

Impact of balloon-assisted enteroscopy on the diagnosis and management of suspected and established small-bowel Crohn's disease

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Bibliography

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Background and aims: The role of recently developed balloon-assisted enteroscopy (BAE) in small-bowel Crohn's disease (CD) is not well established. The purpose of this study is to determine the clinical impact of BAE on patients with suspected and established small-bowel CD.

Methods: This study included 22 patients (group A) with suspected small-bowel CD and 43 patients (group B) with established small-bowel CD with or without previous surgery, who underwent BAE, in a prospective BAE registry of a US academic medical institution. All underwent abdominal imaging studies including computed tomography (CT) or magnetic resonance (MR) enterography before BAE. The main outcome measurements were diagnostic yield and clinical outcomes.

Results: In total, 78 BAE procedures were carried out in 65 patients. In group A (n=22, 25 BAE procedures), enteroscopy led to a diagnosis of CD in

six patients (27.3%). Non-steroidal anti-inflammatory drug-related enteropathy was diagnosed in three patients (13.6%), whereas no lesions were found in the remaining 13 patients. In group B (n=43, 53 BAE procedures) enteroscopy revealed active intestinal inflammation with ulcers and/or luminal stenosis in 18 patients (41.9%), which led to a change and escalation of medical therapy. Five patients without active ulcers underwent successful dilation of small-bowel strictures with resulting resolution of obstructive symptoms. Of the 78 BAE procedures, two patients (2.6%) had bleeding complications which were successfully treated conservatively. One patient (1.3%) underwent surgery due to procedure-related perforation.

Conclusions: The use of BAE may help improve management in patients with suspected and established small-bowel CD.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by a disabling course and transmural inflammation which may involve small and large bowels [1]. In the past, the clinical goal of medical treatment was to achieve clinical remission. However, recent studies have reported better outcomes with mucosal healing, and this has now become the main goal of medical treatment [2]. Small-bowel capsule endoscopy (CE) is a very useful non-invasive tool for evaluating intestinal mucosal lesions in patients with CD with small-bowel involvement. However, it lacks the capacity for a tissue diagnosis and for endoscopic treatment when it is needed [3]. Retention of the capsule endoscope, caused by small-bowel luminal strictures which often exist in patients with CD, is a major concern even when patency capsule endoscopy is available [4,5].

Balloon-assisted enteroscopy (BAE) has recently been developed for managing small-bowel diseases, and includes double balloon enteroscopy (DBE) and single balloon enteroscopy (SBE) systems. DBE has gained widespread acceptance and is the most established deep enteroscopy technique [6–16]. SBE and spiral enteroscopy (SE) are recently introduced techniques in endoscopic evaluation of the small bowel [17–19]. As compared with CE, BAE allows tissue biopsies for histopathology and therapeutic interventions including dilation of strictures [20]. Small-bowel strictures affect more than one-third of patients with CD and often cause intestinal obstruction leading to hospitalization and surgery [21]. The introduction of BAE provides a potential therapeutic alternative to surgery for CD patients with small-bowel strictures.

At present, the role of BAE in patients with small-bowel CD is still not well established. The available reports to date are sparse and mostly have

License terms



examined the utility of DBE and SBE individually in small series [22–25]. The purpose of this study was to assess the diagnostic yield and clinical impact of BAE in suspected and established small-bowel CD.

Materials and methods

We reviewed our prospectively maintained BAE registry. This included DBE and SBE procedures on patients referred to the Cleveland Clinic between January 2005 and January 2012 for the investigation of small-bowel diseases. The database included patient demographics, findings of conventional endoscopy and radiological imaging, indications from procedures, findings from enteroscopy, and procedure-related complications. All patients provided informed consent for the enteroscopy procedures. The BAE registry was approved by the Cleveland Clinic Institutional Review Board. The indications of small-bowel evaluation in CD were: (1) to achieve a definite diagnosis in patients with symptoms and signs indicative of CD, but with inconclusive results from conventional endoscopy (esophagogastroduodenoscopy (EGD) and ileocolonoscopy), CE, and radiological cross-sectional imaging studies; (2) to assess disease activity and extent in uninvestigated CD; (3) to investigate the cause of anemia or obscure gastrointestinal bleeding in CD; (4) to confirm and to treat small-bowel strictures visualized on radiological imaging; (5) to evaluate the extent and activity of CD in postoperative patients deemed at high risk of CE retention. Before the BAE procedures, all patients underwent cross-sectional small-bowel imaging with contrast-enhanced computed tomographic (CT) enterography or magnetic resonance (MR) enterography, which evaluated the pattern of contrast enhancement, involvement of bowel segments, and stricture definition. For the study, we classified patients as suspected or established small-bowel CD [24], and investigated the utility of BAE in these patients.

Inclusion criteria for the analysis were antegrade and retrograde enteroscopy for suspected small-bowel CD after negative EGD and ileocolonoscopy or for characterization of small-bowel pathology detected by CE and/or other diagnostic imaging studies. Exclusion criteria for BAE included known large esophageal varices, fresh abdominal surgical stoma, medical instability, and inability to provide informed consent. Patients who underwent intraoperative enteroscopy were excluded.

The diagnosis of established CD was made based on endoscopic examination as well as from compatible histological examination. Presence of granulomas, patchy distribution of inflammation with skip lesions, longitudinal deep ulcers, presence of small-bowel involvement, presence of fistulizing disease and small-bowel strictures were taken as evidence of CD and classified based on published guidelines. All patients with isolated small-bowel CD had involvement of the ileum diagnosed based on ileocolonoscopy [26].

All procedures were performed by four experienced enteroscopists who had previous experience with BAE and advanced therapeutic endoscopy training. Office consultation and a history and physical examination with supporting laboratory studies were obtained before the procedures and assessed by the enteroscopist to determine the appropriateness of enteroscopy as the standard of care. The decision on using an antegrade or retrograde initial approach was primarily determined by clinical presentation. If the patient's clinical presentation was suggestive of upper small-bowel pathology on imaging or capsule endoscopy,

then an antegrade approach was used for the study. DBE was routinely chosen for enteroscopy if the lesion of interest was beyond the distal jejunum. SBE was chosen if the lesion was proximal to the distal jejunum. If pathology was not reached with the initial insertion route, a tattoo was placed and the opposite anatomic approach was subsequently performed, as deemed clinically appropriate. All patients and their drivers were given standard discharge instructions and phone numbers to call to report any post-procedure problems or suspected complications.

Retrograde procedures were performed after standard bowel preparation. Antegrade procedures required no specific preparation apart from continuing to receive nothing by mouth for at least 8 hours before procedures. Patients were sedated with monitored anesthesia using propofol by an anesthesia provider as deemed appropriate. Fluoroscopy was used in selected cases, which depended on the preference of the performing enteroscopist and technical difficulty. Depth of insertion with DBE and SBE was measured in centimeters by counting the amount of small bowel traversed and cycles on withdrawal in 10-cm increments [27]. At the point of maximal depth of insertion, a tattoo was placed using SPOT ink as appropriate (GI Supply, Camp Hill, Pennsylvania, United States). Complications of enteroscopy in each procedure, if any, were recorded. A complication was defined as any event that changed the health status of a patient negatively, and that occurred during the 30-day period after BAE [28].

In this study, a stricture was defined by at least one of the following criteria, in addition to the clinical symptoms of intestinal obstruction: (1) enteroscopy showed an internal diameter of the small-bowel lumen estimated to be less than 10mm or the enteroscope could not pass through the lesion; (2) a stricture was suggested or identified by other diagnostic modalities. Balloon dilation was performed through the endoscope with a controlled radial expansion wire-guided balloon dilatation catheter (Boston Scientific, Natick, Massachusetts, United States). The balloon was inflated with water to the pressure prescribed by the manufacturer for the size of the balloon. This pressure was maintained for 60 seconds or longer and this was repeated if required. The end point of dilation was the ability to pass the endoscope through the lesion. Balloon dilation might be repeated to treat the same lesion. In some patients with a deep open ulcer and/or a severe long stricture, dilation was not performed owing to a greater risk of intestinal perforation. Dilation was attempted later, if required, after inflammation had resolved following medical treatment with, for example, total parenteral nutrition or infliximab.

We reviewed all of the medications for the patients with a diagnosis of small-bowel CD before and after BAE. Escalation of medical treatment after BAE was defined as the addition of immunomodulators, including methotrexate, azathioprine, and 6-mercaptopurine, and/or the addition of biological agents, including infliximab, adalimumab, certolizumab, and natalizumab, to the existing baseline medical treatment.

DBE procedures were performed using the Fujinon endoscope system (EN-450T5, Fujinon Inc., Saitama, Japan). SBE procedures were performed using the SBE endoscope system (SIF-Q180, Olympus Optical, Tokyo, Japan).

Descriptive statistics were computed for all variables. These included means, medians, ranges for continuous variables, and frequencies and percentages for categorical variables.

Results

Two groups of patients were identified (▶ **Table 1**). The first group (group A) included 22 patients with suspected small-bowel CD (16 men; median age 46; interquartile range 39–64). All had symptoms and signs of chronic enteropathy and underwent standard diagnostic protocols. However, ileocolonoscopy and upper gastrointestinal endoscopy as well as histology had not revealed features diagnostic of CD, whereas other chronic enteropathic disorders had been excluded. The second group (group B) included 43 patients (22 men; median age 41; interquartile range 32–54) with a previous diagnosis of small-bowel CD (▶ **Tables 1 and 2**).

Among the 22 patients in group A with suspected small-bowel CD, 25 BAE procedures were performed (▶ **Fig. 1**). There were no complications in all BAE procedures. All patients underwent

CT or MR enterography before BAE. Twenty patients in this group also underwent CE before BAE. Three patients had CE findings indicative of CD, while the CE findings of the remaining 17 patients were deemed as nonspecific. CE was not performed in two patients due to the findings of luminal strictures on CT or MR enterography. CT or MR enterography revealed increased small-bowel wall thickness and post-contrast enhancement in 12 patients. With the findings of BAE and histopathology from enteroscopic biopsies, small-bowel CD was diagnosed in six patients, of whom one underwent successful balloon dilation of a jejunal stricture. Of the remaining 16 patients, non-steroidal anti-inflammatory drug-induced enteropathy was diagnosed in three patients, whereas no lesions were detected in 13 patients. These 13 patients had normal mucosa on BAE and no interventions were required.

Variable	Suspected CD Group A, n = 22 (25 enteroscopies)	Established CD Group B, n = 43 (53 enteroscopies)
Age, median (interquartile range), y	46 (39–64)	41 (32–54)
Male gender, n (%)	16 (72.7)	22 (51.2)
Type of enteroscopy, n (%)		
DBE	18 (81.8)	26 (49.1)
SBE	7 (18.2)	27 (50.9)
Enteroscopy approach, n (%)		
Antegrade	13 (52)	25 (47.2)
Retrograde	12 (48)	28 (52.8)
Timing of enteroscopy, n (%)		
Morning	12 (48)	25 (47.2)
Afternoon	13 (52)	28 (52.8)
Associated significant EGD findings, n (%)		
Erosive gastritis	2 (9.1)	2 (3.8)
Associated significant colonoscopy findings, n (%)		
Aphthous ulcers	2 (9.1)	2 (3.8)
History of smoking, n (%)	6 (27.3)	21 (48.8)
History of alcohol consumption, n (%)	0	1 (2.3)
Prior abdominal surgery, n (%)	19 (86.4)	36 (83.7)
Antegrade depth of insertion, estimated in cm	159.7 ± 120.5	80.8 ± 40.9
Retrograde depth of insertion, estimated in cm	45.7 ± 29.9	43.6 ± 21.1
Complications, n (%)	0	3 (6.9)

Table 1 Clinical characteristics in suspected and established small-bowel Crohn’s diseases.

DBE, double balloon enteroscopy; SBE, single balloon enteroscopy; EGD, esophagogastroduodenoscopy.

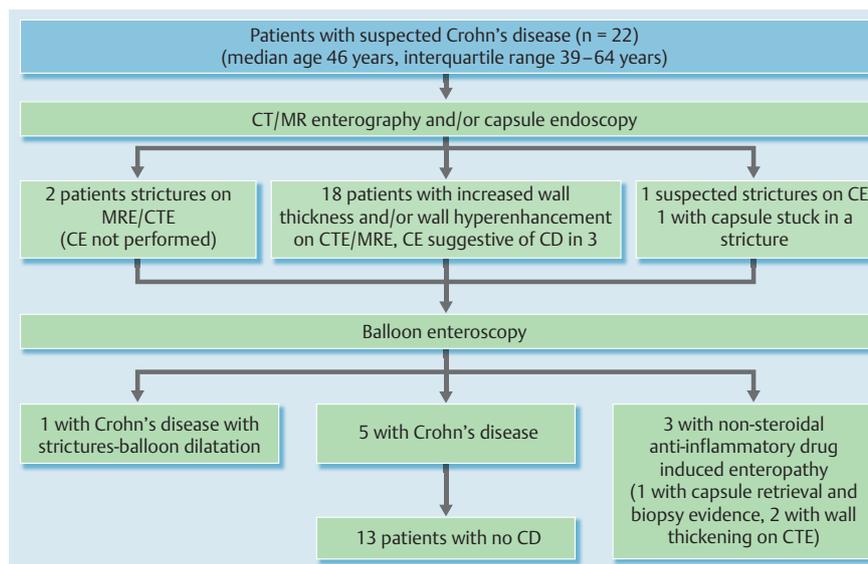


Fig. 1 Diagram summarizing the outcomes in patients with suspected small-bowel Crohn’s disease undergoing balloon assisted enteroscopy (BAE).

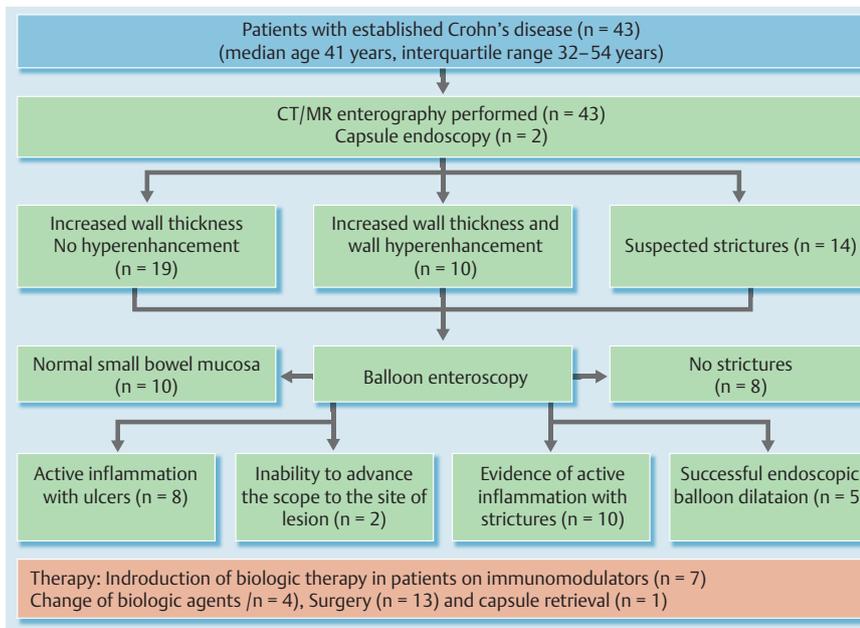


Fig. 2 Diagram summarizing the outcomes in patients with established small-bowel Crohn's disease undergoing balloon assisted enteroscopy (BAE).

We subsequently correlated the findings of CT or MR enterography with the BAE findings. Of the two patients with strictures on enterography, one patient had clear evidence of stricture on BAE, whereas the other patient had inflammation with biopsies suggestive of CD. Twelve patients had increased wall thickness on enterography, of which two patients had NSAID enteropathy. The remaining 10 patients had a normal BAE. Six patients had wall thickening with enhancement, of which four patients had CD and the remaining two patients had a normal BAE. One patient with suspected CD on capsule endoscopy had a normal enterography and a normal BAE. One patient with capsule stuck in a stricture had evidence of stricture on enterography and BAE retrieved the capsule. The overall agreement of enterography with BAE findings was 8/22 (36.4%)

Among the 43 patients in group B with established CD, 53 BAE procedures were performed (Table 1). These patients underwent enteroscopy for further evaluation and management of lesions identified on diagnostic small-bowel imaging. All patients underwent CT or MR enterography before BAE, which revealed increased wall thickness in 19 patients, positive contrast enhancement in 10 patients, and stricture with pre-stenotic dilation in 10 patients and no pre-stenotic dilation in four patients (Fig. 2). CE was performed before BAE in only two patients because of the increased risk of capsule retention in the other patients in this group.

We subsequently correlated the findings of CT or MR enterography with the BAE findings in patients with established CD. Of the 14 patients with suspected strictures on enterography, eight patients had no stricture, while five patients had strictures and underwent balloon dilation of strictures through enteroscopy. One patient had strictures with inflammation which required medical management. Nineteen patients had increased wall thickness on enterography of which eight patients had active inflammation with ulcers, and in one patient, the enteroscope could not be advanced to the site of the lesion. The remaining 10 patients had a normal BAE. Ten patients had wall thickening with enhancement, of which nine patients had active inflammation with strictures whereas in the remaining one patient, the enteroscope could not be advanced to the area of interest. The overall agreement of enterography with BAE findings was 31/41 (75.6%)

Five patients without active intestinal ulceration underwent enteroscopic balloon dilation of small-bowel strictures with success (Fig. 2). Fibrotic strictures were dilated with a through-the-scope balloon (Fig. 3, Fig. 4). All five patients but one had two sessions of balloon dilation to treat the strictures. Acute angulation was encountered in the small bowel during BAE procedures in two other patients in group B because of adhesion-related tethering related to previous surgery, which prevented the enteroscope from reaching the strictures. BAE complications were encountered in three patients in group B with established small-bowel CD. Perforation was present in one patient, and required immediate surgery. Two other patients had bleeding complications. Of these, one required hospitalization for treatment and transfusion, and the other was successfully treated with a local enteroscopic epinephrine injection at the bleeding lesion. Both bleeding episodes subsided with continued conservative management.

With the findings from the BAE investigation, seven patients who were on azathioprine subsequently had step-up treatment with biologics. Active inflammatory CD required an escalation in medical treatment (Fig. 5). In the patients who were already on biologics, four had a change in biological agents from infliximab to adalimumab (Fig. 2). Seven patients elected to under-

Table 2 Characteristics of patients with established Crohn's disease.

Variable (n = 43)	Number (%)
Extent of CD	
Small-bowel CD	14 (32.6)
Ileo-colonic CD	26 (60.5)
Ileo-colonic and duodenum CD	3 (6.9)
Phenotype of CD	
Stricturing CD	32 (74.4)
Fistulizing CD	11 (25.6)
5-Aminosalicylate use	10 (23.3)
Corticosteroid use	17 (39.5)
Azathioprine/6-mercaptopurine use	12 (27.9)
Biologics use	20 (46.5)
Duration of CD, median (range), y	8 (1–14)

CD, Crohn's disease.

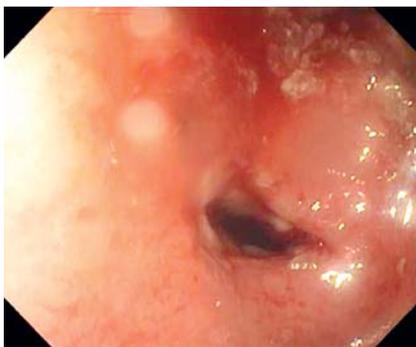


Fig. 3 Fibrotic stricture from Crohn's disease in the mid-jejunum.



Fig. 4 Treatment of the stricture in the mid-jejunum by balloon assisted enteroscopy (BAE) and through-the-scope balloon dilation.



Fig. 5 Active inflammatory stricture from Crohn's disease in the ileum which required an escalation in medical treatment.

go surgery after BAE (two were on biologics, and five declined escalation in medical treatment). Of the 11 patients who received escalation in medical treatment after BAE, five required surgery after a median follow-up of 8 months, whereas the other six remained in clinical remission after a median follow-up of 10 months.

Discussion

This report has shown that the use of BAE improves the clinical management of small-bowel CD. In patients with a diagnosis of small-bowel CD after BAE, adjustment of medical therapy resulted in clinical improvement. Among those who underwent therapeutic balloon dilation procedures, resolution of obstructive symptoms was achieved, which demonstrated that therapeutic BAE may be a valid alternative to surgery. This study showed that BAE is useful in the diagnosis and treatment of small-bowel lesions in CD patients.

Small-bowel involvement in CD is often associated with a complicated disease course including surgery [21,29,30]. Owing to the relapsing nature of CD, it is important to avoid surgical resections as much as possible. Both CE and BAE have been used for endo-

scopic evaluation of the small bowel to establish a diagnosis of Crohn's disease [31]. In our study, enteroscopy appears to be very useful for diagnosing small-bowel CD when the findings of EGD and ileocolonoscopy are inconclusive. With the capability of obtaining histopathology in the small bowel for evaluation, BAE can help establish a diagnosis of small-bowel CD and, hence, direct appropriate treatment.

In patients with established CD, previous studies have shown that both CE and cross-sectional enterography, either CT or MR, are useful diagnostic tools to investigate small-bowel involvement, especially when compared with small-bowel follow-through radiography and ileocolonoscopy [4,5,32–38]. However, CE can be associated with capsule retention in up to 7% of patients with small-bowel lesions [39]. In addition, incomplete small-bowel visualization was reported in up to 30% of CE [40]. Although CT and MR enterography can detect inflammation in the small bowel, BAE has the additional advantages of taking biopsies for histological evaluation to diagnose early mucosal disease and performing therapeutic dilation of intestinal luminal strictures.

We observed that CD patients with small-bowel lesions benefited from adjustment of medical therapy following enteroscopy. Adjusting medical treatment resulted in clinical improvement in most patients. Although we did not perform follow-up enteroscopy to evaluate mucosal healing, improvement of abdominal symptoms had been observed in these patients. In the majority of our patients with small-bowel lesions confirmed by BAE, biological therapy was initiated, intensified or altered, resulting in clinical improvement, which demonstrated an additional benefit of treatment with these biological agents in this particular patient group with a complicated disease phenotype.

In this study, we also observed that BAE was effective in managing small-bowel CD strictures. The management of symptomatic small-bowel CD-associated strictures is challenging because of the generally poor response to medical therapy and the high rate of recurrence after surgical resection. Direct visualization of strictures during BAE procedures allowed the differentiation of patients with active inflammation or ulceration within the strictured bowel segments, who may benefit from medical treatment, from those with tight fibrotic strictures who may need endoscopic or surgical treatment. Our study showed that therapeutic BAE is effective in treating small-bowel strictures and may avoid surgery in selected patients.

There are limitations in this study. First, it was a retrospective analysis, however, the data were collected prospectively as patients were treated. The study population was recruited from a subspecialty tertiary referral center and only included patients in whom small-bowel mucosal activity was suspected. Follow-up enteroscopic evaluation to assess mucosal healing was not routinely performed after medical therapy, because clinical improvement itself was deemed sufficient to not pursue additional invasive investigations in these patients. The depth of maximal insertion was determined by estimation of the distance traversed into the small bowel and may not represent accurate scientific measurements. Carbon dioxide insufflation was not used in this study for comparison. Nonetheless, this is one of the largest studies on small-bowel CD patients, and showed that BAE improves the diagnosis and management of these patients.

Despite the fact that conventional cross-sectional radiological imaging and CE permit noninvasive exploration of the small bowel, the new BAE tools have enhanced our ability to manage small-bowel CD by allowing histological evaluation of small-

bowel mucosa and, thus, the differentiation from other inflammatory intestinal disorders. Moreover, therapeutic BAE provides an invaluable nonsurgical means of treating small-bowel strictures.

In conclusion, our study has demonstrated the clinical usefulness of BAE in patients with suspected or established small-bowel CD. It allows a definite diagnosis of small-bowel CD when the earlier diagnosis was uncertain and improves clinical management and outcomes in patients with established small-bowel CD.

Competing interests: Dr John J. Vargo is on the speakers' bureau of Boston Scientific and is a consultant for Olympus. Drs Udayakumar Navaneethan, K. V. Narayanan Menon, Madhusudhan R. Sanaka and Chung-Jyi Tsai have no conflicts of interest or financial ties to disclose.

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