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# The role of small-bowel endoscopy in inflammatory bowel disease: an updated review on the state-of-the-art in 2021

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**Abstract**

The impact of small-bowel (SB) capsule endoscopy and device-assisted enteroscopy on clinical practice, since their introduction 2 decades ago, has been remarkable. These disruptive technologies have transformed the investigation and management of SB pathology and now have a firmly established place in guidelines and clinical algorithms. Furthermore, recent years have witnessed innovations, driven by the demand of new goals in the management of inflammatory bowel disease (IBD), such as mucosal healing and evolving strategies based on tight monitoring and accelerated escalation of care. These developments in SB endoscopy have also been paralleled by refinement in dedicated radiological SB imaging technologies. This updated review highlights the current state of the art and more recent innovations with a focus on their role in IBD.

**Keywords** Small-bowel endoscopy, enteroscopy, capsule endoscopy, inflammatory bowel disease, Crohn's disease

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## Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic inflammatory bowel diseases (IBD) characterized by relapsing and remitting, immune-mediated inflammatory flare-ups, which mainly affect the gastrointestinal (GI) tract. The incidence of IBD is increasing worldwide [1-3], and although the same elusive etiological factors are implicated in the pathogenesis of both subtypes (genetic polymorphisms, gut microbiome and environmental factors), each has its own distinct clinical features [4]. Inflammation in CD is typically segmental, asymmetrical and transmural, and although CD may affect any part of the GI tract, small-bowel (SB) involvement occurs in up to 80% of cases, while in about 30% of patients, the disease is limited to the SB alone [1,2]. Most patients present with an inflammatory phenotype at diagnosis, but over time more than 50% of affected patients develop more severe, chronic complications, including strictures, fistulas, and/or abscesses, which in turn often warrant recourse to major surgery [5,6]. In approximately 5-15% of patients with endoscopic, radiological and histopathological evidence of chronic IBD confined to the colon, the disease does not fit the characteristic diagnostic criteria specific to either UC or CD. In these patients, the condition is termed IBD-unclassified (IBDU). IBDU is generally considered to be a temporary diagnosis [7,8], until a more definitive diagnosis of either UC or CD can be made.

Patients with suspected or established CD and IBDU, therefore, require frequent investigation to evaluate or exclude SB lesions and the potential need for escalation of care. Furthermore, even in patients with established UC, SB investigation may still be warranted if the clinical picture changes or raises suspicion for an alternative diagnosis of CD [3,9].

Even with current advances, the diagnosis and management of IBD remain challenging. The establishment of new therapeutic goals, such as mucosal healing (MH) and evolving strategies, based on tight monitoring and accelerated escalation of care, has created increasing demands and new indications for endoscopic assessment of disease activity [10,11].

Over the last 2 decades the disruptive endoscopic technologies of SB capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE) [12] have revolutionized our approach to the diagnosis and management of SB pathology. Over the years, these have been adopted into the standard of care, as demonstrated through the development of clinical guidelines by international societies such as the European Society of Gastrointestinal Endoscopy (ESGE) and the European Crohn's and Colitis Organisation (ECCO) [13,14]. In consequence, performance measures for clinical practice, training and competence recommendations were proposed to ensure a high standard of care and improve the quality of SB endoscopy [15,16]. Although these continue to evolve through novel indications, the main respective and complimentary roles of SBCE and DAE in the context of IBD are now well established. SBCE is principally a noninvasive instrument for the assessment of the SB mucosa that supports diagnosis and monitoring of disease activity. SBCE provides excellent mucosal views, while maintaining a high tolerability and safety profile in carefully selected patients [17,18]. DAE compliments SBCE by facilitating tissue biopsy and endotherapy, mainly endoscopic balloon dilation (EBD) of selected strictures [19-21].

The progress of SB endoscopy over the years has been mirrored by equally impressive advances in the quality and availability of dedicated SB cross-sectional imaging, including computed tomographic and magnetic resonance enterography (CTE and MRE, respectively). These complimentary endoscopic and radiological technologies have set new frontiers and now provide more accurate diagnostics, allowing for dynamic disease management and individualized patient care [22-24].

Recently, a novel modified capsule (the PillCam Crohn's™; Medtronic, Dublin, Ireland), with its 2 cameras, wider viewing angle and rapid, adaptive frame rate, is able to provide panenteric mucosal CE (PECE) [25]. This minimally invasive system, designed specifically for the monitoring of disease activity in patients with suspected or established CD [25], allows for extensive evaluation of the entire GI tract and is already being incorporated into routine clinical practice [26]. Recent developments in the field of DAE include the introduction of a new double-balloon enteroscope with a wider (3.2 mm) working channel and higher resolution "Super CCD with CloseFocus™" imaging (EN-580T, Fujifilm, Tokyo, Japan) [27], the introduction of balloon-guided enteroscopy (BGE) (Naviaid™ AB; Pentax Medical, Tokyo, Japan) [28,29] and the novel motorized spiral enteroscopy (NMSE) (PowerSpiral, Olympus Medical, Tokyo, Japan) [30].

## SBCE in CD

A unique reference standard for the diagnosis of CD is still elusive, and this is therefore dependent on a corroboration of clinical, biochemical, endoscopic, radiological and histopathological findings [13]. Although ileocolonoscopy (IC) remains the primary modality for endoscopic evaluation in suspected cases [31], the role of SBCE for the detection of more proximal SB mucosal lesions is increasingly recognized. This is reflected in guidelines and consensus statements [13,14].

The main advantages of SBCE are its "patient-friendly", well-tolerated, noninvasive and ambulatory nature. SBCE also provides the ability to visualize the entire SB with high diagnostic yields (DY) [32]. Detection of innocuous/incidental findings and an inability to biopsy mucosal lesions are its main limitations [33]. Capsule maneuverability, the application of artificial intelligence (AI) and more accurate localization of any identified lesions are the subjects of ongoing research [34,35].

There is growing evidence in the literature to support the use of AI in SBCE as a valuable adjunct to reduce reading times and enhance detection of suspicious abnormalities [36]. Ding *et al* [37] developed a deep-learning algorithm, based on a convolutional neural network (CNN) model to facilitate the identification and characterization of the SB pathology. The authors collected 13,426,569 images from 6970 patients who underwent SBCE over a 2-year period in 77 hospitals in China. The CNN model was initially trained to differentiate normal and pathological findings using 158,235 SBCE images recorded from 1970 procedures. It was found that the CNN model had a higher sensitivity for the identification of abnormalities as compared with conventional analysis by gastroenterologists in per-patient (99.9% vs. 74.6%) and per-lesion analysis (99.9% vs. 76.9%). The reading time with the CNN model was significantly shorter compared with conventional reading by gastroenterologists (5.9 vs. 96.6 min) [37]. Other studies also demonstrated good performance for CNN models in the identification of one category of SB abnormality [38-41]. Soffer *et al* in their systematic review and meta-analysis related to the implementation of deep learning in CE, demonstrated that the pooled sensitivity and specificity for ulcer detection were 0.95 and 0.94, respectively, and the pooled sensitivity and specificity for bleeding/bleeding source were 0.98 and 0.99, respectively [42].

Another potential limitation of SBCE relates to its inability to "wash away" any luminal debris that may affect the views obtained [43]. Although ingestion of purgatives prior to SBCE for better mucosal visualization is recommended by recent guidelines, their use still remains the subject of ongoing debate [44,45]. Contraindications to the use of SBCE include the presence of strictures, suspected GI obstruction and swallowing disorders [46].

The main potential complication of SBCE is capsule retention, defined as persistence of the capsule within the SB for at least 2 weeks after ingestion, requiring intervention for retrieval [47]. Since CD may cause stricturing of the SB, the incidence of this complication is higher in these patients. The risk of capsule retention ranges between 0.5% in patients with suspected CD and up to 13% in patients with established CD [48-55]. A more

recent meta-analysis showed that the retention rates in patients with suspected or known IBD were approximately 4% and 8%, respectively [56]. A thorough clinical history, to exclude obstructive symptoms, along with appropriate use of the patency capsule (PC) (PillCam Patency™, Medtronic, Dublin, Ireland), is mandatory [57]. The PC is designed to disintegrate spontaneously within 72 h of retention while the presence of a radiofrequency identification tag and 5% barium within the PC allow its detection and localization [58,59]. SBCE may subsequently be performed if an intact PC is excreted by 30 h post-ingestion. If the PC is excreted after 30 h, its integrity should be carefully examined, since subsequent SBCE should only be considered if the PC is intact [58,59]. A retrospective study by Yadav *et al* suggested that the negative predictive value (NPV) for CTE, MRE and PC for capsule retention was similar, and that their role might be complimentary [60]. However, another study revealed that cross-sectional imaging is significantly less accurate in the assessment of functional SB patency, frequently overestimating the risk of obstruction [61]. Other studies raise questions about the sensitivity of CTE and MRE in recognizing SB strictures [62,63]. Selective, limited exposure, non-contrast CT, rather than plain abdominal radiography, has been shown to be the best modality for reliable localization of a retained PC [64,65].

### SBCE vs. dedicated SB imaging: MRE, CTE and small-intestinal contrast ultrasound (SICUS)

The most recent meta-analysis by Kopylov *et al*, which included 10 studies comparing SBCE to MRE, demonstrated that the DY of SBCE was similar to that of MRE for detection of SB disease, in both suspected and established CD: odds ratio (OR) 1.17, 95% confidence interval (CI) 0.83-1.67 [32]. These findings are in concordance with those of a previous meta-analysis by Dionysio *et al* [66]. Furthermore, SBCE appeared superior to MRE for the diagnosis of proximal SB CD in both established and suspected CD (OR 2.79, 95%CI 1.2-6.48) [32]. According to another meta-analysis by Yung *et al*, both diagnostic modalities, SBCE (100%, 95%CI 91-100%) and MRE (97%, 95%CI 89-100%) have similar pooled sensitivity in the identification of postoperative recurrence of CD [67], although in a small study performed by González-Suárez SBCE was found to be significantly superior to MRE for the detection of superficial SB lesions (87.5% vs. 56.2%, respectively, P=0.01) [68].

In the same meta-analysis by Kopylov *et al*, the comparison between SBCE and SICUS, exhibited similar DY for suspected and established CD (OR 0.88, 95%CI 0.51-1.53) [32]. Contrarily, the study by Yung *et al* demonstrated a discrepancy for pooled sensitivity between SBCE (95%CI 91-100%) and SICUS (95%CI 85-92%) for the detection of postoperative recurrence of CD [67].

The older meta-analysis by Dionisio *et al* also compared SBCE to CTE, and showed that overall SBCE had superior sensitivity and specificity for both suspected and established CD [66]. Considering the potential risks of repeated exposure to radiation, only a few further studies comparing these 2 modalities have since been published; these confirmed SBCE's superiority [69-72].

### The role of SBCE in IBD clinical practice

#### *SBCE in suspected CD*

Careful mucosal assessment with SBCE has become pivotal to the diagnostic approach in patients with suspected CD (Fig. 1). The ECCO-European Society of Gastrointestinal

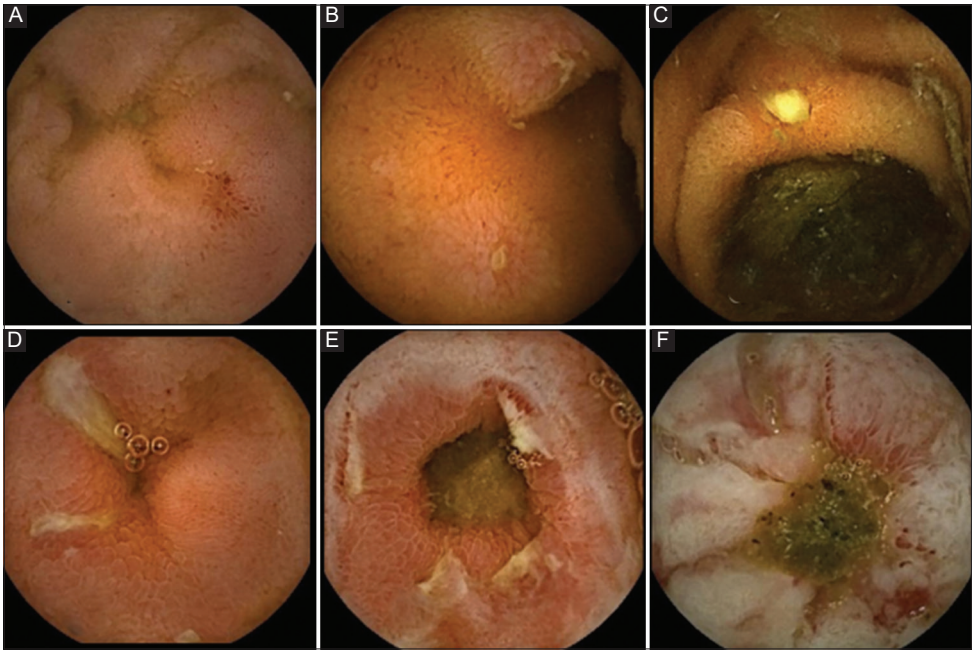


**Figure 1** Inflammatory lesions of the small bowel caused by Crohn's disease, as seen on small-bowel capsule endoscopy (different patients): (A) erythema; (B) aphthous erosion; (C) aphthous ulcer; (D) linear ulcers; (E) ulcerated stricture; (F) fibrotic stricture

and Abdominal Radiology (ESGAR) guidelines state that, in the absence of non-steroidal anti-inflammatory drug use for at least 1 month, the identification of 3 or more SB ulcers by SBCE would support a potential diagnosis of CD [13]. Although IC remains the investigation of first choice in patients with suspected CD, both the ESGE and the ECCO-ESGAR guidelines recommend the use of SBCE if IC is non-contributory and any potential stenosis has been excluded. In cases with suspected stenotic disease, cross-sectional imaging modalities should be used first [13,14].

Direct correlation and the predictive value of biological markers with potential SBCE findings remain inconclusive [73-77]. In their meta-analysis, Kopylov *et al* [78] demonstrated that a cutoff fecal calprotectin (FC) level of 50 μg/g could be a predictor of positive findings on SBCE (sensitivity 0.83, specificity 0.53). Egea-Valenzuela *et al* reported better results (75% sensitivity and 67% specificity) with a higher cutoff value for FC (>100 μg/g) [79]. This was echoed by another study with a threshold value of >95 μg/g [80] (77% sensitivity and 60% specificity). However, the contention lies in the fact that some other studies have failed to confirm any corroborative relationship between FC concentrations and SBCE findings [81,82]. C-reactive protein (CRP) levels were also found to have no correlation with SBCE activity scores [74,83]. SBCE has also been proven to be a valuable diagnostic modality in patients with unexplained fistulas and suspected CD in the context of a negative IC [13].

## SBCE in established CD

The management of IBD remains challenging, even in the modern era of advanced biological therapy. The discrepancy between symptoms and endoscopic findings, and the critical need of detecting worsening disease activity at an early stage, have established new goals in management [10]. MH and evolving strategies based on tight monitoring and accelerated escalation of care ("treat-to-target"), have increased referrals for endoscopic assessment of disease activity [10,84-88].

The need for quantification of inflammatory activity by validated systems led to the development of scoring modalities, including the Lewis score (Table 1) [89] and the CE CD Activity Index (CECDAI) (Table 2) [90]. The CECDAI estimates inflammatory activity, disease extent, and the presence of any stricturing, with localization in relation with the transit time of the capsule [90]. Similarly, the Lewis score reports on the presence and distribution of villous edema, ulceration, and stenosis [89]. These scores are designed to allow for a more objective estimation of SB disease activity and thus more standardized reporting.

In patients with established CD, the ESGE suggests that further evaluation of disease extent and location should be initially performed with cross-sectional imaging, since this may exclude transmural and extraluminal disease [14]. Should cross-sectional imaging be unremarkable or non-diagnostic, disease mapping with the use of SBCE is recommended; if any potential findings are deemed to alter disease management [14]. The ECCO-ESGAR guidelines additionally highlight the role of SBCE for the assessment of MH and response to medical therapy [13].

A recent prospective multicenter study demonstrated that there is concordance between SBCE and IC scores

**Table 1** Lewis score

| Parameters | Number | Longitudinal extent[1] | Descriptors |
|---|---|---|---|
| Villous appearance (worst-affected tertile) | Normal: 0<br>Edematous: 1 | Short segment: 8<br>Long segment: 12<br>Whole tertile: 20 | Single: 1<br>Patchy: 14<br>Diffuse: 17 |
| Ulcer (worst-affected tertile)[2] | None: 0<br>Single: 3<br>Few: 5<br>Multiple: 10 | Short segment: 5<br>Long segment: 10<br>Whole tertile: 15 | <$^1/_4$: 9<br>$^1/_4$ – $^1/_2$: 12<br>> $^1/_2$: 18 |
| Stenosis (whole study) | None: 0<br>Single: 14<br>Multiple: 20 | Ulcerated: 24<br>Non-ulcerated: 2 | Traversed: 7<br>Not traversed: 10 |
| Score calculation | Score of the worst-affected tertile: [(villous parameter × extent × descriptor) + (ulcer number × extent × size)] + stenosis score (number x ulcerated x traversed) | | |
| Comments | 1. Longitudinal extent: short-segment: <10% of the tertile; long-segment: 11-50% of the tertile; whole tertile: >50% of the tertile<br>2. Ulcer number: single: 1; few: 2-7; multiple: ≥8. Ulcer descriptor (size): percentage of the capsule picture filled by the largest ulcer | | |
| Score range | 8-4800 points; <135 normal mucosa; 135-790 mild disease; >790 moderate-to-severe disease | | |

Adapted from Cotter *et al* [89]

**Table 2** Capsule endoscopy Crohn's disease activity index scoring system

| | |
|---|---|
| A. Inflammation | 0 = none<br>1 = mild to moderate edema/hyperemia/ denudation<br>2 = severe edema/hyperemia/denudation<br>3 = bleeding, exudate, aphthae, erosion, small ulcer (<0.5 cm)<br>4 = moderate ulcer (0.5-2 cm), pseudopolyp<br>5 = large ulcer (>2 cm) |
| B. Extent of disease | 0 = no disease – normal examination<br>1 = focal disease (single segment involved)<br>2 = patchy disease (2-3 segments involved)<br>3 = diffuse disease (>3 segments involved) |
| C. Narrowing (stricture) | 0 = none<br>1 = single-passed<br>2 = multiple-passed<br>3 = obstruction |
| Score calculation | Proximal segmental score + distal segmental score = (A1 × B1 + C1) + (A2 × B2 + C2) |
| Comments | Final score is the sum of the proximal and distal small bowel segment scores (according to transit time) |
| Score range | 0-36 |

Adapted from Niv *et al* [90]

for the evaluation of MH. Both Lewis score and CE CD Endoscopic Index of Severity were correlated with the Simple Endoscopic Score for CD (P<0.001, ρ=0.59, and P=0.002, ρ=0.48, respectively). However, within the same study, a poor correlation was shown between endoscopic scores and clinical parameters (Crohn's Disease Activity Index, CRP, erythrocyte sedimentation rate, or FC) [75].

Current recommendations recognize the superior accuracy of SBCE vis-à-vis CTE and MRE for the identification of mucosal lesions within the proximal SB [14,70,91], and its ability to detect proximal SB lesions in up to 50% of patients, with disease previously thought to be confined to the distal ileum [92]. This is of clinical importance, since the presence of CD activity within the proximal SB has been shown to be correlated with phenotype severity, warranting earlier escalation to more intensive management [93,94].

In the context of suspected postoperative ileocolonic disease recurrence, the ESGE recommends that SBCE is indicated if there has been inadequate assessment by IC [14]. The ECCO-ESGAR guidelines suggest that FC, SICUS, MRE and SBCE can all be considered as noninvasive alternatives to detect postoperative recurrence [13]. A recent systematic review demonstrated that SBCE can detect postoperative recurrence to a similar extent as IC, and proximal SB lesions that are beyond the reach of a colonoscope in over 50% of patients [95]. PC use should always be considered before SBCE in this setting in order to rule out any postoperative stricturing, thus mitigating the risk of potential capsule retention.

**Table 3** PillCam Crohn's disease capsule score

| | |
|---|---|
| A. Most common lesion | 0 = none<br>1 = mild<br>2 = moderate<br>3 = severe |
| B. Most severe lesion | 0 = none<br>1 = mild<br>2 = moderate<br>3 = severe |
| C. Extent of disease | 0 = none<br>1 = 10-30%<br>2 = 30-60%<br>3 = 60-100% |
| D. Stricture | 0 = none<br>1 = 1 traversed<br>2 = >1 traversed<br>3 = retention |
| Score calculation | Segmental score = ((A + B) × C) + D<br>Small bowel score is the sum of 3 tertiles (SB1 + SB2 + SB3)<br>Panenteric score is the sum of SC score plus left and right colon scores (SB1 + SB2 + SB3 + RC + LC) |
| Comments | Novel score and needs further validation<br>PillCam Crohn's capsule approximates anatomical small bowel segmentation |

Adapted from Eliakim *et al* [101]

## SBCE in IBDU/UC

SBCE may be used to evaluate any suspected SB inflammatory activity in patients with IBDU. Monteiro *et al* demonstrated that findings on SBCE in keeping with CD were revealed in 25% of patients with IBDU, with a positive predictive value of 100% and a high NPV (94%) [96]. In another study performed by Min *et al*, the use of SBCE helped to reclassify a diagnosis of UC or IBDU to CD in 50% of patients [97]. SBCE identified SB lesions and consequently helped to change the diagnosis to CD in up to 65.2% of patients originally diagnosed with post-surgical pouchitis [95]. Although negative findings on SBCE in patients with IBDU do not rule out a potential diagnosis of CD [98-100], current recommendations recognize the usefulness of SBCE in the reclassification of IBDU and its potential utility in the accelerated management of the underlying disease [13,14].

## Pan-enteric mucosal capsule endoscopy (PECE)

PECE (PillCam Crohn's™; Medtronic, Dublin, Ireland) is a noninvasive imaging technique recently approved as an imaging modality for the monitoring of CD activity (Table 3) [101]. This is a novel capsule system, based on an updated version of the twin-camera colon capsule (second generation colon capsule, PillCam COLON™, Medtronic, Dublin, Ireland) [101], which allows for mucosal evaluation of both the small and large bowel. The PECE combines a long-lasting battery (up to 14 h battery life) with wide-angle cameras (336° view), together with an adaptive frame rate, to provide excellent visualization of the entire GI tract during a single procedure [101,102]. Also, the novel software (Rapid 9™, Medtronic, Dublin, Ireland) allows estimated localization of any mucosal lesions and the scoring of disease extent and activity [101,103]. The main indications of PECE in established CD include disease classification, monitoring for MH, and evaluation of unexplained symptoms and anemia [101]. PECE shows higher sensitivity than IC and MRE for the detection of active CD in the proximal SB, as well as higher specificity than MRE [26]. It may therefore allow for a more accurate evaluation of prognosis and guidance for escalation or de-escalation of treatment [103]. Other studies confirm the high technical and diagnostic performances of PECE for both initial diagnosis and monitoring of established IBD [25,102]. PECE promises to be a low-risk and cost-effective investigation, which may reduce the number and invasiveness of investigations required to establish effective and timely care, with potential earlier recovery [26,104]. According to ESGE recommendations, a patency capsule should be offered to all CD patients prior to SBCE to ensure functional patency of the SB, irrespective of previous unremarkable cross-sectional imaging [14]. If the correct protocol is followed, it has been shown to be very safe, with a very low risk of capsule retention [25,104].

## DAE in CD

DAE allows direct and potentially complete visualization of the SB through both the oral (anterograde) and/or the anal (retrograde) route [12,14]. Since its introduction in

2001 [12], DAE has superseded push enteroscopy (PE) and intraoperative enteroscopy (IOE) as the preferred modality for flexible endoscopy of the SB [14]. PE only allows examination of a limited part of the proximal SB, while IOE is an inherently invasive procedure, with risks of significant morbidity and mortality [105]. Nevertheless, both still have a limited role to play, especially in cases where DAE is not available or where surgical management cannot be avoided [14,106].

DAE allows deep for intubation of the SB, usually facilitated by balloon(s), and overtube. DAE includes double and single-balloon enteroscopy (DBE and SBE, respectively), BGE and the former manual spiral enteroscopy, recently relaunched as NMSE. BGE is assisted by an on-demand, through-the-scope balloon working as an anchor into the SB [28]. DBE and SBE use a stabilizing overtube with incorporated distal balloon. This is used in conjunction with a balloon attached to the tip of the enteroscope in the case of DBE [12,107]. Both DBE and SBE achieve deep SB intubation with a combination of insertion and retraction of the enteroscope while the inflated balloons gently grip the intestine, allowing SB manipulation. This "push-and-pull" technique leads to progressive shortening of the SB and pleating onto the overtube. The lack of a second balloon in SBE is countered by the "hook-and-suck" technique that entails suction of the SB mucosa and tip-of-the-scope angulation [108,109]. SE requires an overtube equipped with a spiral-shaped silicone elevation; in the case of the recently introduced NMSE, this is connected to an electric motor that powers its rotation. Clockwise and anticlockwise rotation of the spiral overtube pleats the SB, allowing for advancement and withdrawal of the enteroscope into and out of the SB, respectively [110,111]. The safety and efficacy of NMSE are the subject of ongoing clinical studies [112,113].

The efficacy and DY of DAE have been addressed through several studies [28,111,114-122]. Since it was the first form of DAE to be introduced into clinical practice, most of the evidence relates to DBE [12,117,118,120-122]. Comparisons between DBE and SBE enteroscopy have varied and interchangeable results regarding DY, depth of insertion and adverse events, while SE appeared to have the advantage of a shorter SB insertion time [123-126]. The ESGE and ECCO-ESGAR recommendations suggest that DAE techniques have similar efficiency and safety considerations and can be applied according to local availability and expertise [9,13-14,44,127]. Studies in pediatric patients support the safe use of balloon-assisted enteroscopy (BAE) in children, when clinically indicated [128-133]. Although the safety profile of NMSE requires further evaluation in routine clinical practice, it has been shown to be contraindicated in pediatric patients [134].

Excluding NMSE, DAE has been associated with an overall intraprocedural complication rate of 0.72%; these complications include bleeding (0.07%), perforation (0.2%), and pancreatitis (0.3%) [135]. Potential adverse events relating to deep sedation and anesthesia should also be considered, and to mitigate these, preprocedural assessment by an anesthetist is advised. The complication rate appears to be relatively higher in patients with IBD and is increased when endotherapy is applied [136,137].

While DAE is not considered to be a first-line diagnostic tool for CD, it may facilitate diagnosis in cases with non-diagnostic IC and suspicious radiological and/or SBCE findings [9,14,127] (Fig. 2). DAE may allow direct inspection of the entire SB and provide histopathological samples to corroborate a final diagnosis. Additionally, DAE is useful when patients with established CD require endotherapy. Even though enteroscopy is a relatively safe procedure, careful planning is needed, as DAE is more invasive in its nature, with technical challenges and possible adverse events [14,108,109].

DAE can provide additional corroborative findings, should initial, less invasive investigations prove inconclusive. The DY of DAE varies significantly; initial studies (albeit including small numbers of patients) reported a DY for DBE that ranged from 22-60% [120,121]. More recent studies reported a DY of 79% in cases with suspected CD, depending on the presence or absence of endoscopic findings. Biopsy sampling during DAE helped to establish a diagnosis of CD in up to 40% of cases [117]. DBE facilitated a final diagnosis of SB CD in 67% of cases (12/18) with histopathological confirmation, when patient selection followed radiological and SBCE investigation [122]. A larger retrospective cohort of 122 DBE procedures in 100 patients reported endoscopic findings indicative of CD in 60% of cases, even though histopathological confirmation was significantly lower (38%) [118]. A smaller study from Italy showed a DY of 39% when SBE was performed in 13 patients suspected of having CD [119]. DBE and SBE performance has been further evaluated during the last decade, and their efficacy and DY are comparable [125]. Although large studies evaluating the role of NMSE in the diagnosis of CD are still lacking, a recently published experience from a single center showed that it helped to establish a diagnosis of CD in 16 of 25 patients (64%) in whom CD was suspected [111].

DBE can also help achieve a definitive diagnosis of CD in a pediatric setting. This was shown in another recent study, in

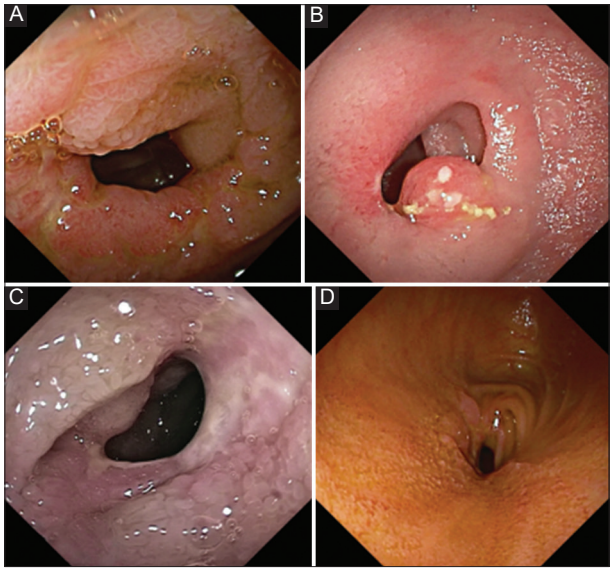


**Figure 2** (A,B,C) Fibrotic strictures of the small bowel (SB) as seen on double-balloon enteroscopy. (D) Fibrotic stricture of the SB with pre-stenotic pseudosacculation

which 16 of 61 children (26%) with non-specific symptoms were diagnosed with CD. Children with abdominal pain, diarrhea and/or SB obstruction had a 30% confirmation of CD after tissue sampling [128]. Similarly, SBE identified the presence of endoscopic findings in 60% of any suspected IBD cases and guided a diagnosis of CD in 8 of 14 (57%) pediatric patients [129].

The diagnostic role of DAE in suspected CD should be reserved for cases where a definitive diagnosis remains elusive, despite the use of less invasive imaging (CTE, MRE and SBCE). Nonetheless, its role remains important in the management of patients with established CD [14,127]. DAE allows for the direct evaluation of disease activity and its extent, it facilitates direct monitoring of MH and response to therapy, the retrieval of retained SB capsules and EBD of SB strictures.

EBD is the main endotherapeutic intervention for patients with SB CD (Fig. 3). EBD is less invasive than surgical alternatives and repeat dilations can be performed, if and when clinically indicated (Fig. 4). The use of fluoroscopy is advised when EBD is performed [14,108]; treatment algorithms have been proposed [109] and novel dedicated accessories, such as the calibrated small-caliber tip hood, have been introduced, to improve the quality and safety of the procedure [138]. DAE-facilitated EBD is usually performed using a transparent through-the-scope balloon dilator. This is gradually inflated with water (±contrast), under direct endoscopic and fluoroscopic visualization.

Numerous reports have documented the efficacy and safety of EBD in carefully selected cases [19,139-142]. EBD can improve symptoms and delay or obviate recourse to surgery [108]. According to international guidelines, SB strictures suitable for endoscopic dilation are those ≤5 cm in length with proximal dilation and without active inflammation, deep ulcers, abscesses and/or fistulas. Sharp-angulation of the SB is an additional unfavorable factor [14,19,44,108,143] that may increase the risk of complications. The optimal DAE insertion route should be guided by SB imaging prior to the procedure. To date, the majority of studies relating to EBD used BAE to apply endotherapy [19,136,137,139-141,144-147]. Although in a recent study, NMSE facilitated dilation of 3 strictures, along with retrieval of a retained capsule, without any adverse events, additional studies are warranted to further evaluate the safety and effectiveness of this recently introduced modality [134].

The first large Japanese studies on EBD success and safety documented encouraging results, regardless of the type of BAE used. DBE-facilitated EBD was applied successfully in 52 symptomatic patients, with a short-term success rate of 92.3% and a total complication rate of 9.2% (perforation rate: 1.5%). In total, 26.2% of the study population needed surgical management and almost half of the previously dilated patients needed an additional EBD during the next 24 months [136]. Similarly, another study reported on SBE-facilitated EBD in 37 patients. In this study, there was a 76.2% reduction in the severity of obstructive symptoms and no major adverse event. Repeated DAE with additional EBD was deemed necessary in 48.6% (18/37) of the patients; 5 of these required surgical intervention [137]. These results were reflected in a large pooled analysis with 3213 EBD procedures in 1463 patients with primary and anastomotic, predominantly ileal strictures. Technical success was achieved in 90% and symptomatic relief was achieved in 80%; the complication rate was 2.8%. Nevertheless, almost 75% of the patients needed repeat dilation and 43% required surgery within 24 months [142]. A systematic review of SB dilation facilitated by DBE reported an 80% long-term success rate, with a complication rate of 2.6% per dilation and 4.8% per patient. After an average 32 months of follow up, only 17% of patients had required surgery; however, 46% required additional EBD [148].

The first prospective multi-center study of BAE-facilitated EBD for patients with SB strictures relating to CD was performed in Japan in 2018 and included 95 patients [139]. Technical success of EBD was reported in 89 (93.7%) patients, and 66 (69.5%) patients reported a 4-week, short-term improvement in symptoms. Although the overall complication rate was 5%, there were no perforations and only 1 patient needed surgical intervention within the follow-up period [139]. The apparent trend is that long-term EBD outcomes are improving as experience, enteroscopes and accessories are further refined [140,149]. Among 85 patients with SB strictures due to CD, who underwent a total of 473 successful EBDs, the overall surgery-free rate was 87.3% after 1 year, 78.1% after 3 years and 74.2% after 5 years. In total 21 patients (24.7%) eventually needed surgical intervention. Adverse events were reported in 1% of all procedures, with a 0.8% perforation risk per dilation and a 4.7% risk per patient [140]. In a smaller cohort of 26 patients with CD, who all achieved short-term improvement, the long-term outcomes were also encouraging, with a cumulative surgery-free rate of 90.3% at both 2 and 3 years after initial dilation. Only 2 patients (7.7%)

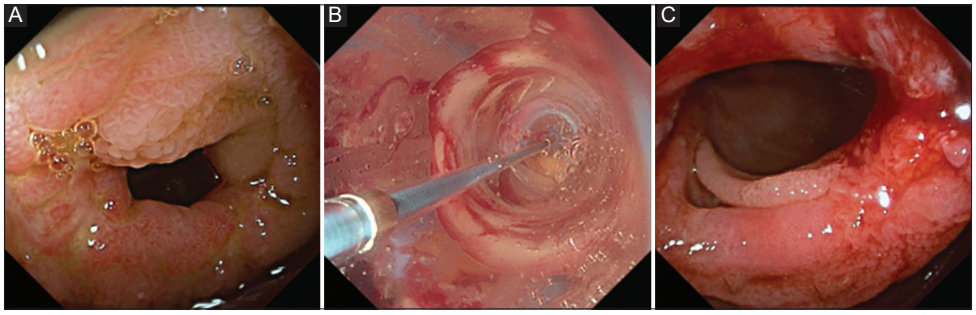


**Figure 3** (A) Fibrotic stricture of the small bowel, as seen on double-balloon enteroscopy (DBE). (B) Through-the-balloon view at endoscopic balloon dilation (EBD) of a small bowel fibrotic stricture, as seen on DBE. (C) Post-EBD of the same stricture, as seen on DBE

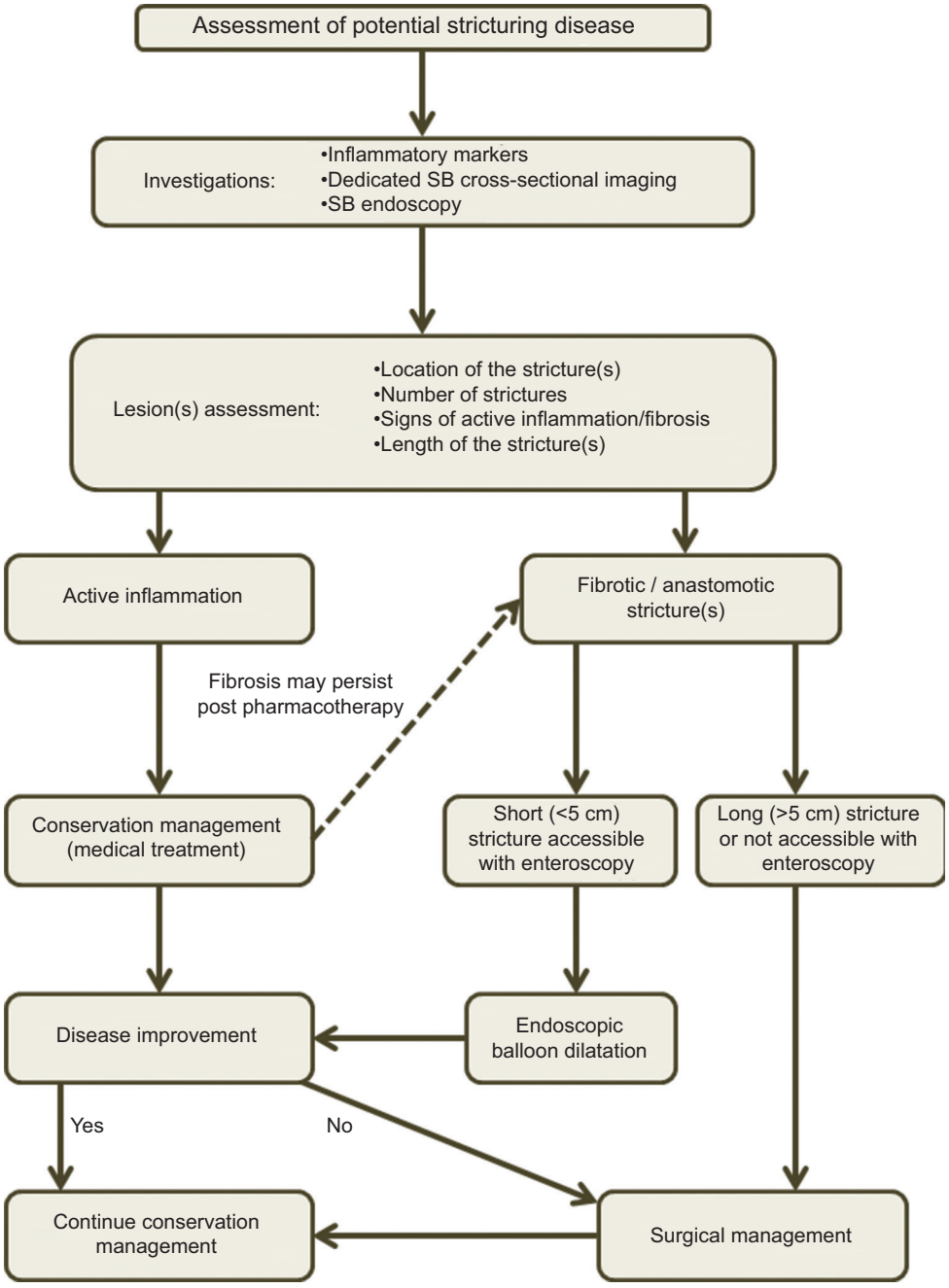


**Figure 4** Algorithm for the management of small-bowel (SB) strictures caused by Crohn's disease [109]

needed surgery during this period of follow up. These results were achieved with repeat EBD in 42% of patients; thus, the cumulative redilation-free rate was 47.8% and 31.9% at 2 and 3 years post initial EBD, respectively [149]. Lastly, a multicenter retrospective study included 305 patients, 100 of whom underwent successful EBD facilitated by BAE. After initial dilation, the cumulative surgery-free rate was 93.8%, 72.8% and 62.9% after 1, 5 and 10 years, respectively; all rates were higher compared with the surgery-free rate of the cohort. Postprocedural complications were reported in 3 cases, 1 of which was a perforation requiring surgical management (1%). The authors reported a less satisfactory response to EBD when patients were active smokers [141].

According to long-term outcomes, there is an evident need for frequent repeat EBD due to recurrence of symptoms [139,140]. Repeat DAE and prophylactic EBD may be required to prolong the surgical-free period and for the prevention of symptom recurrence [148]. Pre-stenotic dilation, active disease and an Asian heritage are some factors associated with a greater recourse to surgery in the multivariate analysis of a large systematic review [142]. Similarly, the main risk factor regarding any intervention (endotherapy or surgery),

was the presence of active disease, while medication with anti-tumor necrosis factor reduced the need for reintervention. Patients with short fibrotic strictures (≤5 cm) and without active inflammatory disease were shown to be ideal candidates for dilation with a low risk of relapse [142]. Thus, a longer time interval between initial EBD and repeat procedure has been associated with lower surgical risk. Interestingly, any association between the presence of multiple strictures and a greater risk for surgery remains unproven [141].

Since the introduction of DBE in 2001 [12], DAE has played an important role in the diagnosis and management of CD. Apart from assistance in the differential diagnosis of CD in patients with noncontributory investigations, the main advantage of DAE is that it enables endotherapy. DAE facilitates the retrieval of foreign bodies (mainly retained capsules) and EBD, with high success rates and a low frequency of intra- and postprocedural complications in expert hands. EBD can be repeated, depending on the clinical presentation, and may postpone or obviate the need for intestinal resection, improving the patient's overall quality of life.

## Concluding remarks

Since their introduction 2 decades ago, both SBCE and DAE have established key roles in the diagnosis and management of IBD of the SB; a complementary role reflected in current guidelines and clinical algorithms. Also complemented by further refinement in dedicated radiological cross-sectional imaging, the recent developments seen in SBCE now allow for panenteric, minimally invasive monitoring of disease activity with objective assessment of response to treatment, facilitating the goal of personalized medical therapy. The last 2 decades of experience with DAE have also allowed the accumulation of broader expertise and evidence to support the safe and effective use of EBD as a minimally invasive alternative to surgery, in selected patients with stricturing disease of the SB. At the same time, SB endoscopy has evolved from a novel concept into an indispensable part of clinical practice, with specific prerequisites and quality measures ensuring optimal care and patient safety.

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