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Small bowel enteroscopy in Crohn's disease

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Abstract

Endoscopic assessment of the small bowel is difficult because of its long and tortuous anatomy. However, recent developments have greatly improved the insertion depth and diagnostic yield, by means of device-assisted enteroscopy (DAE). Therefore, DAE may be of specific interest in the diagnostic and therapeutic approach of patients with inflammatory bowel disease. It may be of help in the diagnostic assessment of intestinal disease extent and severity and complications, with an impact on the therapeutic management. Moreover, local treatment within the small bowel is also feasible with DAE. This review aims to provide an overview of the currently available literature data on the use of enteroscopy in inflammatory bowel disease, and Crohn's disease in particular.

Keywords inflammatory bowel disease, Crohn's disease, enteroscopy, device-assisted enteroscopy, review

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Introduction

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD), ulcerative colitis (UC) and IBD of unclassified type (IBDU) [1]. UC is confined to the colon whereas CD can occur throughout the entire gastrointestinal (GI) tract with the highest prevalence at the ileocecal junction. Assessment of the small bowel is of specific interest in case of CD and to further differentiate the diagnosis of IBDU. Small bowel involvement of CD is mostly confined to the (terminal) ileum. However, proximal intestinal inflammation can occur in 10% of the patients with normal segments interspersed between pathological lesions [2]. The diagnosis of CD is based on the combination of clinical suspicion, biochemical parameters, radiological and endoscopic lesions and specific histopathological criteria. It is necessary to perform both upper GI endoscopy visualizing the esophagus, stomach and duodenum and lower GI endoscopy visualizing the colon and if possible the terminal ileum [3].

In case of suspected extended intestinal involvement or complicated intestinal disease like stenosis, fistula and malignancy or in case of IBDU, several diagnostic options are available to assess the small bowel [2-5]. Radiology and endoscopy are complementary techniques to define the extent of disease and to detect intestinal complications. This review focuses on the currently available data on small bowel endoscopy (enteroscopy) in Crohn's disease.

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Conflict of Interest: None

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Radiology

Until a decade ago, visualization of the small bowel was generally performed with classical barium follow-through or enteroclysis with a nasojejunal tube [6]. These radiological techniques allow determination of the extent of intestinal involvement and complications like stenosis with proximal dilation, fistula and malignancy. However, because of better accuracy, enterography or enteroclysis by means of computed tomography (CT) or magnetic resonance imaging (MRI) are currently the preferred radiological techniques to assess CD small bowel involvement [2]. In addition to the disease extent, CT and MRI can also assess the disease activity, based on wall thickness and intravenous contrast enhancement, and the presence of extraluminal disease. Apart from the excellent diagnostic accuracy, CT and MRI enterography/enteroclysis envision drawbacks because of patient's discomfort (forced bowel distension and nasojejunal tube placement), radiation exposure (CT), availability (MRI) and their merely diagnostic nature [7]. In some centers, small bowel ultrasound, with or without Doppler is also used to assess ileal involvement of CD, but this diagnostic technique is very operator dependent [8].

Endoscopy

In addition to radiological methods, new endoscopic techniques have emerged to evaluate the small bowel [9]. The

advantage of enteroscopy over radiological enterography is its real-time viewing and its therapeutic potential, ranging from mucosal biopsy sampling, local hemostasis, balloon dilation of stenosis and even fistula closure. The history of enteroscopy started in the 1970's and became more routinely used with the development of push-enteroscopy (PE) and intra-operative enteroscopy in the 1980's. The main disadvantages of these conventional enteroscopy techniques are the inability to visualize the entire small bowel (push-enteroscopy) and the invasiveness (intra-operative enteroscopy).

Wireless capsule enteroscopy: To deal with the problem of incomplete visualization of the small bowel, non-invasive wireless capsule enteroscopy (WCE) was developed and became available in 2000, enabling complete endoscopic visualization of the small bowel in an elegant way. Since then numerous new WCE developments have emerged, like improved image quality, number of images recorded per second, battery life duration and the software to read the images [10]. It has been shown that WCE is more accurate to detect small and superficial mucosal CD lesions as compared to radiological techniques, but suspicion of small bowel stenosis is a contraindication because of the risk of capsule retention [3,11,12]. Recent guidelines by ECCO (European Crohn's and Colitis Organisation), ESGE (European Society of Gastrointestinal Endoscopy) and OMED (World Organisation of Digestive Endoscopy) have established the role of WCE in the assessment of IBD: it is useful in patients with high clinical suspicion of CD despite negative radiological and conventional upper and lower GI endoscopy or in case of further differentiation of IBDU [2,11-14]. Moreover, WCE can be useful in the setting of established CD with unexplained symptoms like persistent anemia, abdominal pain or malabsorption [14]. In case of recurrent abdominal pain, intestinal stricture should be excluded before WCE can be safely performed [3]. A normal WCE examination has a high negative predictive value for active small bowel CD [2].

Enteroscopy: Parallel to the development of the still merely diagnostic WCE, conventional push-enteroscopy via the oral route was also subjected to a new evolution in order to perform all conventional endoscopic interventions throughout the entire small bowel [9]. Device-assisted enteroscopy (DAE) improves enteroscopy performance by means of specialized overtubes (Fig. 1). The use of a semi-rigid overtube allows deeper intubation of the jejunum because it helps to straighten the enteroscope avoiding jejunal stretching [15]. However, overtube-guided push-enteroscopy only allows peroral intubation of the jejunum without complete enteroscopy [16].

The concept of balloon-assisted enteroscopy is a second breakthrough in the evolution of DAE and can be performed via the oral and the anal route [9]. Both double- and single-balloon enteroscopy (DBE and SBE) are currently widely available. The addition of an inflatable balloon at the distal end of the overtube with (DBE) or without (SBE) a second inflatable balloon at the tip of the enteroscope allows better mucosal grip of the enteroscope and overtube stabilizing its position within the intestinal lumen. Both balloon-assisted methods are based upon the push-and-pull principle [17,18]. It is a stepwise progression of the enteroscope through the small intestine with the balloon-loaded overtube used as a straightening device. Both balloon-assisted methods allow deep and even complete intubation of the small bowel within a reasonable procedure time, although often a combined approach through the mouth and the anus is necessary to complete enteroscopy [17,18]. In addition, all conventional endoscopic interventions, ranging from mucosal tissue sampling, local hemostasis, polypectomy and balloon dilation, can now be performed throughout the length of the small bowel thanks to balloon-assisted enteroscopy.

Next to balloon-assisted enteroscopy, spiral overtube enteroscopy (SE) is the most recent development of DAE. It also allows rapid and deep intubation of the small bowel through the oral and anal route [19]. The enteroscope remains in a stable position and by rotating the overtube with its raised helices, the small bowel is pulled backwards over the enteroscope. Primary results of recent comparative studies between DBE, SBE and SE show that all three DAE methods allow comparable insertion depths with similar diagnostic yields and low complication rates [18,20,21].

Enteroscopy in Crohn's disease

Current guidelines: Endoscopic investigation of the small bowel is not indicated in every patient with IBD. ECCO and OMED guidelines state that DAE should be used when intestinal tissue samples for pathological examination are needed when conventional radiological and endoscopic imaging have been inconclusive or when therapeutic manoeuvres are required [2,13,14]. However, these guidelines are mostly graded levels C and D (based upon case series and expert opinion).

Current literature: Recent studies also suggest that endoscopic small bowel assessment may have impact on future therapy, both medically and surgically. Local therapy appears feasible under the form of intestinal stricture balloon dilation or submucosal injection of anti-inflammatory drugs in

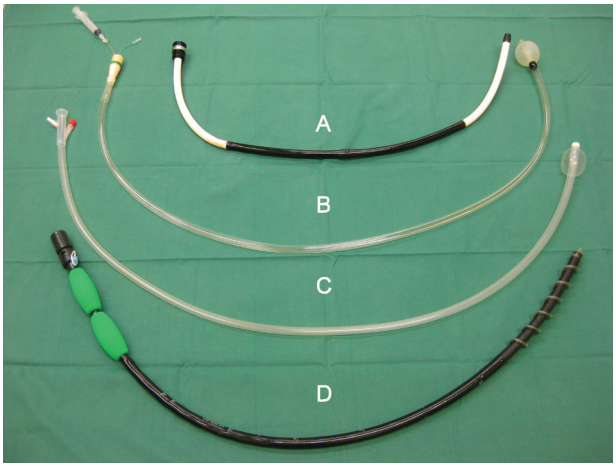

Figure 1 Device-assisted enteroscopy (DAE) with different overtubes: **A** Conventional semi-rigid overtube (Olympus), **B** Double-balloon overtube (Fujinon), **C** Single-balloon overtube (Olympus), **D** Spiral overtube (Spirus Medical).

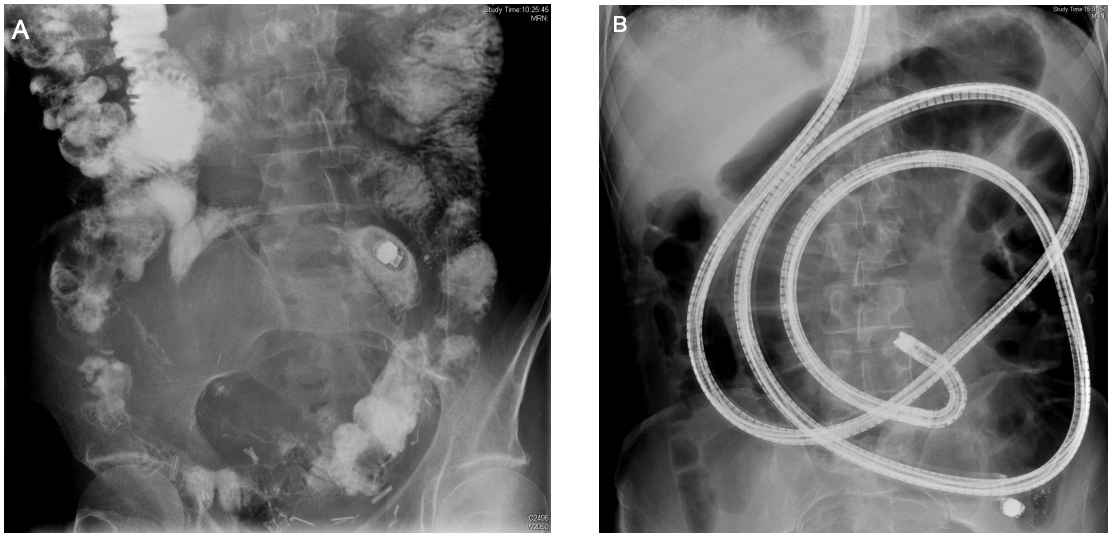

Figure 2 A Gastrografin small bowel follow-through showing a retained wired videocapsule at an ileal Crohn's disease stricture, **B** Single-balloon enteroscopy to retrieve the retained wireless videocapsule.

strictures. Finally, enteroscopic retrieval of a retained WCE capsule has been described several times due to CD intestinal stricture (Fig. 2). Most published patient series on DAE focus on small bowel pathology in general and obscure GI bleeding in particular. Therefore, they also include some patients with IBD and (suspected) CD. Only a limited number of studies was specifically designed (both retrospectively and prospectively) to assess the role of DAE in CD. An overview is provided in Table 1.

Table 1 Device-associated enteroscopy (DAE) in Crohn's disease

Author [Reference]	Year	Patients	DAE	Indication	Intervention
Perez-Cuadrado [22]	1997	8	PE	diagnosis	biopsy
Perez-Cuadrado [23]	2001	1	PE	stricture	dilation
Chong [24]	2005	22	PE	diagnosis	biopsy
Oshitani [25]	2006	40	DBE (o/a)	diagnosis / stricture	biopsy / capsule retrieval
Gay [26]	2007	12	DBE (o/a)	diagnosis / stricture	biopsy / dilation
Pohl [27]	2007	19	DBE (o/a)	stricture	dilation
Seiderer [28]	2007	10	DBE (o/a)	diagnosis	biopsy
Semrad [29]	2007	2	DBE (o/a)	diagnosis	biopsy
Despott [30]	2009	11	DBE (o/a)	stricture	dilation / capsule retrieval
Kodaira [31]	2009	1	DBE (a)	diagnosis	biopsy
Manes [32]	2009	37	DBE (o/a)	diagnosis	biopsy
Mensink [33]	2009	40	DBE (o/a)	diagnosis / stricture	biopsy / dilation
Zuber-Jerger [34]	2009	1	DBE (o)	stricture	capsule retrieval
Mensink [35]	2010	50	DBE (o/a)	diagnosis	
Naganuma [36]	2011	20	SBE (a)	diagnosis	
Sharma [37]	2011	1	SBE (o)	stricture	capsule retrieval
Story [38]	2011	1	SE (a)	diagnosis / stricture	biopsy / dilation
Zhou [39]	2011	6	DBE (o/a)	diagnosis	biopsy
Di Nardo [40]	2011	30	SBE (o/a)	diagnosis / stricure	biopsy / dilation

PE, push-enteroscopy; DBE, double-balloon enteroscopy; SBE, single-balloon enteroscopy; SE, spiral enteroscopy; o, oral route; a, anal route

Table 2 Endoscopic Crohn's disease (CD) findings in the small bowel during device-associated enteroscopy (DAE) [41]

Endoscopic finding	Description
aphthoid ulcer	small, shallow depressed lesion with loss of villi
longitudinal ulcer	typical Crohn ulcers, usually occurring on the mesenteric side of the intestine
cobblestone appearance	result of inflammatory changes and edema in the mucosa left by ulcers
stricture	repeated formation and healing of ulcers causes cicatricial contraction of the intestinal mucosa
fistula	usually occurs proximal to a stricture
pseudo-diverticulum	multiple strictures may lead to the formation of pseudo-diverticula
neoplastic lesions	both adenocarcinoma and lymphoma may occur in intestinal CD

Interpretation of the literature: Review of the literature reveals several interesting and promising aspects of DAE in CD. Most data are available for DBE, but also conventional PE and the more recent SBE and SE can be useful for the assessment or treatment of the small bowel in CD, even in the pediatric population. Apart from PE, only performed via the oral route, all other DAE procedures can be used both orally and anally, significantly increasing the diagnostic and therapeutic yield. Indications to perform DAE in CD appear wider than suggested in the recent ECCO, ESGE and OMED guidelines [2,13,14]. Unexplained anemia, hypomagnesemia, chronic diarrhea or recurrent obscure GI bleeding can be caused by (undiagnosed) CD small bowel lesions, which can now be reached by DAE [22,23,33,35]. Moreover, local hemostasis is also feasible during enteroscopy, rendering DAE an interesting tool for this indication. Also screening for CD-related small bowel malignancy, under the form of adenocarcinoma, lymphoma and carcinoid tumor, can be performed by DAE [31,32,42]. Tables 2 and 3 demonstrate the endoscopic grading scales that have been established to describe the appearance of intestinal CD lesions and to grade the severity of disease activity (Fig. 3) [33,41]. Uniformity in description of lesions is important for several reasons: comparison between different patients, comparison between different time-points in the same patient (effect of therapy), development of a standardized severity scale with prognostic value, validated scales are necessary for multicenter interventional trials. Future studies should validate these endoscopic grading scales and evaluate their clinical usefulness. Several studies have shown that DAE may have an impact on the therapeutic strategies in CD, leading to clinical, biochemical and endoscopic improvement [22,24-27,29,32,33,35,36,39,40]. Also, postoperative intestinal CD recurrence can be adequately assessed with DAE, and may prove useful in therapeutic decision making, both in pediatric and adult patients [32,36,40]. To avoid surgical intervention in case of clinically important intestinal strictures, (repeated) enteroscopic balloon dilation can be advised for a non-ulcerative stricture of no longer than 4-6 cm [23,26,27,30,33,38,40,41]. In case of long or inflammatory strictures, balloon dilation may significantly increase the risk of perforation [41]. Therefore, inflammatory and ulcerative strictures should be primarily treated by rigorous medical therapy. Several cases have described retained WCE due to intestinal CD strictures, successfully removed by DAE, again avoiding surgical intervention [25,30,34,37]. Finally, local injection of immunomodulatory drugs like corticosteroids and the anti-tumor-necrosis-factor-α antibody infliximab in the four quadrants of CD stricture may become a potentially interesting therapeutic strategy [43].

Complications: In general, diagnostic DAE has a low complication rate of less than 1%, mainly presented as post-procedural abdominal pain and pancreatitis after an oral procedure [44,45]. Complication rates of therapeutic DAE may reach up to 5%, with a substantial risk of bleeding and perforation [44,45]. Perforation may occur after intestinal polypectomy, after Argon plasma coagulation of intestinal arteriovenous malformations and after balloon dilation of intestinal strictures. In CD more specifically, complication rates tend to be higher, especially in patients with a history of intestinal surgery, in whom perforation may occur even in merely diagnostic DAE procedures, and after balloon dilation of intestinal strictures [25,30,37]. However, DAE in pediatric (postoperative) Crohn's disease does not appear to have a higher complication risk [40].

Future directions: Since levels of evidence in current

Table 3 Endoscopic severity scale of small bowel Crohn's disease (CD) [33]

Score	Grade	Description
0	absent	no lesions in small bowel
1	minor	erythematous and/or edematous mucosa and/or small ulcerative lesions <0.5 mm within normal mucosa
2	moderate	larger ulcerative lesions ≥0.5 mm and <20 mm
3	severe	ulcerative lesions ≥20 mm and/or non-significant stenotic lesions
4	stenotic	significant stenotic lesions, with or without inflammation

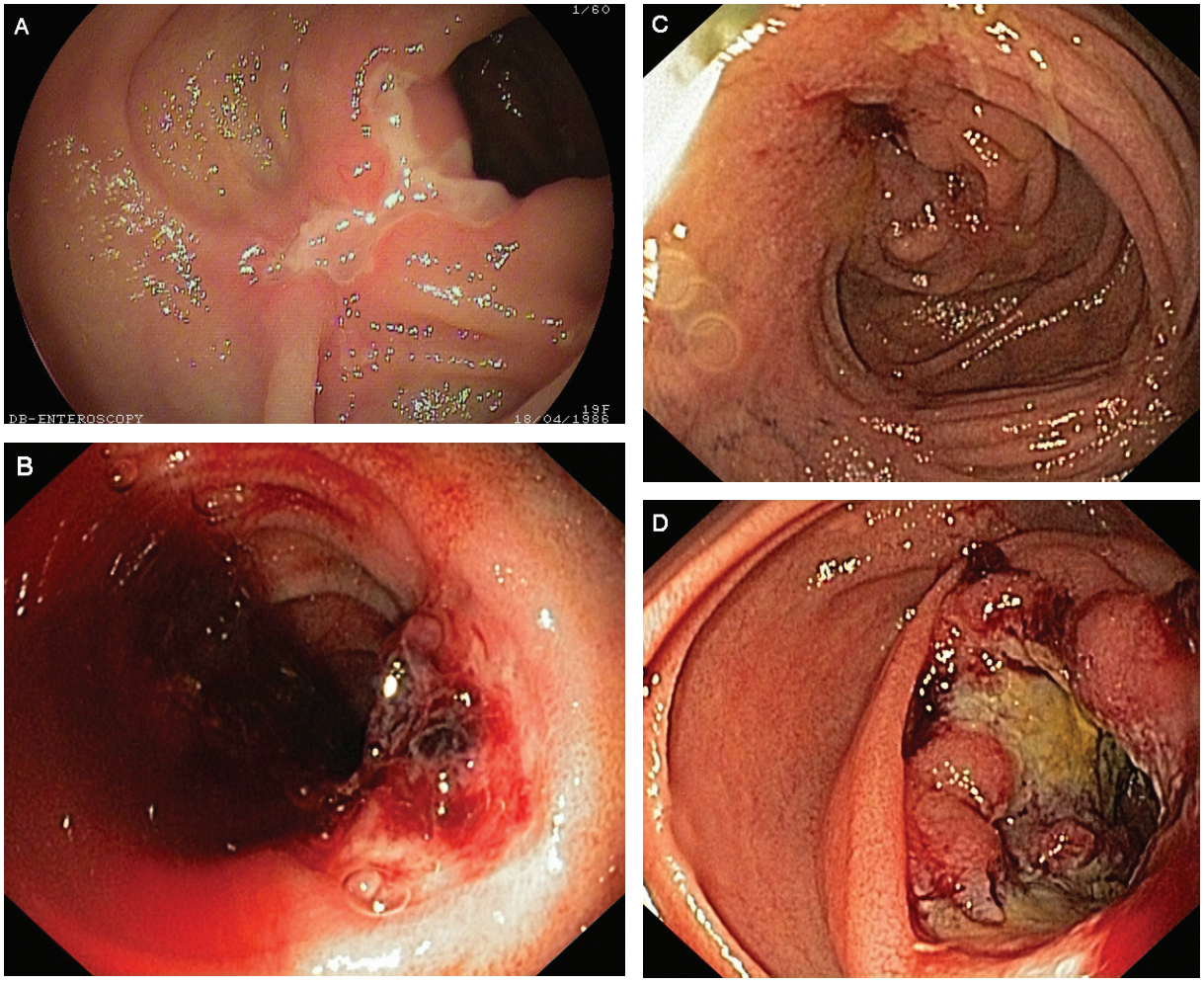

Figure 3 **A** Typical Crohn's disease longitudinal ulceration in the jejunum, **B** Bleeding Crohn's disease ulceration in the ileum, **C** Crohn's disease-related stenosis of the jejunum, **D** Crohn's disease-related adenocarcinoma of the jejunum.

guidelines are mainly graded C and D and since currently available literature has only highlighted some aspects of DAE in CD, future research should aim to provide a more definite answer to the following remaining questions:

1. What is the clinical validity of currently available grading scales of mucosal lesions and severity of disease?
2. What is the definite position of DAE in the diagnostic evaluation of (postoperative) intestinal CD (in relation to radiology and WCE)?
3. What is the impact of diagnostic DAE on therapeutic strategies for CD?
4. How often should DAE be performed in CD?
5. Should DAE be used as screening for small bowel malignancy in CD?
6. What is the local therapeutic potential of DAE in small bowel CD?
7. What is the safety and complication rate of DAE in (postoperative) CD?
8. Should every gastroenterologist treating IBD patients also perform DAE?
9. Can the diagnostic and therapeutic yield of DAE in CD be improved with newer developments?
10. What is the position of DAE in the pediatric CD population?

Conclusions

The small bowel has regained much attention since the development of WCE in the year 2000. Since then, both new radiological and endoscopic techniques have emerged to explore the small bowel. DAE is an innovative and still developing endoscopic procedure enabling deep and even complete enteroscopy. The design of specialized overtubes was shown to be of major importance in this development. Nowadays, both single- and double-balloon enteroscopy are widely available and have been shown to be equally effective. Also the spiral overtube enables fast and deep enteroscopy. With the help of these different DAE methods, all conven-

tional endoscopic interventions like biopsy sampling, local hemostasis, polypectomy etc. are now possible throughout the length of the small bowel.

Since IBD, and CD in particular, often affect the small bowel, DAE may be useful in the assessment of the intestine. Previously, ECCO, ESGE and OMED have defined guidelines on the use of DAE in IBD. However, most of these guidelines are based on case series and expert opinion (evidence levels C and D). This review provided an overview of the currently available literature data on the use of DAE in IBD. The majority of studies are retrospective case series with only a few prospective trials. However, they provide preliminary but promising answers to pertinent questions regarding both the diagnostic and therapeutic potential and safety of DAE in CD. Future research should aim to consolidate the role of DAE in IBD and to further improve the procedure of DAE.

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