



ELSEVIER

2

Enteroscopy

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Until the end of the 20th century, push enteroscopy (PE) was the most commonly used method for the endoscopic investigation of the small bowel. However, PE has been almost completely replaced by double balloon enteroscopy (DBE). Undoubtedly the major endoscopic breakthrough of the last decade, DBE has contributed to the better diagnosis and understanding of diseases of the small bowel, opening-up this obscure part of the gastrointestinal tract to visualisation. Modern diagnostic and therapeutic DBE allows for a deeper and more thorough evaluation of the small bowel than PE, enabling the detection of more pathological lesions. In addition, DBE has for the first time enabled endoscopists to observe the entire small intestine, and has provided endoscopic interventions such as cauterisation of bleeding lesions, polypectomy, placement of small bowel stents, and foreign-body extraction.

Key words: Coeliac disease; Crohn's disease; Double balloon enteroscopy; Enteroscopy; Gastrointestinal bleeding; Push-and-pull enteroscopy; Small bowel.

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INTRODUCTION

The small intestine is the most difficult area of the gastrointestinal (GI) tract to evaluate using endoscopic methods. A major breakthrough in imaging of the small intestine came with capsule endoscopy (CE), which for the first time permitted a detailed view of the mucosal surface.^{1,2} However, CE has several limitations, including: the inability to obtain tissue for diagnosis; the inability to provide endoscopic intervention such as polyp removal, dilation of strictures, or cauterisation of angiodysplasias; and the inability to evaluate a lesion in a to-and-fro manner. Thus, when tissue for diagnosis is essential or therapeutic interventions are mandatory, traditional endoscopic methods that permit biopsy retrieval and application of therapeutic interventions through the endoscopic channel are essential.

Until the end of the 20th century, the traditional method for endoscopic investigation of the small bowel was push enteroscopy (PE).³ This has now been almost completely replaced by double balloon enteroscopy (DBE), which was first described by Yamamoto et al in 2001.^{4,5} DBE for the first time enabled endoscopists to observe the entire small intestine and to provide treatment without excessive stress on the patient. DBE allows for a deeper and more thorough evaluation of the small intestine than PE, allowing the detection of more pathological lesions.^{6,7} The utility of DBE for the diagnosis and therapy of small-bowel disorders has been demonstrated in several prospective and retrospective single- and multi-centre studies (see Tables 1–3).^{8–16} A single balloon enteroscope (SBE) has recently been developed.^{17–23} Various studies confirm that deep, small-bowel intubation can be achieved

Table 1. Summary of double balloon enteroscopy studies for obscure gastrointestinal bleeding

Author	Year	No. of patients	Diagnosis	Endoscopic therapy
Kaffes et al	2007	60	45 (75%)	57%
Mönkemüller et al	2007	104	53 (51%)	70%
Suzuki et al	2007	19	15 (79%)	16%
Zhong et al	2007	191	154 (80.6%)	NR
Byeon et al	2007	43	30 (69.8%)	NR
Hsu et al	2007	20	15 (75%)	55%
Ohmiya et al	2007	479	277 (58%)	36%
Safatle-Ribeiro et al	2007	20	15 (75%)	64%
Zhi et al	2007	92	85 (92%)	NR
Sun et al	2006	152	115 (76%)	12%
Manabe et al	2006	31	23 (74%)	10%
May et al	2006	52	38 (73%)	50%
Heine et al	2006	168	123 (73)	36%
Mönkemüller et al	2006	29	11 (38%)	28%
Hadithi et al	2006	35	21 (60%)	60%
Mehdizadeh et al	2006	130	66 (51%)	27%
Nakamura et al	2006	28	12 (43%)	11%
Akahoshi et al	2006	20	5 (25%)	20%
Di Caro et al	2005	33	29 (88%)	55%
Ell et al	2005	64	40 (55.5%)	37%
Yamamoto et al	2004	66	50 (76%)	20%
May et al	2003	7	7 (100%)	43%

NR, not reported.

in the majority of patients. However, further studies using SBE, as well as prospective studies comparing DBE versus SBE are needed, and for now DBE remains the method of choice for modern diagnostic and therapeutic enteroscopy; for this reason, this chapter focuses on DBE.^{24,25}

TECHNICAL ASPECTS OF DOUBLE BALLOON ENTEROSCOPY

Instruments

Two types of double balloon enteroscope are currently available for investigation of the small bowel.^{5,8-16} The working length of both EN-450P5 and EN-450T5 is 200 cm. The external diameter of the therapeutic DBE is 9.4 mm, whereas the diagnostic DBE has a diameter of 8.5 mm. The diameter of the working channel of the therapeutic DBE is 2.8 mm whereas that of the diagnostic DBE is 2.2 mm. These details are important so that the appropriate accessory materials (e.g. biopsy forceps, snares, and needles) can be selected. Both channels allow for the passage of the standard biopsy forceps, snare, injection needle, standard biliary catheter, and the thin argon plasma. The EN-450T5 is used with a 145-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm. EC-450BI5 is used with a 105-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm. The channel of this enteroscope allows passage of all the above mentioned accessories as well as seven Fr plastic stents.^{4,5,8-16}

Technique

The use of the DBE in the pig and the Erlangen training models has increased our understanding of the mechanics and handling of DBE.²⁶ The major advantage of the DBE system is the presence of the balloons on both the overtube and endoscope. These balloons help to anchor the scope and/or overtube in difficult positions, providing further stability during the procedure.⁴⁻¹² Stabilisation of the intestine by gripping the intestinal wall with a balloon attached to the distal end of a flexible overtube makes it possible to advance the enteroscope deeply; the overtube prevents further bending or looping of the intestine. Furthermore, the balloon attached to the endoscopic tip anchors the endoscope during the advancement of the overtube, thus preventing the intestine sliding back as the overtube is advanced towards the enteroscope.^{4,5} The endoscope moves forward using two balloons in sequence, folding and shortening the long intestine onto the overtube and making a concentric circle with its shaft.

DBE is a complex examination and should be carried out only by experienced endoscopists who are well versed with the various pathologies of the small bowel. Skilled interventional endoscopists will also have the advantage of being able to utilise the enteroscope for biliary procedures, investigate the excluded stomach in patients with gastric bypass operations, or perform colonoscopies in patients with previously failed colonoscopy.²⁷⁻³² Before attempting this procedure, a thorough review of the basic principles of DBE is mandatory. Some experts advocate participation in workshops using Erlangen or animal models. However, as with most endoscopic procedures, there is no better substitute than one-on-one training with an experienced endoscopist.

Two groups have evaluated the learning curve of DBE.^{33,34} Both assessed the performance parameters from the endoscopists' initial cases and compared them to the subsequent examinations. In a multicenter study involving six US tertiary centres with a total of 188 subjects undergoing 237 procedures, Mehdizadeh et al investigated the technical details the learning curve associated with DBE.³³ The main outcome measurements were exam duration, depth of insertion, and findings on DBE examination. DBE was introduced by mouth in 149 (63%) cases, by rectum in 77 (33%) cases. The mean (\pm SD) duration was 109.1 ± 44.6 min for the first 10 cases and 92.4 ± 37.6 min for subsequent cases ($P = 0.005$) but did not change for rectal DBE procedures. There was no change in mean depth of insertion, but the mean fluoroscopy time declined significantly ($P = 0.025$). Diagnostic or therapeutic manoeuvres were performed in 64% of cases; DBE led to a diagnosis in 81 (43%) patients. Retrograde DBE failed to reach the small bowel in 24 (31%) cases.³³ The authors concluded that there was a significant decline in overall procedural time and fluoroscopy time after the initial 10 DBE cases. There was no improvement in performance parameters when DBE was performed via the rectal approach despite increased, but limited, operator experience.

Our group (Mönkemüller et al)³⁴ found that there was a steady improvement after 10–15 cases, with the procedure time decreasing an average of 30 min after the first 15 cases and the depth of insertion increasing by more than one metre. The depth of insertion was significantly greater when using the oral route than when the anal approach was used. Although there was a gradual improvement in the depth of insertion when using the anal route, ileal intubation remained difficult despite advanced experience.³⁴ Recognition of this learning curve will help endoscopists who are planning to perform DBE to plan the caseload of individual endoscopy units and to establish base-lines for DBE skill certification.

The standard approach to performing DBE requires two individuals: operator and assistant. In the standard DBE method, an assistant constantly holds the overtube, while an operator handles the enteroscope; the two movements of the push-and-pull manoeuvre are performed by both assistant and operator. However, Araki et al³⁵ have described a single-endoscopist method in which these two movements are performed using only the right hand of one operator, catching the proximal end of the overtube with the thumb and the forefinger, and gripping the endoscope with the little and the third fingers and the posterior part of the palm. The operator's right hand is used to insert the endoscope through the overtube; the left hand is used to pull back the endoscope and hold the endoscope handle. This method appears to be equivalent to the 'two-endoscopists' approach. We believe, however, that this single-operator DBE method should be used only with general anaesthesia. There tends to be patient movement during the procedure when conscious sedation is used; the additional physician is necessary not only to assist during the procedure, but also to aid in patient supervision in these situations.

Determination of the primary route of insertion (oral or antegrade versus anal or retrograde)

The choice between the oral and the anal routes depends on the suspected location of the lesions within the small bowel; this is based on the clinical manifestations and on the results of laboratory, radiological, and CE examinations.^{4–18} For conditions such as familial adenomatous polyposis syndrome (FAP), Peutz–Jegher syndrome (PJS), and

coeliac disease it is generally best to start with an oral DBE, because small-bowel adenomatous polyps (FAP), enteropathy-associated T-cell lymphoma (coeliac disease), or adenocarcinoma (coeliac disease, FAP) are most common in the duodenum and jejunum.⁴⁻¹⁸

CE is currently the main instrument used to indicate the preferential endoscope insertion route for DBE in obscure gastrointestinal bleeding (OGIB). Two studies have evaluated the 'CE-directed approach'.^{36,37} Pennazio et al used this approach in a group of 44 patients and found that a one-sided procedure (oral or anal) was sufficient to reach the lesion of interest in almost 90% of the DBE-examinations.³⁶ Gay et al reported on similar high yields.³⁷ In cases of obscure GI bleeding, the stool colour can also help to direct the DBE route: the oral route in the case of melaena and the anal route in the case of haematochezia; however, this approach has not been validated. In general, total enteroscopy by DBE is not required in the majority of the patients with OGIB, as the potential bleeding source can be generally identified without visualisation of the entire small bowel. Nonetheless, about one-third of patients will require two separate DBEs to make a diagnosis.

Unfortunately, total enteroscopy is not always achievable. Success rates of total small-bowel investigation (oral insertion and reaching the cecum) using the antegrade approach range from 0% to 5%, and total enteroscopy using oral and anal approach ranges from 0% to 86%.⁴⁻¹⁸ Reasons for failing to achieve total enteroscopy include marked intestinal adhesion caused by previous abdominal or pelvic surgery, type of endoscope used (thin diagnostic DBE versus therapeutic DBE), and the endoscopist's level of experience.^{4,18,38}

Complications of double balloon enteroscopy

Besides post-polypectomy bleeding and perforation, several unique complications related to DBE have been reported, including pancreatitis, intestinal necrosis from an epinephrine injection, intramural haematoma, and paralytic ileus.³⁹⁻⁵⁰ Two large studies have reported on the complications associated DBE.^{40,41} A large, multicenter international complication survey was presented by Mensink et al.⁴⁰ A total of 10 centres across four continents were participated in the study and reported on a total of 40 complications in 2362 DBE procedures, 13 in 1728 diagnostic DBE (0.8%), and 27 during 634 therapeutic procedures (4.3%). The complications were rated minor in 21 (0.9%), moderate in 6 (0.3%), and severe in 13 procedures (0.6%). No fatal complications were reported. Seven cases of pancreatitis were reported, six after diagnostic (0.3%) and one after therapeutic (0.2%) DBE.⁴⁰ Pancreatitis should therefore always be considered in patients with persistent abdominal complaints after DBE.

In another study, Moeschler et al contacted all endoscopic units using DBE in Germany and collected data over a three-year period.⁴¹ In all, 64 of 85 endoscopic centres responded to the questionnaire. From a total of 3894 reported DBE-examinations (2685 using the oral route and 1209 using the anal route), including 1086 therapeutic interventions [857 argon plasma coagulation (APC) therapy, 177 polypectomies, 26 dilatations, and 26 other], a total of 48 complications were reported (1.2%). The most common complications were acute pancreatitis in nine patients (0.34%) with one lethality, perforation in eight cases (six post-polypectomy), major bleeding in six patients (four in the context of polypectomy and two after biopsy).⁴¹ All patients received endoscopic treatment and recovered from this complication.

Pancreatitis is the most commonly reported complication after DBE.^{40–48} In the largest prospective, single-centre study reporting on post-DBE pancreatitis, Jarbandhan et al noted an incidence of 1.5% (6 out of 403 patients undergoing 600 procedures), all after antegrade DBE.⁴³ There was no association with gender, duration of procedure, or type of endoscope. Four patients had severe pancreatitis. The reasons why patients undergoing DBE develop pancreatitis are unclear. One hypothesis is that the inflation of the balloon (or balloons) in the duodenum creates duodenal luminal hypertension, which might overcome the pressure gradient provided by an intact sphincter of Oddi and pancreatic juice flow and lead to duodenal reflux and subsequent development of acute pancreatitis.⁴⁵ However, we have observed one case of pancreatitis in a patient undergoing enteroscopy with a colonoscope. The second hypothesis suggests that post-DBE pancreatitis is caused by repetitive mechanical strain on the pancreas. Two groups have specifically measured amylase levels in patients before and after DBE.^{47,49} Honda et al found that 46% of patients undergoing DBE develop hyperamylasemia.⁴⁷ Kopáčová et al prospectively investigated on the significance of hyperamylasemia in patients undergoing DBE.⁴⁹ Thirty-five oral DBEs were carried out in 31 patients and serum amylase, lipase, C-reactive protein (CRP), and urine amylase were taken before the procedure and 4 and 24 h after the investigation. One patient (2.8%) had acute pancreatitis after DBE. However, elevation of amylase levels after the procedure was found in 51.4% and abdominal pain or nausea or vomiting in 34.3%, although 8.6% of these patients had no hyperamylasemia after DBE.⁴⁹

INDICATIONS

The most common indications for DBE are OGIB and evaluation of suspected Crohn's disease (Figures 1–3).^{4–18,51–57} However, DBE is used increasingly to confirm lesions seen on CE, to evaluate patients with coeliac disease for the presence of enteropathy-associated T-cell lymphoma (EATL), and to screen and survey patients with familial polyposis syndromes (FAP and PJS) (Figure 4). Box 1 shows the current indications for enteroscopy.



Figure 1. The most common cause of small-bowel bleeding is angioectasias.

DBE also is useful for evaluation of abnormal findings on CE. This issue is becoming increasingly important. At present, the significance of mucosal breaks and nonspecific ulcerations, and the management of thickened folds and suspected polyps photographed by CE are not known.

Box 1 Indications and potential therapeutic interventions using the double balloon enteroscope (DBE)

- Small bowel bleeding
 - haemostasis:
 - argon plasma coagulation (APC);
 - injection of epinephrine;
 - injection of Histoacryl;
 - placement of clips.
- Crohn's disease
 - stricture dilation.
- Coeliac disease (surveillance)
- Polyposis syndromes (surveillance)
 - polypectomy;
 - endoscopic mucosal resection.
- NSAID enteropathy
 - balloon dilation of strictures.
- Tumours (adenocarcinoma, search for neuroendocrine tumours)
 - submucosal injection with India ink;
 - small bowel and colonic stent placement.
- Removal of foreign body
- PEG in altered bowel anatomy (gastric bypass and roux-Y)
- Biliary interventions
 - ERCP.

Bleeding and anaemia

OGIB accounts for approximately 5% of all GI bleeds and is currently defined as bleeding of unknown origin that persists or recurs after a negative initial EGD and colonoscopy.⁵¹⁻⁵⁴ Because most OGIB originates in the small bowel, distal to the ligament of Treitz and proximal to the terminal ileum, OGIB is also rightly called mid-GI or mid-gut bleeding (Figure 1).⁵² When evaluating patients with OGIB, it is important to repeat both EGD and colonoscopy because a significant number of these patients will have bleeding lesions in the oesophagus, stomach, or colon that were overlooked during the initial work-up.⁵⁷

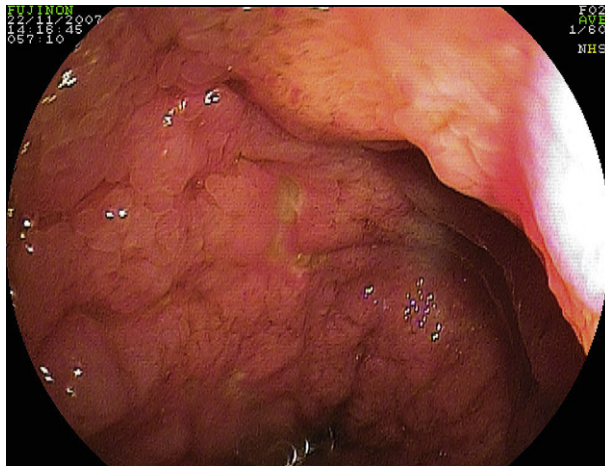


Figure 2. The major advantage of performing double balloon enteroscopy in patients with suspected Crohn's disease is the ability to obtain excellent endoscopic visualisation of the lesions, to investigate them in a to-and-fro manner and to obtain tissue. Note the cobblestone appearance of the mucosa.

DIAGNOSTIC YIELD OF DOUBLE BALLOON ENTEROSCOPY IN PATIENTS WITH OGIB

The diagnostic yield for DBE in OGIB varies from 38% to 91% (Table 2).^{4-18,51-77} Pasha et al performed a systematic review of the literature to determine the diagnostic and therapeutic yield of DBE in patients with OGIB.⁷⁶ Thirteen studies including 906 patients were analysed. DBE detected a potential bleeding source in 66% of patients, which included angioectasias (25.6%), inflammatory lesions (16.1%), and small-bowel

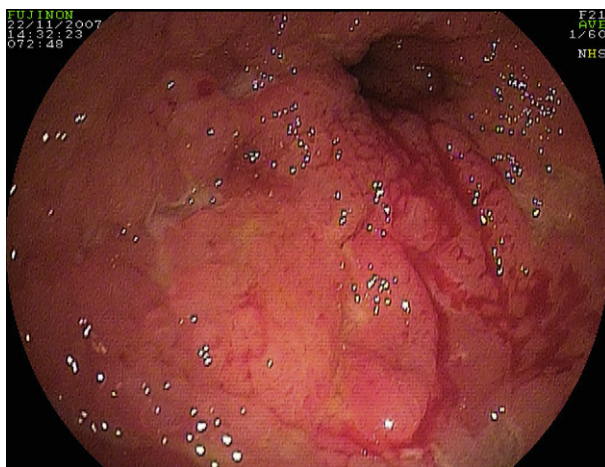


Figure 3. Involvement of the small bowel occurs in at least 30% of patients with Crohn's disease. Strictures are a feared complication of Crohn's disease. If these are short, single, and nonfibrotic, double balloon enteroscopy-assisted balloon dilation might be useful.

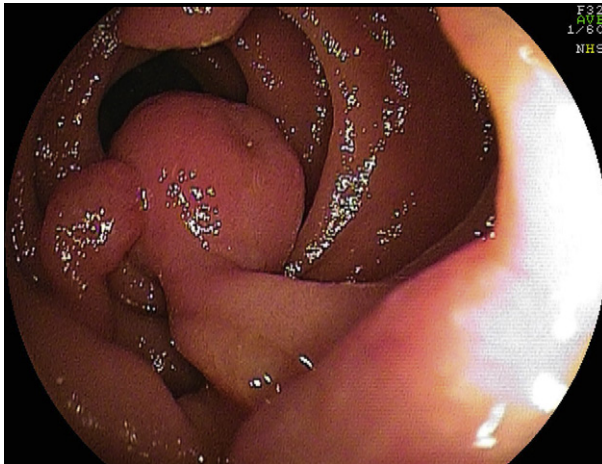


Figure 4. Typical hamartomatous polyp in patients with Peutz-Jegher's syndrome.

neoplasms (13.9%) (Figures 5 and 6). Interestingly, small-bowel ulcers and tumours are the most common diagnostic findings in series originating from Far Eastern countries, whereas in European and North/South American studies the most common diagnostic findings are angioectasias. DBE directly influences management in 44–80% patients, resulting in a new diagnosis, change in management, or improved outcomes in 60–70% of patients with OGIB.⁷⁶

It is not clear why the diagnostic rates are so variable. It is likely that the difference in diagnostic yield depends on a combination of factors, including indication (obscure overt versus obscure occult), quality, and completeness of pre-DBE endoscopic investigations, timing of DBE, as well as performance of a pre-DBE CE. Studies with the highest yield included a large amount of patients with previous CE, whereas lower yields were achieved in patients investigated without previous CE.^{51–77} In a series of 162 OGIB patients, the clinical relevance of findings at prior CE and the oral access route were found to be associated with a significantly higher yield of DBE.⁷⁷ Also, higher yields are generally achieved when the indication was obscure overt bleeding as compared to obscure occult.^{59–77}

Table 2. Studies comparing diagnostic yields of capsule endoscopy and double balloon enteroscopy in patients with obscure gastrointestinal bleeding

Author	Year	No. of patients	Results
Hadithi et al	2006	35	CE > DBE
Mehdizadeh et al	2006	115	CE ≈ DBE
Nakamura et al	2006	28	CE ≈ DBE
Damian et al	2006	28	CE > DBE
Kameda et al	2006	24	CE ≈ DBE
Wi et al	2006	10	DBE > CE
Matsumoto et al	2005	13	CE ≈ DBE
Zhang et al	2004	24	DBE > CE

CE, capsule endoscopy; DBE, double balloon enteroscopy.

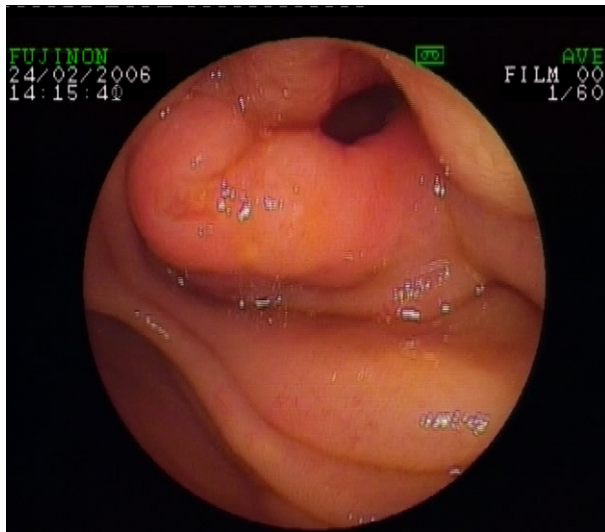


Figure 5. Double balloon enteroscopy has facilitated the diagnosis of jejunal adenocarcinoma – a condition that was formerly diagnosed only at post-mortem or after the tumour had resulted in total small-bowel obstruction.

COMPARISON OF DOUBLE BALLOON ENTEROSCOPY WITH CAPSULE ENDOSCOPY

Several studies have compared DBE to CE in patients with OGIB (Table 3).^{70–72,78–82} Most studies report concordant findings but two prospective studies report higher yields for CE than DBE.^{70,78} In a prospective study of 35 patients with OGIB, the diagnostic rate of small-bowel abnormalities by CE (80%) was significantly higher than by

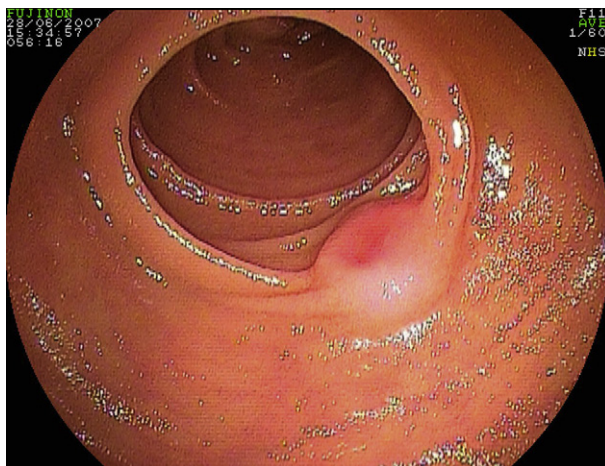


Figure 6. Double balloon enteroscopy is helpful in localising primary neuroendocrine tumours of the small bowel.

Table 3. Published data on the use of double balloon enteroscopy and capsule endoscopy for diagnosis and treatment of small-bowel polyps in polyposis syndromes

Author (year)	DBE/CE	Polyposis syndrome	Number of polyps	Size of polyps	No. of patients	Percentage patients with small-bowel polyps	Site of polyps	Impact on treatment
Schulmann et al (2005)	CE	FAP, PJ	FAP: 1 to >40; PJ: 1 to >100	FAP: 2–30 mm; PJ: <3 mm–7 cm	FAP: 9; PJ: 11	FAP: 72%; PJ: 91%	FAP + PJ: duodenum, jejunum, ileum	+
Mönkemüller et al (2007)	DBE	FAP	1–50	2–12 mm	9	88%	Duodenum (+ papilla), jejunum Jejunum, ileum	+
Matsumoto et al (2005)	DBE/CE	FAP, PJ, MET, MLP	DBE: 1–23; CE: 1–123	ND	9	DBE: 66.7%; CE: 33.3%	Jejunum, ileum	+
Safatle-Ribeiro et al (2007)	DBE	FAP, Gardner's syndrome; PJ	Gardner's: multiple; FAP: multiple; PJ: multiple	Gardner's: 3–20 mm; FAP: ND; PJ: 5–15 mm	4	100%	FAP: duodenum, jejunum, ileum PJ::stomach, duodenum, jejunum Gardner's: duodenum Jejunum, ileum	+
Ross et al (2006)	DBE, laparoscopically assisted	PJ	1–6	0.5–5 cm	3	100%	Jejunum, ileum	+
Soares et al (2004)	CE	PJ	1 to >21	<5 to > 11 mm	14	100%	Stomach, duodenum, jejunum, ileum	+
Wong et al (2006)	CE/push enteroscopy	FAP	1 to >400	1–20 mm	32			
Burke et al (2005)	CE	FAP, PJ	FAP: 1 to >20; PJ: >20	FAP: 1–10 mm; PJ: >10 mm	FAP: 15; PJ: 4	FAP: 60%; PJ: 75%	Duodenum, jejunum, ileum	+

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Table 3 (continued)

Author (year)	DBE/CE	Polyposis syndrome	Number of polyps	Size of polyps	No. of patients	Percentage patients with small-bowel polyps	Site of polyps	Impact on treatment
Ohmiya et al (2005)	DBE	PJ	Multiple	10–60 mm	2	100%	Duodenum, jejunum/ileum	+
Heine et al (2006)	DBE	PJ; FAP/ Gardner's	ND	ND	PJ: 14; FAP/ Gardner's: 6	ND	Jejunum, ileum	+
Brown et al (2006)	CE	PJ	1–18	To 3.5 cm	19	89%	Duodenum, jejunum, ileum	+
Mata et al (2005)	CE	FAP; PJ	FAP: 1–7; PJ: 1–14	ND	FAP: 20; PJ: 4	FAP: 20%; PJ: 75%	Duodenum, jejunum, ileum	+
Perez-Cuadrado et al (2006)	DBE	PJ	1–15	To 3.5 cm	3	100%	Ileum/ND	+
Caspari et al (2004)	CE	FAP; PJ	FAP: 1–2; PJ: 42–148	FAP: 1–5 mm; PJ: 1- to > 15 mm	FAP: 16; PJ: 4	FAP: 25%; PJ: 100%	ND	?
May et al (2005)	DBE	FAP; PJ	ND	To 5 cm	FAP: 9; PJ: 3	100%	ND	+

CE: capsule endoscopy; DBE, double balloon enteroscopy; FAP, familial adenomatous polyp syndrome; MET, multiple endocrine tumours; MLP, multiple lymphomatous polyposis; ND, no data; PJ, Peutz-Jegher's syndrome.

DBE (60%).⁷⁰ Another prospective study showed a diagnostic rate by CE of 59.4% compared to 42.9% for DBE.⁷⁸

In a large, multicenter study in the US, the diagnostic yield of DBE and CE was evaluated retrospectively in a group of 115 patients with OGIB.³³ CE identified a potential bleeding source in 55% of patients. In these patients, DBE confirmed a potential bleeding source in 41.65%. These results are hypothesised to depend on an overestimation of CE findings. In the 52 patients with negative CE, DBE was positive in 16.30%. Of note, DBE detected four large adenocarcinomas that were missed by CE.³³ This is a very important finding and a clinician should not be reassured with a negative finding in a patient with persistent anaemia.

Current algorithm for OGIB

The ideal place of DBE for the investigation of patients with acute obscure overt GI bleeding remains to be defined (Figure 7). However, we believe that the diagnostic work-up of patients with OGIB should be individualised on the basis of their clinical presentation. In cases of obscure occult bleeding, it appears best to start with a CE, and perform DBE only if a potential source is identified (Figure 7).^{51,54,56} In patients with suspicious findings, DBE can be used to either confirm the lesion through visualisation and retrieval of tissue or to provide endoscopic therapy. However, as showed in various reports, relevant lesions can be missed by CE.^{51,54,56,60–64} Thus, DBE should be strongly considered in patients being at higher risk of a small-bowel lesion despite negative CE. These include patients with iron-deficiency anaemia, weight loss, and diarrhoea.

In patients with obscure overt GI bleeding, it appears that DBE should be the initial test because of the high likelihood of finding a potentially treatable lesion.^{4–18,60–64} Nevertheless, there are no prospective studies comparing the diagnostic yield of CE

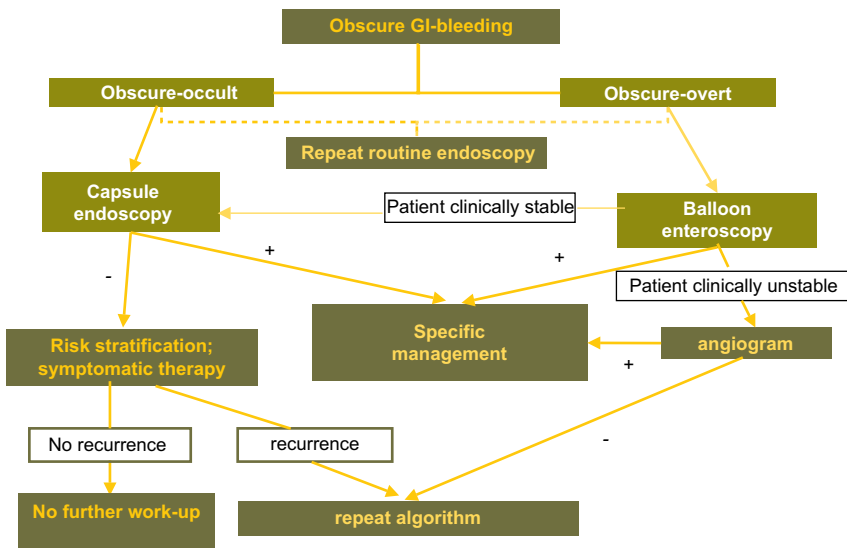


Figure 7. Proposed algorithm for the approach to obscure gastrointestinal bleeding.

and DBE in this setting. Definite indications for starting with a DBE in this setting are suspicion of small-bowel stricture (clinically or by other imaging techniques) and patients with surgically modified anatomy (especially those with an afferent intestinal loop).^{83,84}

Furthermore, the timing of DBE in obscure overt GI bleeding has not been defined, and it is commonly considered 'emergent' when performed within the first 48 h of presentation. In our opinion, a true emergent DBE should be performed within 24 h, and preferably 12 h, of patient presentation.

CROHN'S DISEASE AND INFLAMMATORY BOWEL DISEASE

The diagnosis of Crohn's disease (CD), especially in cases of isolated small-bowel involvement, remains challenging. CE is limited by its ability to retrieve tissue and the diagnosis is based on inspection of the endoscopic appearance.

There are now several reports on the clinical utility of DBE in the diagnosis and management of small bowel CD.⁸⁴⁻⁹³ A retrospective study analysed the results of 35 investigations performed in 26 patients with known or suspected CD.^{84,85} A diagnosis of active disease was achieved in 71%, with the additional finding of previously unknown structuring disease in four patients. The medical therapy was changed in all of these patients after the findings of DBE. DBE had a clinical impact of 70% in patients with ill-defined or unexplained symptoms after negative conventional investigations.⁸⁴ Another study revealed approximately the same percentage of clinical impact.⁸⁴ Thirty-five patients, 17 with known and 18 with suspected CD, were extracted from a prospectively collected database of five tertiary centres in the US. DBE results altered clinical management in a total of 63% of patients. Of 12 patients with small-bowel lesions in CE, seven could be confirmed to have definite CD after a biopsy taken during DBE.⁸⁴ In an unblinded study, Oshitani et al reported the results of retrograde DBE in 38 patients with established CD.⁹² Twenty-four patients (63%) had ileal involvement more than 20 cm proximal to the terminal ileum, without any involvement of the distal terminal ileum. In 4 of 18 patients (22.2%) small-bowel barium studies failed to identify mucosal changes that were identified on DBE. CE was performed in eight patients, one of whom had mucosal abnormalities not detected by DBE or barium small-bowel follow-through. The authors report two additional cases of CD presenting with GI haemorrhage diagnosed for the first time by DBE.

A meta-analysis evaluated 18 prospective studies comparing CE with push enteroscopy, small-bowel radiography, CT-enterography, ileocolonoscopy, and MR-enterography.⁹⁴ CE has the highest diagnostic yield in the evaluation of nonstricturing small-bowel CD, whereas MR-enterography had a slightly better diagnostic impact in patients with known CD. Therefore, CE might be a first-line investigation for initial diagnosis of CD.⁴ It must be pointed out that for the possible presence of asymptomatic strictures in known CD a radiological investigation, possibly MR-enterography, should precede CE in the diagnostic algorithm (Figure 8).

COELIAC DISEASE

Patients with coeliac disease who improve on a gluten-free diet (GFD) can be monitored using conventional EGD with duodenal biopsy specimens.⁹⁵ However, DBE should be considered in patients with CD who are persistently symptomatic despite a GFD, especially if they are older than 50 years. Patients with weight loss, abdominal

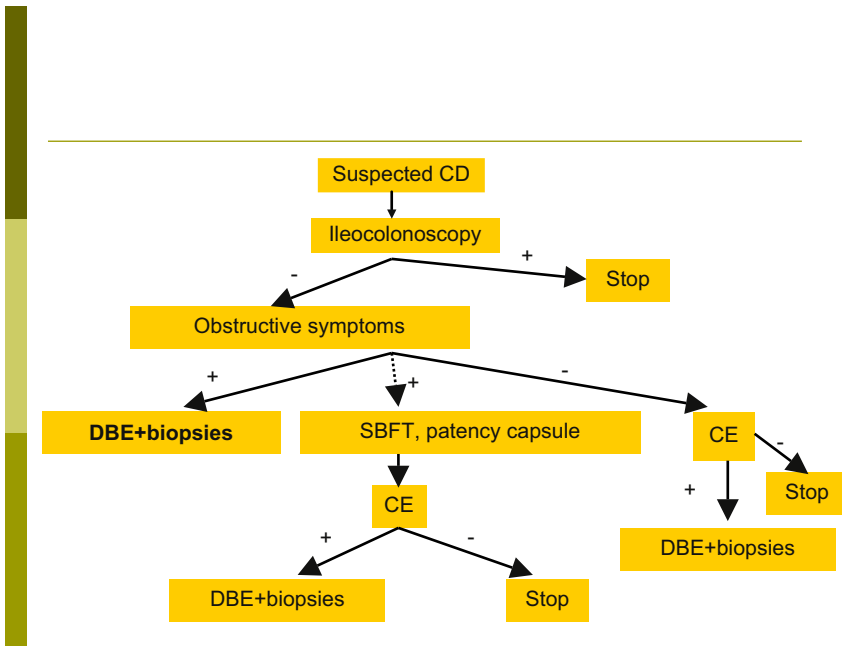


Figure 8. Proposed algorithm for the diagnosis of small-bowel Crohn's disease.

pain, diarrhoea, or anaemia, or who have a history or clinical, radiological or CE findings suggestive of small-bowel stenosis should also be considered for DBE as they might have developed ulcerative jejunitis, enteropathy-associated T-cell lymphoma (EATL) or small bowel adenocarcinoma.^{96–101}

EATLs have a wide spectrum of endoscopic appearance including absent or flat mucosal villi; small, round or confluent ulcers; or large ulcerated masses, frequently with associated necrosis or stenosis.^{100,102–104} Not infrequently, patients with EATL or ulcerative jejunitis have normal findings on conventional EGD. As CD-related abnormalities are almost exclusively located in the duodenum and jejunum, the preferred route of insertion should be antegrade.

It is important to remember that patients with CD have a much higher risk of developing small bowel adenocarcinoma, with odds ratios ranging from 17-fold to 67-fold higher than the general population.^{101,102} Thus, DBE might be useful in patients with CD and alarm symptoms. Whether DBE is superior to MRI or other radiological methods is not known. However, it appears sound to perform DBE instead of CE in these patients, as CE might be retained if a tumour is present.

POLYPOSIS SYNDROMES AND SMALL-BOWEL TUMOURS

Patients with familial and nonfamilial polyposis syndromes are at increased risk of small-bowel polyps and tumours.^{105–109} The risk of small-bowel adenocarcinoma varies according to the syndrome. The overall risk of small-bowel cancer in FAP is 4–12%, or up to 300-fold higher than the general population.^{105–107} Adenomatous polyps have traditionally been thought to be the only type of polyp to present the

risk of malignant transformation, but newer data show that hamartomatous polyps also have foci of adenoma, and that these have also been associated with an increased risk of cancer development.^{105–108} Patients with the Cronkite–Canada syndrome are also at increased risk of developing small-bowel cancer.¹⁰⁹

Until a few years ago, primary surgical resection and intraoperative endoscopy and polypectomy were the only available means of treating polyps in the mid-small bowel.^{110,111} Surveillance of this group of patients is important to detect and resect polyps of the GI tract in order to decrease the incidence of cancer and to avoid complications such as bleeding, obstruction, and intussusception. Several studies evaluating the usefulness of DBE for polyp detection and removal in polyposis syndromes have been published, [Table 3](#).^{112–118}

Plum et al treated a total of 16 patients with PJS during a 3-year period.¹¹⁸ A total of 37 procedures were performed, revealing a total of 55 polyps measuring more than 10 mm (mean: 24 mm, range: 10–50 mm) and 112 polyps measuring 10 mm or less. Thirty-four polyps were removed by endoscopic polypectomy. A total of four complications occurred in two patients (two episodes of bleeding, one perforation and one propofol-associated decrease in oxygen saturation) Heine et al presented their experience of 20 DBE in 14 patients with suspected PJS and six patients with Gardner syndrome.¹¹ Treatment of obstructive polyps was the indication for the procedure in 71% of patients with PJS. Successfully endoscopic treatment was achieved in 90% of patients. We have performed seven DBEs in three patients with confirmed PJS and in two patients with suspected PJS. All patients with confirmed PJS had small-bowel polyps and polypectomy of up to 18 polyps per session was performed.

DBE is also helpful for the evaluation of small bowel polyps in patients with FAP.¹¹⁹ We have shown that DBE-assisted chromoendoscopy was of further assistance for the detection of jejunal polyps.¹¹⁹ Several investigators have shown that the type of mutation in FAP, such as mutations in exon 15, is associated with the presence of small-bowel adenomas.^{108,109,119} Thus, genetic testing in these individuals might be of help to select patients for small-bowel investigation. Current guidelines recommend screening and surveying patients with FAP, with EGD and duodenoscopy. However, due to the increased risk of small-bowel adenocarcinoma and the lack of effect of medical therapies to eliminate small-bowel adenomas, it appears beneficial to also offer a detailed small-bowel investigation to patients affected by FAP. DBE will now also allow the detection of these polyps, but they can be eliminated during enteroscopy using either polypectomy or argon plasma coagulation.

DILATION OF SMALL-BOWEL STRICTURES

Small-bowel strictures are an important clinical problem in patients with CD; up to 30% of patients with CD have a stricturing phenotype as defined by the Vienna Classification (see [Figure 3](#)).^{87–93} These patients often require surgical resection of the small bowel, or stricturoplasty. DBE enables endoscopic balloon dilation (EBD) of small-bowel strictures.^{120–127} The therapeutic DBE with a working channel of 2.8 mm allows the use of through-the-scope (TTS) dilation balloons. The working channel of the enteroscope should be lubricated with a small amount of silicone to diminish friction when inserting the TTS balloon. Sunada et al evaluated the clinical outcomes of EBD using the DBE in 18 patients with CD.¹²¹ Most patients could be treated with a single dilation, but additional dilations were necessary in seven patients. Dilation resulted in perforation in one patient and two patients required surgical

procedure due to the recurrence of complicated strictures in one patient and development of ileal bladder fistula in the other patient. The remaining 15 patients were free from surgical intervention for an average of 11 months after dilatation therapy. Pohl et al reported on 19 patients with CD and strictures evaluated with DBE.¹²⁷ In their study, a total of nine patients could not be treated with EBD because of anatomical reasons or complex strictures. A total of 15 dilations were performed in the remaining 10 patients, with 60% of patients achieving symptomatic relief during a median follow-up of 10 months. Ohmiya et al performed 32 EBD in 15 patients with various types of small-intestinal strictures.¹²⁰ EBD was useful in 70% of patients with strictures due to CD and all five patients with non-CD strictures. Complications included two episodes of pancreatitis and one exacerbation of obstruction.

Prospective, multicenter trials evaluating larger numbers of patients are needed to confirm these positive retrospective results. We suspect that the reported patients represent a minority of patients with small-bowel strictures due to CD, as most small-bowel strictures in these patients are complex, fibrotic, long or multiple. In this group of patients, a therapeutic DBE is not helpful and might lead to complications.

SMALL-BOWEL STENTS

DBE also permits the placement of self-expanding stents for the palliation of malignant obstruction.^{128,129} Two types of self-expanding metal stent (SEMS) can be used: the Ultraflex™ (Boston Scientific, Natick, Massachusetts) and the Wallflex™ (Boston Scientific).^{128,129} Unlike its predecessor, the enteral Wallstent™, the Wallflex™ has rounded edges and a long, flexible delivery system. This makes it ideal for use within distal segments of the small bowel, where the intestinal wall may be thin and prone to perforation due to the sharp edges of earlier stent designs.

SUMMARY

DBE has been a major endoscopic breakthrough in the last decade. DBE has undoubtedly contributed to the better diagnosis and understanding of diseases of the small bowel and has opened this obscure part of the GI tract to visualisation. One of the major areas where DBE has increased our diagnostic accuracy is in the evaluation and therapy of obscure GI bleeding. It has enhanced our understanding of GI bleeding, which is no longer divided into merely upper (GI bleeding originating in the upper GI tract, above the ligament of Treitz) and lower (GI bleeding originating distal to the ligament of Treitz), but now includes mid-GI bleeding (i.e. bleeding of the small bowel originating distal to the angle of Treitz and proximal to the terminal ileum).

One of the major weaknesses of DBE is that it is a time-consuming procedure, requiring special training and more staff than for standard endoscopies. However, reaching a diagnosis and establishing a therapeutic plan in patients with previously negative upper and lower endoscopies and radiologic studies are certainly rewarding and worth the time spent pushing and pulling the DBE. The complication rates of DBE are similar or less than for other endoscopic interventions. Pancreatitis appears to be a unique complication associated with DBE. The overall quality of endoscopic performance is good but not excellent: Although enables examination of the entire small bowel in most patients, there are still many patients in whom deep small-bowel inspection remains unsatisfactory. These are patients with previous abdominal surgery or poor performance status, who are unable to receive adequate sedation for such an extensive

procedure. Nevertheless, we are diagnosing conditions previously found only post-mortem or during intraoperative endoscopy. We are also discovering new conditions and are able to provide endoscopic therapy for various small-bowel disorders. Endoscopic performance has gradually improved since the first description of DBE and further refinements of the enteroscopes and accessory materials are expected. A basic message remains that training should be optimised by first having a thorough clinical knowledge of small-bowel pathologies and having one-on-one training with an expert endoscopist. Animal- and dummy-based models are useful for training and perfecting skills.

DBE plays now a crucial role in the diagnosis and management of various small-bowel disorders, and has become an integral part of the algorithm for OGIB, CD, coeliac disease, and polyposis syndromes. Although some experts propose the routine use of CE before DBE, we believe that DBE should be the first method in the investigation of small-bowel disorders in situations when a diagnostic biopsy or therapeutic interventions are anticipated. In patients without anticipated intervention (biopsy or endoscopic therapy), it appears that the optimal evaluation of the small intestine should start with a noninvasive CE and a targeted DBE could be performed afterwards if a suspicious lesion is found.

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