

## Non-small-bowel lesions encountered during double-balloon enteroscopy performed for obscure gastrointestinal bleeding

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**Author contributions:** Tee HP and Kaffes AJ collated the data, performed the statistical analysis and wrote the paper; Kaffes AJ performed the bulk of the procedures; Tee HP assisted the more recent cases.

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**CONCLUSION:** A significant proportion of patients (24.6%) had lesions within reach of conventional endoscopy. Careful repeat examination with gastroscopy and colonoscopy might be required.

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**Key words:** Bleeding; Obscure gastrointestinal bleeding; Endoscopy; Double-balloon enteroscopy

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### Abstract

**AIM:** To report the incidence of non-small-bowel bleeding pathologies encountered during double-balloon enteroscopy (DBE) procedures and to analyse their significance.

**METHODS:** A retrospective study of a prospective DBE database conducted in a tertiary-referral center was conducted. A total of 179 patients with obscure gastrointestinal bleeding (OGIB) referred for DBE from June 2004 to November 2008 were analysed looking for the incidence of non-small-bowel lesions (NSBLs; all and newly diagnosed) encountered during DBE.

**RESULTS:** There were 228 (150 antegrade and 78 retrograde) DBE procedures performed in 179 patients. The mean number of DBE procedures was 1.27 per patient. The mean age (SD) of the patients was 62 ± 16 years old. There were 94 females (52.5%). The positive yield for a bleeding lesion was 65.9%. Of the 179 patients, 44 (24.6%) had NSBLs (19 of them had dual pathology with small-bowel lesions and NSBLs); 27 (15.1%) had lesions not detected by previous endoscopies. The most common type of missed lesions were vascular lesions.

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### INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) accounts for approximately 5% of all patients with gastrointestinal (GI) bleeding<sup>[1]</sup>, and in approximately 75% of these patients, lesions can be found in the small bowel<sup>[2-4]</sup>.

Double balloon enteroscopy (DBE) was introduced by Hironori Yamamoto in 2001<sup>[5]</sup> and in the same year, the United States Food and Drug Administration approved the use of capsule endoscopy (CE)<sup>[6]</sup>. With the advent of CE and DBE, the management of OGIB has been revolutionised<sup>[7]</sup>. Mid-GI bleeding, previously considered almost inaccessible, is now effectively diagnosed and treated by a combination of CE and DBE as ambulatory procedures.

Often non-small-bowel lesions (NSBLs) are identified

during the search for pathology in the small bowel. This was a commonly reported phenomenon in push enteroscopy studies<sup>[8,9]</sup> and has been re-confirmed in CE studies, showing an incidence of NSBL of between 6.4%<sup>[10]</sup> and 38.8%<sup>[11]</sup>. The only DBE series looking at NSBL in OGIB reported a missed rate of 24.3%<sup>[12]</sup>; however, most of these patients had no prior CE. Our study investigated the incidence and clinical relevance of NSBL encountered during DBE performed for OGIB in patients who had prior CE and standard endoscopies.

## MATERIALS AND METHODS

### Study protocol

This is a single-center retrospective study in a tertiary referral teaching hospital in Sydney, Australia, conducted between June 2004 and November 2008. One endoscopist with experience in DBE and in therapeutic endoscopy performed the DBEs, with trainee registrars assisting with the outer tube. DBE was performed using the Fujinon enteroscope (Fujinon EN-450T5, Fujinon Corp., Saitama, Japan). DBE was performed *via* the antegrade (oral) or retrograde (anal) route, and the intention was to perform a targeted approach with the DBE. The approach was determined by the endoscopist, based on the time a lesion was seen in relation to the total small-bowel transit time on the CE study. If the lesion was within the proximal two thirds of the small bowel, then an antegrade DBE was used.

The DBE was performed with the patient either conscious or under deep sedation with a combination of intravenous midazolam (Pfizer, Bentley, Australia), fentanyl (Mayne Pharma Ltd., Mulgrave, Australia), and propofol (Fresofol 1%, Pharmatel Fresenius Kabi Pty Ltd, Hornby, Australia) administered by the assistant or attending anaesthetist. The preparation for the procedures included a fasting period of 8 h before the oral procedure and a routine sodium picosulphate-based bowel preparation (Picoprep, Pharmatel Fresenius Kabi Pty Ltd., Hornby, Australia), or sodium phosphate-based preparations (Fleet, Ferring Pharmaceuticals, Gordon, Australia) with a clear fluid diet the day before the procedure for the anal approach. The DBE technique was as previously described by the innovator H Yamamoto<sup>[5]</sup>.

A failed retrograde DBE was defined as failure to insert the tip of the scope beyond the terminal ileum (approximately 20cm beyond the ileocaecal valve), as previously defined by Fry *et al*<sup>[12]</sup>. The antegrade DBE was considered to be a failure if the endoscopist failed to pass the duodeno-jejunal flexure.

### Patients

All patients were referred by their specialist gastroenterologists or gastrointestinal surgeons to our tertiary referral service. All patients included in the study had OGIB as defined by the American Gastroenterological Association (AGA) criteria<sup>[13]</sup>. Thus, all patients had their initial investigations (EGD and colonoscopy) performed by their

referring gastroenterologists within 6 mo of their CE. Information on patient demographics, previous investigations (endoscopic and radiological), findings and intervention with DBE, limitations of insertion, complication rates, and follow-up after therapy were all retrieved. Ethics board approval was obtained before data collection.

Patients were excluded if they had no prior CE, if the procedure could not be completed due to poor bowel preparation not allowing progress through the colon, procedures performed for colonic indications, sedation failure and technical/equipment failure.

NSBLs were defined as bleeding lesions proximal to the papilla of Vater or distal to the ileocecal valve (i.e. within reach of conventional upper and lower endoscopes). Small-bowel lesions (SBLs) were defined as bleeding lesions that lie between papilla of Vater and ileocaecal valve. Bleeding lesions were defined as lesions that definitely or probably explain the patient's bleeding or anaemia, such as active bleeding lesions, lesions with recent evidence of bleeding, or healed/healing lesions likely to have recently bled. Red marks and classical telangiectatic angioectasia were considered bleeding lesions whereas red spots were not.

### Statistical analysis

The statistical software package SPSS for Windows Version 14 (SPSS Inc., Chicago, Ill) was used to analyse the data. mean  $\pm$  SD was used to summarise data for continuous variables, whereas percentages were used for categorical variables.

## RESULTS

### Demographics

We identified 179 patients with OGIB who were referred for DBE. Two hundred and twenty eight DBE procedures (150 antegrade; 78 retrograde) were performed. Twenty seven patients had both antegrade and retrograde procedures. The mean number of DBE procedures was 1.27 per patient. The mean age (SD) of the patients was 62  $\pm$  16 years. There were 94 females (52.5%).

### Findings

DBE found a bleeding lesion in 118 (65.9%) patients and the distribution of bleeding lesions is summarised in Table 1. Ninety-three out of the total 179 patients (51.9%) had a positive finding localised to SBLs, with the most common being angioectasia ( $n = 64$ ), followed by tumours/polyps ( $n = 13$ ), and small bowel ulcers ( $n = 11$ ) (Table 2). NSBLs were found in 44 (24.6%) patients (Table 3). Nineteen (10.6%) patients had dual bleeding pathologies in both the small bowel and outside the small bowel. Six (3.4%) were inconclusive due to failed procedures and all of them were of the retrograde group. Normal examinations were seen in 55 (30.7%) patients.

A total of 46 NSBLs were found in 44 patients. The majority of these 46 NSBLs were of vascular origin ( $n = 27$ ), and the others were of peptic ( $n = 13$ ) and neoplastic

**Table 1 Findings by DBE performed for OGIB and anatomical distribution of bleeding lesions *n* (%)**

Findings and distributions	Subjects
Positive for bleeding lesions	118 (65.9)
Small bowel only	74 (41.3)
Non-small bowel only	25 (14.0)
Small bowel and non-small bowel	19 (10.6)
Negative findings/normal	55 (30.7)
Inconclusive (failure of procedure)	6 (3.4)
Total	179 (100.0)

DBE: Double balloon enteroscopy; OGIB: Obscure gastrointestinal bleeding.

**Table 2 Small-bowel bleeding lesions found in the study cohort**

Small-bowel lesions	<i>n</i>
Angioectasia	64
Tumours/polyps	13
Ulcers	11
Bleeding mucosa	2
Bleeding diverticula	2
Meckel's diverticulum	1
Stricture	1
Total	94 <sup>a</sup>

<sup>a</sup>Ninety-four small bowel bleeding lesions were found in 93 patients. Nineteen patients also had NSBLs. NSBLs: Non-small-bowel lesions.

(*n* = 6) origins. Thirty-four of the lesions were found in the upper GIT; whereas 12 of the others were in the lower GIT. Of the 44 patients who had NSBL, 27 (15.1% from the total cohort) of their lesions were newly diagnosed during DBE, despite their prior investigations. These included angioectasia (*n* = 12), hiatus hernia with Cameron's erosions (*n* = 3), gastric ulcers (*n* = 2), and others (Table 3).

### Interventions

Endoscopic interventions were performed in 96/118 (81.4%) patients who had positive bleeding lesions; 80 patients had therapeutic interventions (argon plasma coagulation in 75 and polypectomy in five), 14 patients had diagnostic biopsy, and two patients had tattoo placement for targeted surgery. Nineteen patients required medical treatment (18 were given proton pump inhibitors, one received chemotherapy for lymphoma), 11 patients were referred for surgery (eight neoplastic tumours, two bleeds that failed to be controlled endoscopically, and one Meckel's diverticulum).

Among the 44 patients who had NSBLs, endoscopic interventions were given in 23 patients; 20 of them had argon plasma coagulation and three had biopsies. Twenty one patients required medical treatments (18 required proton pump inhibitors and three were given treatment for variceal control). One patient had surgical resection for cecal carcinoma.

## DISCUSSION

The AGA position paper concerning the evaluation and

**Table 3 Classification of NSBLs according to the nature and site of the lesions with totals for all and newly diagnosed lesions by DBE**

Classification of NSBLs encountered on DBE	NSBL ( <i>n</i> )	Newly diagnosed NSBL ( <i>n</i> )
Vascular	27	16
Upper		
Stomach/duodenal angioectasia	12	8
GAVE	3	1
Oesophageal varices	2	1
Gastric varices	1	1
Lower		
Colonic angioectasia	6	4
Haemorrhoids	3	1
Peptic	13	9
Upper		
Hiatus hernia with Cameron's ulcer	5	3
Gastric ulcers/erosions	3	2
GERD (Los Angeles grade 3 or 4)	2	1
Haemorrhagic gastritis	1	1
Duodenal ulcers	1	1
Lower		
Colonic ulcer	1	1
Neoplastic	6	3
Upper		
Gastric polyps	4	1
Lower		
Colonic polyp	1	1
Colorectal carcinoma	1	1
Total	46 <sup>a</sup>	28 <sup>b</sup>

<sup>a</sup>46 NSBLs were found in 44 patients. Nineteen patients also had SBLs; <sup>b</sup>28 newly diagnosed NSBLs were found in 27 patients. GAVE: Gastric antral vascular ectasia; GERD: Gastro-oesophageal reflux disease.

management of obscure GI bleeding was published in January 2000<sup>[14]</sup> and revised in 2007<sup>[13]</sup> following the availability of CE and DBE. The revised guidelines included CE as a pivotal investigation in OGIB. Depending of the findings on CE, DBE plays a key role in delivering targeted therapy or additional diagnostic clarification. One key element in the revised recommendations is for the inclusion of a repeat EGD and colonoscopy. The main point of contention is the timing of repeat procedures, as data is limited and hence the optimal timing of repeat procedures remains unclear.

Missed NSBLs have been a problem previously recorded in many published series. The literature for push enteroscopy has shown missed NSBL to account for up to 64.0% of all positive findings<sup>[8]</sup>. In another push enteroscopy series, missed upper GIT lesions accounted for 10.2% of 233 patients who had OGIB<sup>[9]</sup>. This issue has continued into the CE data, with several reports now showing missed NSBL in the order of 6.4%<sup>[10]</sup> to 38.8%<sup>[11]</sup>. Not surprisingly, Fry *et al.*<sup>[12]</sup> in their DBE series reported the missed NSBL rate to be 24.3%; however, in that series CE was not available for all of their patients. In our cohort, NSBLs were detected in 24.6% of patients, a number strikingly similar to Fry *et al.*<sup>[12]</sup>. However, all our patients had prior CE. In such circumstances, it stands to reason that CE would have identified some missed lesions and our figure should have been lower than that of Fry *et al.*<sup>[12]</sup>. There was one clear explanation

for this. Not all NSBLs in our series were in fact completely missed. A significant number of these NSBLs were suspected or known by the referring doctors. However, referrals were made to exclude dual pathology (SBL and NSBL). Excluding those NSBLs that were known by previous investigations, the true missed rate for NSBL in our cohort was actually 15.1%.

There are several reasons to explain why lesions could be missed on conventional endoscopies. Lesions such as Dieulafoy's can be very difficult to diagnose as they can "resolve" by the time patients have their endoscopy. Often small-bowel bleeding can be caused by similar types of lesions and hence are dependent on the "timing" of DBE. This is best illustrated in study by Pennazio *et al*<sup>[15]</sup>, in which the group of patients with ongoing overt bleeding had a 92.3% positive yield on CE when compared to groups with previous overt bleeding (12.9%) and guaiac-positive stool/iron deficiency anaemia (44.2%). If DBE could be performed during active bleeding then similar diagnostic rates with the addition of therapy should be achieved, limited only by the inferior total enteroscopy rates of DBE (77.5%<sup>[16]</sup> in the hands of experts).

Lesions such as Cameron's erosions also depend on the timing of endoscopy to confirm them as the bleeding source. Often, gastroenterologists referred such patients to our service with a high index of suspicion for Cameron's lesions but with no successful endoscopic timing. Hypovolemia and anaemia could cause lesions to look less obvious and this is particularly the case with small angioectasia, and could account for some missed lesions. Inadequate endoscopic examination also remains an issue. Despite the ease of EGD, careful examination for small lesions placed in awkward or in blind spots should be considered, and a more diligent and thorough examination is warranted in patients with OGIB. Likewise, an excellent colon preparation is required with a careful mucosal examination to exclude small mucosal bleeding points.

Missed lesions are highly relevant in the management of OGIB. Hartmann *et al*<sup>[17]</sup> studied 47 patients who had OGIB and were subjected to CE and intraoperative enteroscopy. Despite the accurate diagnosis from total small bowel examination and curative endoscopic and surgical treatments, on a mean follow up of 346 d, 25.5% of the patients had a re-bleed, and 19.1% of them required further interventions or blood transfusion. This suggests that despite the gold standard diagnostic and therapeutic approaches (in this case CE and IOE), many patients continue to bleed. Missed lesions could play a key role in these patients. In some series of patients with OGIB and a negative CE who continue to bleed, a repeat CE can find a lesion in up to 75% of patients<sup>[18]</sup>. Hence, patients who re-bleed need repeat examination of their entire GI tract to look for missed lesions.

In our cohort, 19 patients with NSBL had dual bleeding pathologies with both NSBL and SBL involvement. This suggests that if a significant NSBL is found during DBE, the small bowel examination should be completed, as approximately half of these patients will

also have a significant small bowel finding. Conversely, if a definite bleeding site is found in the small bowel, then careful examination for NSBL is still warranted, even when no suspicion exists for NSBL due to the high true missed rate in our cohort of 15.1%.

The low diagnostic rates in our cohort reflect some real issues in managing patients with OGIB. Not all findings at CE are relevant and often the role of DBE is to exclude a lesion. One recurrent and classic situation is folds of bowel that appear like a polyp or a submucosal lesion. In addition, flecks of transported blood or mucous on the bowel surface could be mistaken as angioectasia or ulcers. Several studies, including our previous work<sup>[19]</sup>, found that many CE findings are false positives.

We recognised the limitation of this study as being a retrospective series. It was difficult to classify all lesions into bleeding and non-bleeding lesions. We had to include a group of lesions as probable bleeders due to the size, appearance, history, and behaviour of the lesions. For instance, large polyps, extensive ulcerative disease, and malignant-looking lesions were considered probable bleeders, even though no blood or altered blood was detected on endoscopy. Likewise, diverticular disease might be considered a bleeder or non-bleeder based on their number and appearance.

In conclusion, NSBLs are a common finding during DBE, despite prior endoscopic examinations. Importantly, 15.1% of patients had unsuspected findings and hence careful examination of the entire GI tract is essential in all patients.

## COMMENTS

### Background

The problem of "missed" lesions seen at subsequent endoscopic examinations has been well documented in patients with obscure gastrointestinal bleeding (OGIB). The exact degree of this problem in the new era of capsule endoscopy and double-balloon enteroscopy remains unclear.

### Research frontiers

The degree of the problem, the type of lesions missed, and the timing of repeat endoscopic examinations require further evaluation.

### Innovations and breakthroughs

This paper shows that in a tertiary referral practice, the rate of missed lesions can be as high as 1 in 4 patients and thus highlights the relevance of repeat examinations in patients with ongoing OGIB.

### Applications

In patients with ongoing OGIB without a definite finding on endoscopic evaluation, repeat procedures are worthwhile.

### Terminology

OGIB is defined as bleeding with a negative endoscopy and colonoscopy.

### Peer review

This paper is well written and provides new information on missed sites of bleeding within reach of conventional endoscopy and colonoscopy following capsule and regular endoscopy. The value of double balloon enteroscopy is also highlighted in diagnostic and therapeutic terms.

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