, small ulcers, red spots, small polyps) or a negative CE, had a significantly higher rate of re-bleeding than those with significant findings on CE. These patients should have careful follow up, whilst being mindful that the bleeding may not be originating from the small bowel<sup>[18]</sup>. Viazis *et al*<sup>[85]</sup> found that 65% of patients with a negative initial CE continued to have OGIB after a mean follow up period of 24 mo. Development of overt bleeding and a haemoglobin drop of 4 g/dL or more were significant predictive factors for a diagnostic repeat CE. Similar to its influence on diagnostic yield, the nature of bleeding in OGIB also impacts on rebleeding rates. In the Pennazio *et al*<sup>[16]</sup> study, complete resolution of bleeding occurred significantly more often in patients with ongoing overt and occult OGIB than with previous OGIB.

In regards to other outcome measures, Leighton *et al*<sup>[36]</sup> demonstrated significant reductions in the requirement for blood transfusions, gastrointestinal procedures and hospitalisation as well as significant improvements in haemoglobin levels at 1 year follow-up of 20 patients undergoing CE for investigation of OGIB. Hindryckx *et al*<sup>[86]</sup> also confirmed favourable outcomes in 66.3% of their patients after CE guided therapy which led to a decrease in the need for blood transfusions and significantly higher haemoglobin levels after a mean follow up of 635.5 d.

### DBE

Kaffes *et al*<sup>[38]</sup> reported significant reductions in further bleeding (80%), blood transfusions and iron requirements in a prospective cohort study of 60 patients with positive CE findings undergoing DBE treatment after  $10 \pm 5.2$  mo follow up. Seventy-seven percent of patients maintained a normal haemoglobin. Hsu *et al*<sup>[59]</sup> similarly found significantly less rebleeding in patients who were treated for an identified lesion when compared to patients in whom no lesion was found (20% *vs* 80%).

Byeon *et al*<sup>[87]</sup> found that repeat DBE in the same direction may detect a source of bleeding in 53% of recurrent OGIB patients, particularly in patients with a previous positive DBE (81% yield). Angiodysplasias were the most common cause of OGIB in both DBEs. An-



gioidysplasia has been identified as a common source of rebleeding in studies exploring outcome in patients with OGIB after PE, CE and or DBE<sup>[88,89]</sup>.

Most studies follow up patients for up to 12 mo. Larger prospective studies with longer follow up are required to evaluate long term outcomes of OGIB patients following DBE.

### Push enteroscopy

Several small studies suggest that patient outcomes are improved after PE<sup>[4]</sup>. In one study of 105 patients with OGIB with a mean follow up of 29 mo, resolution of bleeding occurred in 69% of patients<sup>[90]</sup>. PE impacts upon clinical management in 40%-50% of patients with OGIB<sup>[74,91]</sup>. Decreased transfusion requirements and improvement in functional status one year post treatment have been found with PE<sup>[92]</sup>.

### Other modalities

There are limited data on outcomes of OGIB patients after investigation with other modalities. However, similar to data from CE, DBE and PE, patients who underwent endoscopic treatment for an identified lesion had better outcomes than those without treatment.

Williamson *et al.*<sup>[37]</sup> followed up 61 patients undergoing spiral enteroscopy for OGIB. The mean time to recurrent overt bleeding was 10.4 months. Patients who had endoscopic treatment for bleeding lesions during spiral enteroscopy were significantly less likely to have further overt bleeding (26% *vs* 64%). Increased haemoglobin levels and reduced requirements for blood transfusions, iron supplementation and additional procedures were all observed after spiral enteroscopy.

A retrospective study of IOE demonstrated, at 32 mo follow up, bleeding had resolved in 52% of patients with OGIB in whom a lesion was detected and treated during IOE. Bleeding persisted in 20% and recurred in 8% of patients<sup>[93]</sup>. Angiodysplasias were responsible for the majority of patients with ongoing bleeding<sup>[4]</sup>.

In a retrospective study, Shin *et al.*<sup>[1]</sup> showed that CTE discovered the source of bleeding in only 26.7% of patients with OGIB. The overall re-bleeding rate was 21.7% during a mean follow up of 17.6 mo. Again, patients with positive CTE who were treated endoscopically had significantly reduced rebleeding rates. A negative CTE did not predict lower long term rebleeding, and thus these patients should be closely observed and have further diagnostic work up (such as with CE or DBE) if there is a high clinical suspicion of small bowel bleeding.

## CONCLUSION

Obscure gastrointestinal bleeding is a common problem and remains a diagnostic challenge to gastroenterologists. Various endoscopic, radiological and surgical modalities exist for the investigation of OGIB each with their own advantages, disadvantages and indications in which they should be used. Both CE and DBE remain the corner-

stone of investigation and management of OGIB, with other modalities assuming a more selective role. Ultimately patient factors and resource availability determine the modality used. The short-term outcomes of OGIB patients with a treated lesion are good; however rebleeding is common especially in patients where no source of bleeding was found. Further studies are required to evaluate long-term outcomes. With ongoing development and experience in new techniques, the clinical conundrum that is OGIB may no longer be so obscure.

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