Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED–ECCO consensus

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DOI 10.1055/s-0029-1214790
Endoscopy 2009; 41: 618–637 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

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Crohn's disease and ulcerative colitis are lifelong diseases seen predominantly in the developed countries of the world. Whereas ulcerative colitis is a chronic inflammatory condition causing diffuse and continuous mucosal inflammation of the colon, Crohn's disease is a heterogeneous entity comprised of several different phenotypes, but can affect the entire gastrointestinal tract. A change in diagnosis from Crohn's disease to ulcerative colitis during the first year of illness occurs in about 10%–15% of cases. Inflammatory bowel disease (IBD) restricted to the colon that cannot be characterized as either ulcerative colitis or Crohn's disease is termed IBD-unclassified (IBDU). The advent of capsule and both single- and double-balloon-assisted enteroscopy is revolutionizing small-bowel imaging and has major implications for diagnosis, classification, therapeutic decision making and outcomes in the management of IBD. The role of these investigations in the diagnosis and management of IBD, however, is unclear.This document sets out the current Consensus reached by a group of international experts in the fields of endoscopy and IBD at a meeting held in Brussels, 12–13th December 2008, organised jointly by the European Crohn's and Colitis Organisation (ECCO) and the Organisation Mondiale d'Endoscopie Digestive (OMED). The Consensus is grouped into seven sections: definitions and diagnosis; suspected Crohn's disease; established Crohn's disease; IBDU; ulcerative colitis (including ileal pouch–anal anastomosis [IPAA]); paediatric practice; and complications and unresolved questions.Consensus guideline statements are followed by comments on the evidence and opinion. Statements are intended to be read in context with qualifying comments and not read in isolation.

Introduction

Crohn's disease and ulcerative colitis are lifelong diseases observed predominantly in the developed countries of the world. Within Europe there is a distinct north–south gradient, but the incidence appears to have increased in southern countries in recent years [1]. Both diseases are marked by frequent relapses and patients often undergo repeated investigations. Whereas ulcerative colitis is a chronic inflammatory condition causing diffuse and continuous mucosal inflammation of the colon, Crohn's disease is a heterogeneous entity comprised of several different phenotypes, but can affect the entire gastrointestinal tract. A change in diagnosis from Crohn's disease to ulcerative colitis during the first year of illness occurs in about 10%–15% of cases. Inflammatory bowel disease (IBD) restricted to the colon that cannot be characterized as either ulcerative colitis or Crohn's disease is termed IBD-unclassified (IBDU). By common consent the term „IBDU" has replaced the inappropriate term „indeterminate colitis" [2].

The advent of capsule and both single- and double-balloon-assisted enteroscopy is revolutionizing small-bowel imaging and has major implications for diagnosis, classification, therapeutic decision making, and outcomes in the management of IBD. Until a decade ago, mucosal visualization of the small bowel was limited to the reach of the push enteroscope (excluding invasive and expensive intraoperative enteroscopy). The advent of small-bowel capsule endoscopy (SBCE) allowed for the first time direct visualisation of the entire small bowel, albeit without the ability for tissue sampling. As both ulcerative colitis and Crohn's disease are diagnosed on the basis of the combination of endoscopic, histological, radiological, and biochemical investigations [3,4] the clinical application of SBCE in the management of all IBD is unclear. This is important, because up to 13% of

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Table 1 Levels of evidence (EL) and grades of recommendation (RG), adapted from the criteria of the Oxford Centre for Evidence-Based Medicine [6].

Levels of evidence		
Level	**Individual study**	**Technique**
1a	Systematic review with homogeneity of level 1 diagnostic studies	Systematic review with homogeneity of randomized controlled trials (RCTs)
1b	Validating cohort study with good reference standards	Individual RCT (with narrow confidence interval)
1c	Specificity is so high that a positive result rules in the diagnosis („SpPin") or sensitivity is so high that a negative result rules out the diagnosis („SnNout")	All or none
2a	Systematic review with homogeneity of level > 2 diagnostic studies	Systematic review (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; e. g., < 80 % follow-up)
2c		„Outcomes" Research; Ecological studies
3a	Systematic review with homogeneity of 3b and better studies	Systematic review with homogeneity of case–control studies
3b	Nonconsecutive study; or without consistently applied reference standards	Individual case-control study
4	Case–control study, poor or nonindependent reference standard	Case series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or „first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or „first principles"
Grades of recommendation		
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies *or* extrapolations from level 1 studies	
C	Level 4 studies *or* extrapolations from level 2 or 3 studies	
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level	

normal, asymptomatic people are found to have lesions of unknown clinical significance in the small bowel at SBCE. It has been difficult to correlate the findings at SBCE with clinical presentation in the absence of definitive histopathology. More recently, advanced endoscopic techniques of balloon-assisted and spiral enteroscopy have allowed direct tissue sampling for histopathology and therapeutic procedures in the small bowel. The role of these investigations in the diagnosis and management of IBD, however, is unclear. In the absence of national and international recommendations, we believed that a formal Consensus conference on this topic would help to standardize and optimize patient care.

This Consensus aims to provide a worldwide perspective on the use of small-bowel endoscopy in the management of IBD. Since the development of guidelines is an expensive and time-consuming process, it may help to avoid duplication of effort in the future. This document sets out the current Consensus reached by a group of international experts in the fields of endoscopy and IBD at a meeting held in Brussels, 12 – 13th December 2008, organised jointly by the European Crohn's and Colitis Organisation (ECCO) and the Organisation Mondiale d'Endoscopie Digestive (OMED). The Consensus is grouped into seven sections: definitions and diagnosis; suspected Crohn's disease; established Crohn's disease; IBDU; ulcerative colitis (including ileal pouch–anal anastomosis [IPAA]); paediatric practice; and complications and unresolved questions.

The strategy to reach the Consensus involved five steps:

Relevant questions on each of the seven separate topics were devised by the Steering Committee and sent to seven working groups of endoscopy and IBD specialists, who were selected for their interest in the field. Each group had a leader and two or more contributing members. The leader was encouraged to invite a young gastroenterologist (age < 35 years!) to join the group.

1. The questions were focused on current practice and areas of controversy in the task force topic, and sent to all participants in the Consensus conference. Working groups were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure) [5].
2. The working parties performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed/EMBASE and the Cochrane database, as well as their own files. The evidence level (EL) was graded (**Table 1**) according to the system of the Oxford Centre for Evidence-Based Medicine [6].
3. Working groups wrote provisional guideline statements on their topic, based on answers to the questionnaire as well as the literature search, and these were circulated among the participants.
4. The working parties of 40 participants then met in Brussels 12 – 13th December 2008 to agree on the final version of each guideline statement. Statements were revised until a consensus was reached. Consensus was defined as agreement by > 80 % of participants, termed a Consensus Statement, and numbered for convenience in the document. Each recommendation was graded (RG) according to the system of the Oxford Centre for Evidence-Based Medicine [6], based on the level of evidence (**Table 1**).
5. The members of the working party wrote the final document on their topic, and these are presented here. Consensus guideline statements are followed by comments on the evidence and opinion. The statements are intended to be read in context with the qualifying comments and not read in isola-

tion. The final text was edited for consistency of style by A. Ignjatovic and A. Bourreille before being circulated and approved by the participants. In some areas the level of evidence was generally low, reflecting the paucity of randomized controlled trials. Consequently expert opinion was included where appropriate.

SECTION 1
Procedural definitions and description

The Consensus group agreed on definitions, some of which are recognized to be arbitary, and descriptions of the commonly used terminology. These should provide standardization within the field and allow for direct comparisons between research groups.

1.1 Small-bowel endoscopy

'Small-bowel endoscopy' is defined as any endoluminal examination of the small bowel, including capsule endoscopy, push enteroscopy and balloon- or other device-assisted endoscopy.

1.2 Small-bowel capsule endoscopy

Small-bowel capsule endoscopy (SBCE) is a method of endoluminal examination of the small bowel using a wireless capsule-shaped tool which is usually swallowed and then propelled through the gastrointestinal tract by gut motility. Synonyms include: capsule enteroscopy, wireless capsule enteroscopy, video capsule endoscopy.

SBCE utilizes a miniaturized complementary metal oxide semiconductor (CMOS) or charge-coupled device (CCD)-based camera, embedded in a 11 mm × 26 mm capsule-shaped instrument. The capsule also contains batteries, light-emitting diode (LED)-based illumination, and a transmitter for wireless transfer of images to an external antenna and receiving storage unit. During the battery life of the capsule, images are recorded, usually from the upper gastrointestinal tract and small bowel. The images are reformatted into a continuous video file that can be reviewed on a normal computer using specially adapted software. After 8–10 hours, the antenna and storage unit are removed and the images transferred to a computer for analysis and review by an experienced capsule endoscopist.

The main advantages of the SBCE method are the ability to visualize all of the small bowel with minimal discomfort for the patient. The procedure also requires less physician training than advanced endoscopic techniques.

The main disadvantages are the inability to manoeuvre the capsule, the lack of therapeutic capabilities, and the relative contraindication of possible strictures, because of the risk of impaction [7,8]. Furthermore, although most images are excellent, they are still not comparable to the view achieved at conventional endoscopy with gas insufflation.

1.3 Push enteroscopy

Push enteroscopy is an endoluminal examination of the proximal jejunum using a long, flexible endoscope.

Until the last decade, the complete assessment of the small intestine eluded gastroenterologists. Push enteroscopy allowed examination of the proximal small bowel. The tipp of a long endoscope (colonoscope, paediatric colonoscope, or enteroscope) was passed beyond the ligament of Treitz, sometimes through an overtube to avoid intragastric loops. Push enteroscopy did not permit visualization of the distal portions of the small intestine but allowed tissue sampling, polypectomy, and treatment of bleeding lesions [9]. In recent years, balloon-assisted endoscopic techniques have largely replaced push enteroscopy in examination of the small bowel.

1.4 Double-balloon enteroscopy

Double-balloon enteroscopy (DBE) is defined as endoluminal examination of the small bowel using a double-balloon endoscope.

DBE, first described by Yamamoto and colleagues in 2001 [10], allows deep (even complete) intubation of the small bowel by pleating the bowel onto a long, flexible endoscope fitted with an overtube. The endoscope and the accompanying overtube have balloons at their distal end. By intermittent inflation and deflation of these two balloons, combined with instrument insertion and retraction, large portions of the small bowel can be visualized directly. Oral and anal routes, alone or in combination, are used to achieve complete small-bowel examination. The procedure is performed with conscious sedation or general anaesthesia. A range of accessories has been developed to allow tissue sampling and therapeutic procedures. DBE is a complex examination and should only be carried out by trained and experienced endoscopists. The standard method requires two individuals, an operator who handles the enterosocope and an assistant who handles the overtube.

1.5 Single-balloon enteroscopy

Single-balloon enteroscopy (SBE) is defined as endoluminal examination of the small bowel using a single-balloon endoscope.

Manufacturers have developed their own versions of instruments able to achieve complete examination of the small bowel (such as the single-balloon enteroscope) using principles similar to DBE. The tipp of a single-balloon enteroscope, which does not have a distal end balloon [11], is fixed by tipp angulation. An overtube with an integrated channel for a balloon catheter has also been developed. DBE has been used in the majority of studies published to date. There are no studies comparing different balloon-assisted enteroscopes.

1.6 Balloon-assisted enteroscopy

Balloon-assisted enteroscopy (BAE) is a generic term for endoluminal examination of the small bowel by any endoscopic technique that includes balloon-assisted progression.

1.7 Device-assisted enteroscopy

Device-assisted enteroscopy (DAE) is a generic term for endoluminal examination of the small bowel by any endoscopic technique that includes assisted progression (e.g. by a balloon, overtube, or other stiffening device).

1.8 Intraoperative enteroscopy

Intraoperative enteroscopy (IOE) is defined as an endoluminal examination of the small bowel during abdominal surgery with manual external assistance for endoscope progression.

By definition, IOE is an exploration of the small intestine with an endoscope (gastroscope, colonoscope, pediatric colonoscope, or enteroscope) during a surgical procedure. The endoscope can be introduced either orally or via an enterotomy. The progression of the endoscope through the intestine is facilitated by the manual assistance of the surgeon. Like SBCE, IOE detects lesions inaccessible to conventional endoscopy [12–14]. Before surgery, these lesions are not detected in more than half of the patients. No

study has compared the performance of IOE with other endoscopic techniques in the detection of small-bowel lesions in Crohn's disease patients. Indications for IOE are limited by the invasiveness of the procedure. Furthermore, observation of small-bowel lesions at enteroscopy but without removal at ileocolonic resection does not alter the risk of postoperative endoscopic recurrence [14].

1.9 Spiral enteroscopy

Spiral enteroscopy is a recently developed technique. An enteroscope, introduced orally, is passed through a single-use overtube, which has helical spirals at its distal end and rotates independently from the enteroscope. The enteroscope can be locked in the overtube allowing the option of spiral enteroscopy, or unlocked and advanced through the overtube [15, 16]. The feasibility of the technique has not been demonstrated in patients with IBD, and no study has compared spiral enteroscopy with other endoscopic techniques.

SECTION 2
Suspected Crohn's disease

▼

2.1 Introduction

There is no single, gold standard diagnostic test for Crohn's disease. The diagnosis is based on a constellation of findings, including the history and physical examination, endoscopic and radiological features, and laboratory and pathology findings [4]. Studies have suggested that up to 30% of patients diagnosed with Crohn's disease will have only small-bowel involvement [17, 18]. Until recently, the diagnosis of small-bowel Crohn's disease was made on the basis of small-bowel radiology and ileocolonoscopy, occasionally augmented by push enteroscopy or IOE. Options are still limited for histopathological confirmation of the diagnosis of small-bowel Crohn's disease, especially when attempting to confirm a new diagnosis.

The new endoscopic techniques improve the clinician's ability to identify subtle lesions that may be associated with an initial presentation of Crohn's disease [19]. In parallel with these endoscopic advances, the resolution of radiographic studies of the small bowel has markedly improved. Clinicians have access to more sensitive radiographic studies to secure a diagnosis of Crohn's disease. Small-bowel follow-through (SBFT) and enteroclysis, until now considered the gold standards for radiographic assessment of the small bowel, are being replaced by computerized tomography (CT)- and magnetic resonance (MR)-based enterography studies that may be more accurate for diagnosing small-bowel Crohn's disease.

The place that these new procedures and technologies will occupy in the diagnostic algorithm of suspected Crohn's disease remains to be fully determined. Early studies have shown them to be complementary to upper endoscopy and ileocolonoscopy, as well as complementary to one another.

2.2 SBCE in patients with suspected Crohn's disease

2.2.1 Indications for SBCE in patients with suspected Crohn's disease

Statement 2A

- Ileocolonoscopy must be performed prior to SBCE for the diagnosis of Crohn's disease [**EL4, RG C**]
- Small-bowel cross-sectional imaging should generally precede SBCE. The choice of radiographic imaging depends on local availability and expertise [**EL5, RG D**]
- There is no available evidence to support a particular bowel preparation for SBCE in the subset of patients with suspected Crohn's disease [**EL5 RG D**]

Diagnosis of terminal ileal Crohn's disease can be usually made at ileocolonoscopy, which should be performed before SBCE is contemplated. If the ileocaecal valve proves impossible to intubate, SBCE may be considered unless there is evidence of strictures: SBCE findings consistent with Crohn's disease were reported in 2/4 patients with an incomplete colonoscopy [20]. A study examining the sensitivity and specificity of different combinations of ileocolonoscopy, CT enterography (CTE), SBCE, and SBFT found that ileocolonoscopy with either CTE or SBFT was more accurate than SBCE with CTE, SBFT, or ileocolonoscopy, because of the lower specificity of SBCE [21]. These findings suggest that SBCE should be reserved for cases in which ileocolonoscopy plus small-bowel radiography is not diagnostic, but the suspicion of Crohn's disease remains high. SBCE offers the advantage of visualizing the entire small bowel, although the caecum is not reached in 8% – 40% of SBCE studies [19 – 26].

Suboptimal bowel preparation can limit image quality in the distal small bowel. Preparations for a SBCE study usually include 8 – 12 hours' fasting and some method of bowel cleansing (e.g. ingestion of 2 L of polyethylene glycol [PEG] solution. A meta-analysis, yet to be reported in full, has found that the diagnostic yield of SBCE and the quality of small-bowel visualization were significantly higher in patients who had a purgative bowel preparation (n = 263) compared with those given a liquid diet alone (n = 213), with a pooled odds ratio [OR] of 1.81 (95% confidence interval [CI] 1.25 – 2.62, $P = 0.002$) and OR of 2.11 (95%CI 1.25 – 3.57), respectively [27]. However, the number of patients with suspected or established Crohn's disease included in the different studies was low and it has not been shown that cleanliness of the small bowel affects the diagnostic yield in the subset of patients with suspected Crohn's disease. Prokinetics or simethicone have been used to improve the results, but are not generally recommended [28].

Statement 2B

- SBCE is able to identify mucosal lesions compatible with Crohn's disease in some patients in whom conventional endoscopic and small-bowel radiographic imaging modalities have been nondiagnostic [**EL4, RG C**]
- As with other imaging modalities, a diagnosis of Crohn's disease should not be based on the appearances at capsule endoscopy alone [**EL5, RG D**]
- A normal capsule endoscopy has a high negative predictive value for active small-bowel Crohn's disease [**EL4, RG D**]

Table 2 Criteria used to diagnose Crohn's disease on small-bowel capsule endoscopy (SBCE).

	Patients (suspected Crohn's), n	Comparator	Diagnostic criteria (SBCE)	Findings
Costamagna et al. 2002 [37]	20 (1)	SBFT	Medically significant	Ulcers
Eliakim et al. 2004 [67]	25 (25)	SBFT/CT	Medically significant	Ulcers, erosions, erythema, aphthae, nodular lymphoid hyperplasia
Dubcenco et al. 2005 [23]	44 (11)	SBFT	≥ 3 ulcerations	Erythema, oedema, loss of villi, stricture, mucosal fissure, fistula scarring
Chong et al. 2005 [24]	43 (21)	SBFT/push enteroscopy	Medically significant	Erosions, ulcers
Hara et al. 2006 [20]	17 (8)	SBFT/CT	Consistent with Crohn's disease	Erosion, ulcer, stricture
Golder et al. 2006 [25]	36 (2)	MR enteroclysis	> 1 aphthoid ulcer	Not described
Solem et al. 2008 [21]	41 (?)	SBFT/CT	Consistent with Crohn's disease	Unknown

SBFT, small-bowel follow-through; CT, computed tomography; MR, magnetic resonance.

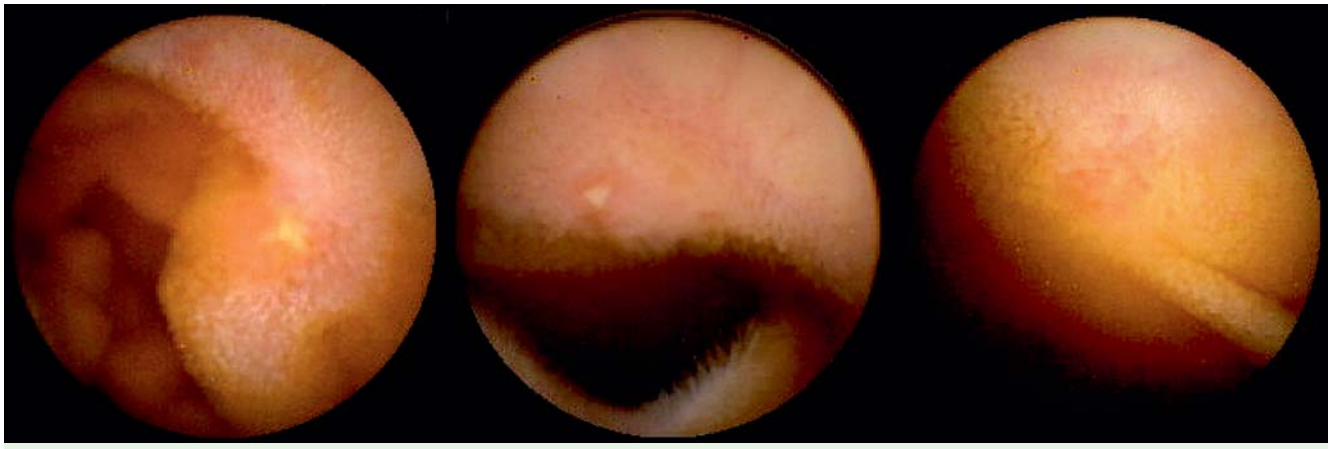

Fig. 1 Subtle lesions as seen at small-bowel capsule endoscopy (SBCE).

While most studies use similar definitions for a diagnosis of Crohn's disease based on SBCE (**Table 2**), this definition is arbitrary and has not been prospectively validated. This may increase the number of false-positive findings. No studies, to date, have defined precisely findings on SBCE that constitute a diagnosis of Crohn's disease. Lesions detected by SBCE are nonspecific and cannot be distinguished from lesions seen in patients treated by nonsteroidal anti-inflammatory drugs (NSAIDs). Discrimination of ulcerative lesions in the small bowel between those related to Crohn's disease, NSAIDs, or other aetiologies seems impossible on the basis of endoscopic images (**Fig. 1**). Some small-bowel lesions may be found in up to 75% of NSAID users, even after 2 weeks' ingestion of such drugs [29,30]. Selective cyclooxygenase-2 (COX2) inhibitors are associated with small-bowel lesions less frequently than conventional NSAIDs [31]. Taking a thorough clinical history, including recent NSAID ingestion, is therefore essential to improve the predictive value of findings at SBCE (see also section 7.4.2).

Statement 2C

- There are no validated diagnostic criteria for SBCE for the diagnosis of Crohn's disease

It is important to understand that many lesions described in studies of suspected Crohn's disease are not specific and this could explain the variability of the 'diagnostic yield' of SBCE. The 'diagnostic yield' is the number of examinations with abnormal findings divided by the total number of examinations, and should not be confused with either 'sensitivity' (the number of true-positive examinations divided by the total of true-positive and false-negative examinations), or 'specificity' (the number of true-negative examinations divided by the total of true-negatives and false-positives). A test with a high diagnostic yield does not necessarily mean the test has high sensitivity or specificity. SBCE may reveal small alterations such as lymphangiectasia, villous denudation, or nodular lymphoid hyperplasia. These nonspecific lesions have all been considered to be early manifestations of Crohn's disease in some series, but not in others (**Table 2**). There are no prospectively validated diagnostic criteria. The presence of more than three ulcerations, in the absence of NSAIDs ingestion, constitutes the most commonly used diagnostic criterion for Crohn's disease, proposed by Mow et al. [19].

Existing endoscopic scores and indices of severity for Crohn's disease have only been validated for ileocolonoscopy and include both the Crohn's Disease Endoscopic Index of Severity (CDEIS) [32] and the Simple Endoscopic Score for Crohn's Disease (SES-Crohn's disease) [33]. The Rutgeerts' score is applied to the postoperative neoterminal ileum and can help predict the risk of clinical recurrence [34]. Recently developed capsule endoscopy as-

sessment scores are based on the degree of villous oedema, ulceration and stenosis [35], or degree of inflammation, extent of disease and strictures [36], but need to be prospectively validated. Scores for diagnosis and for assessing the activity or severity of Crohn's disease by SBCE or DAE should correlate with clinical disease activity and influence therapeutic measures and outcome.

2.2.2 How does SBCE compare with other imaging modalities in patients with suspected Crohn's disease?

2.2.2.1 SBCE compared with SBFT/enteroclysis

Statement 2D

- SBCE may be better than small-bowel follow-through or enteroclysis at identifying small-bowel mucosal lesions consistent with Crohn's disease [**EL3a, RG C**]

At least seven studies, which included patients with suspected Crohn's disease and largely excluded those with a suspected or known small-bowel stricture, have compared SBCE with SBFT [20,21,23,24,37–39]. Most of the studies have shown that the diagnostic yield of SBCE is superior to that of SBFT, but these differences reached statistical significance in only one study [39]. Two studies used a consensus gold standard for final diagnosis, and both reported a trend towards improved sensitivity with SBCE [21,23]. However, the results for patients with suspected Crohn's disease were not separated from those with known Crohn's disease. One meta-analysis reported a pooled OR for SBCE of 13.0 (95%CI 3.2–16.3; $P<0.0001$) compared with SBFT in detecting small-bowel abnormalities in patients with known or suspected Crohn's disease [40]. However, as mentioned previously, one must proceed very cautiously when examining diagnostic yield without taking into account specificity.

Other studies have compared SBCE with enteroclysis, but small sample sizes have limited the ability to show a significant advantage [24,41,42]. In one meta-analysis, the pooled OR for detecting abnormalities in patients with known or suspected Crohn's disease was 5.4 (95%CI 3.0–9.9) for SBCE compared with enteroclysis [40], but this again needs to be interpreted cautiously without information about the specificity of the procedure.

Another meta-analysis evaluated 97 patients with suspected Crohn's disease, but could not detect a significant difference in diagnostic yield between SBCE and SBFT/enteroclysis [43]. SBCE was found to have an increased diagnostic yield of 30% using a fixed-effect model, which decreased to a nonsignificant increased yield of 24% using a random-effect model ($P=0.09$).

2.2.2.2 SBCE compared with magnetic resonance (MR) enterography

Statement 2E

- SBCE may be superior to MR enterography for detection of mucosal lesions consistent with Crohn's disease [**EL3a, RG C**]

Another study of just 25 patients with suspected Crohn's disease used a composite gold standard for diagnosis, and compared SBCE with MR enteroclysis [44]. SBCE had a sensitivity of 92% and specificity of 100%, compared with a sensitivity of 77% and specificity of 80% for magnetic resonance imaging (MRI). In two patients, SBCE was the only confirmatory test, after a nondiagnostic MRI and enteroclysis. A study which included only two patients with suspected Crohn's disease compared SBCE with MR enterography and found no difference [25].

2.2.2.3 SBCE compared with computed tomographic enterography (CTE)/CT enteroclysis

Statement 2F

- SBCE may be superior to CTE or CT enteroclysis for detection of mucosal lesions consistent with Crohn's disease [**EL3a, RG C**]

One group has compared SBCE with CT enteroclysis in the evaluation of suspected Crohn's disease [45]. Among 22 patients with suspected small-bowel disease, eight had suspected Crohn's disease and no difference was found between the modalities ($P=0.12$), but the study was clearly underpowered and the subset of patients with suspected Crohn's disease was not reported separately. Three studies have compared SBCE with CTE [20,21,39]. Two studies found no difference in diagnostic yield or sensitivity, although one reported a higher specificity for CTE [21]. In the third study of 35 individuals with suspected Crohn's disease, SBCE had an incremental diagnostic yield of 57% compared with CTE, which was statistically significant [39]. A meta-analysis of 43 patients with suspected Crohn's disease found an incremental diagnostic yield of 40% with SBCE compared with CT enteroclysis and CTE, but this difference did not reach statistical significance ($P=0.07$) [43].

2.3 Device-assisted endoscopy (DAE) in patients with suspected Crohn's disease

2.3.1 Indications for DAE in patients with suspected Crohn's disease

Statement 2G

- DAE can be used to diagnose Crohn's disease, because histological corroboration is available [**EL5, RG D**]
- There are not enough data to recommend DAE, unless conventional studies including ileocolonoscopy and radiographic imaging have been inconclusive and histological diagnosis would alter disease management

Two small studies have reported a 30%–48% diagnostic yield of double-balloon endoscopy (DBE) when evaluating patients with suspected Crohn's disease [46,47]. In a study of single-balloon endoscopy (SBE) in 41 individuals, of whom 17 had suspected Crohn's disease [11], 16/41 had Crohn's disease as their final diagnosis, although the results were not reported by indication.

The advantages of balloon-assisted endoscopy (BAE) compared with SBCE include the evaluation of atypical lesions, the ability to obtain biopsies for histopathology, and the potential for therapeutic intervention (e.g. dilation) [48,49].

Overall, BAE is safe in the assessment of suspected Crohn's disease, with few reports of complications [11,47,49,50] (see Section 7).

2.3.2 How does BAE compare with other imaging modalities in patients with suspected Crohn's disease?

2.3.2.1 BAE compared with SBCE

Two abstracts report a comparison between DBE and SBCE in suspected Crohn's disease. In a preliminary study, 44 patients with suspected small-bowel Crohn's disease who had a prior SBCE underwent DBE [51]. A new diagnosis of Crohn's disease was made in 14% after DBE, and Crohn's disease was excluded in 9%, but the analysis was not performed separately for established and suspected Crohn's disease. DBE led to treatment changes in 73% of subjects. These are all clinically relevant end points. Another preliminary study included 12 patients with suspected Crohn's disease among 129 undergoing DBE; 88 patients had undergone a prior SBCE [52]. Of SBCE findings, 65% were confirmed by DBE and 10% of DBE findings were missed by SBCE.

2.3.2.2 BAE compared with SBFT

One study only published as an abstract compared DBE with SBFT in 18 patients with suspected small-bowel disease, but not specifically with suspected Crohn's disease [53]. Agreement between DBE and SBFT was reported in 60%, 60% and 50% of patients with gastrointestinal bleeding, abdominal pain, and diarrhoea, respectively.

2.3.2.3 BAE compared with MR enterography

A study on 10 patients with suspected Crohn's disease proximal to the terminal ileum compared DBE with MR enteroclysis [49]. All DBE examinations used the oral route, with complete small-bowel examination achieved in only one patient. MR enteroclysis and DBE agreed in 21 bowel segments (75%) and were discordant in 7 (25%). Five patients had abnormal findings detected by both modalities. In all DBE cases, Crohn's disease was verified histologically. Although the value of MR enteroclysis appeared limited in patients with subtle or superficial mucosal lesions, incomplete examination by DBE was a major limiting factor.

2.3.3 Specific considerations or investigations recommended prior to SBE/DBE in patients with suspected Crohn's disease

Statement 2H

- The decision on whether SBCE or DAE should be performed first depends on the nature and location of the small-bowel lesion, as well as local availability and expertise
- For suspected Crohn's disease where other investigations are inconclusive, SBCE is generally appropriate

DAE should not be the first-line procedure in the evaluation of suspected small-bowel Crohn's disease. SBCE can be complementary to BAE, since findings may help direct the most effective route of intubation (oral versus anal), in order to obtain a histopathological diagnosis, or therapeutic intervention [47,48,51]. DAE may be preferable to SBCE if there is a clinical suspicion of obstruction, because it may allow therapeutic intervention and be safer, simply by avoiding capsule retention [46]. Disadvantages associated with DAE are the invasiveness of the examination, the need for sedation, limited availability of the procedure (specialized centres), difficulty in examining the entire small bowel, and the time and expense required for the procedure [11,47,50].

SECTION 3 Established Crohn's disease

3.1 Introduction

Endoscopy plays an important role in the evaluation and monitoring of established Crohn's disease [4]. Ileocolonoscopy and upper gastrointestinal endoscopy have well-established roles for assessment of disease activity and therapeutic intervention; the small bowel beyond the duodenum and proximal to the (neo) terminal ileum is inaccessible to conventional endoscopy. Prior to the advent of current techniques of DAE, push enteroscopy was a practical alternative to IOE, which was too invasive for all but the most unusual circumstances. Push enteroscopy, however, could effectively only examine 50 to 150 cm beyond the ligament of Treitz [54–56]. The roles for SBCE and BAE in the assessment and treatment of established Crohn's disease [11,57–63] still need to be defined.

3.2 SBCE in patients with established Crohn's disease

3.2.1 Indications for SBCE in patients with established Crohn's disease

Statement 3A

- The role of SBCE in patients with established Crohn's disease should focus on patients with unexplained symptoms when other investigations are inconclusive, if this will alter management [**EL5, RG D**]
- Radiographic imaging takes precedence over SBCE because it can potentially identify obstructive strictures, extraluminal disease, the transmural nature, or anatomical distribution of disease

Most patients with Crohn's disease have lesions located in the (neo)terminal ileum, accessible by ileocolonoscopy. These patients can usually be managed without the need for additional small-bowel endoscopy. However those patients with unexplained symptoms and inconclusive radiographic imaging and/or ileocolonoscopy, may well have subtle small-bowel lesions. SBCE allows these superficial lesions to be detected, which may affect the therapeutic management. It should be remembered that in contrast to SBCE, imaging by CTE or MR enterography can assess transmural damage and extraintestinal features or complications and may also give an indication of disease activity. The potential for capsule retention in established Crohn's disease should also be considered (see Section 7) [64–66].

3.2.2 How does SBCE compare with other imaging modalities in patients with established Crohn's disease?

Statement 3B

- For patients with established Crohn's disease, SBCE is better at identifying small-bowel mucosal lesions than barium and may be better than CT or MR enterography or enteroclysis [**EL3a, RG C**], but the clinical significance of this potential difference remains to be defined

The role of SBCE in suspected Crohn's disease is covered in Section 2 [20–22,26,42,43,67,68]. In patients with established Crohn's disease, one meta-analysis has reported a 78% diagnostic yield for SBCE compared with 32% for SBFT ($P < 0.001$). Further-

more, SBCE had a 68% diagnostic yield for active Crohn's disease, compared with 38% for CT enterography/enteroclysis ($P < 0.001$) [43].

One study compared SBCE with MR enterography in 27 patients with established Crohn's disease. Diagnostic yields for SBCE and MR enterography were 93% and 79%, respectively [44], but it is not clear how this correlated with either symptoms or the outcome of therapeutic intervention. This is important, because knowing that a segment of small bowel looks abnormal in 93% of patients with established Crohn's disease does not provide much useful information unless it affects a patient's management.

Another study evaluated 19 patients with proven Crohn's disease using MR enteroclysis and SBCE; overall MR enteroclysis and SBCE showed good correlation in the detection and locating of inflammatory bowel disease. MR enteroclysis underestimated degree of pathology in 14% of segments and revealed more severe pathology in 12% segments; SBCE identified subtle (n = 7) or severe (n = 2) mucosal pathology while MR enteroclysis was normal. SBCE entirely missed severe inflammatory mural changes identified by MR enteroclysis in 1/52 (2%) segments. Both modalities can be complementary [69].

A notable limitation of SBCE is that it evaluates only nonstricturing Crohn's disease and cannot usefully assess transmural or extraintestinal disease.

Statement 3C

- For assessment of postoperative recurrence of Crohn's disease, SBCE should only be considered if ileocolonoscopy is contraindicated or unsuccessful
- SBCE may identify lesions in the small bowel that have not been detected by ileocolonoscopy after ileocolic resection
- SBCE has a potential role in the assessment of mucosal healing after drug therapy [**EL4, RG C**]

Endoscopic recurrence in the neoterminal ileum has been reported in 73%–93% of patients at 1 year after ileocolonic resection [34, 70]. The severity of endoscopic lesions is associated with the risk of clinical relapse.

Two studies have investigated SBCE for detecting recurrence in patients with Crohn's disease after surgery. In one study, recurrence defined by a Rutgeerts' score ≥i1 (see Section 2.2.1) occured in 21 patients (68%) and was detected by ileocolonoscopy in 19 patients. Sensitivity of ileocolonocopy was 90% and specificity 100%, and the sensitivity of SBCE was 62%–76% and specificity 100%. The severity of lesions as assessed by both methods correlated significantly ($P < 0.05$) [71].

In a second prospective study of 24 patients with Crohn's disease, recurrence (Rutgeerts' score ≥i2) was visualized by ileocolonoscopy in 25% and SBCE in 62%. SBCE detected proximal involvement in 13 patients [72].

SBCE has a potential role in the assessment of mucosal healing after drug therapy [73].

3.3 DAE in patients with established Crohn's disease

3.3.1 Indications for DAE in patients with established Crohn's disease

Statement 3D

- DAE is indicated when endoscopic visualization and biopsies are necessary from areas of the small bowel inaccessible to conventional endoscopy [**EL5, RG C**]

Statement 3E

- SBCE provides information on the optimal route of approach (i.e., oral or rectal) by subsequent BAE [**EL3b, RG C**]

Statement 3F

- In patients with established Crohn's disease, adhesions may limit examination by DAE, and, in these circumstances, DBE may be preferred to SBE [**EL5, RG D**]
- In a patient with stricturing active Crohn's disease, there appears to be a higher risk of complications [**EL4, RG C**]

Statement 3G

- DAE has the capacity for endoscopic therapy, including dilation of Crohn's disease small-bowel strictures, retrieving foreign bodies, and treatment of bleeding lesions [**EL4, RG C**]

DAE is indicated in established Crohn's disease when direct visualization of the small intestine beyond the reach of ileocolonoscopy is necessary, in order to exclude an alternative diagnosis (including tuberculosis, lymphoma, or carcinoma) [11, 59, 63, 74], or undertake a therapeutic procedure including dilation of small-bowel strictures, or removal of foreign bodies such as a capsule or bezoar [60, 75 – 80]. In the rare instances where Crohn's disease is complicated by major haemorrhage, DAE may identify and treat the bleeding source beyond the reach of standard endoscopes.

The best route of approach during DAE may be determined by prior SBCE [81]. Total enteroscopy rates using both oral and anal approaches range from 20% to 80% [82, 83]. In patients with established Crohn's disease, DAE (similarly to ileocolonoscopy) may be particularly challenging because of adhesions angulating the small bowel. Complications are discussed in detail in Section 7.2; the risk of complication has been reported to be higher in patients with active Crohn's disease. In a recent report on the USA experience, with 2254 DBE examinations to date, the complication rate was 10 times higher than that of colonoscopy [84]. Perforations were more common in patients with altered surgical anatomy and two occurred during retrograde DBE in patients with Crohn's disease who had ulceration at the ileoanal or ileocolonic anastomosis [84].

3.3.2 How does DAE compare with other imaging modalities in patients with established Crohn's disease?

Prospective, well-designed studies comparing DAE, SBCE, and other imaging modalities in established Crohn's disease are lacking. The evidence available to date comes from unblinded case series performed by expert endoscopists in specialist centres. Patients included in those series were heterogeneous both in terms of indications for the procedure and the therapy performed [11, 49, 79, 80, 85]. A meta-analysis of 11 of these studies reported that BAE (almost all were DBE) had a similar sensitivity to SBCE in the diagnosis of small-intestinal inflammatory lesions [86]. Stud-

ies assessing the performance of SBE are only just emerging [11,59,60,62,63,74] so no formal comparison with the other techniques is possible.

SECTION 4
Inflammatory bowel disease-unclassified (IBDU)

4.1 Introduction

Population-based studies have demonstrated that in 4%–10% of adult patients with all IBD affecting the colon, it is impossible to distinguish between Crohn's disease and ulcerative colitis using current diagnostic techniques [87,88]. Establishing a definitive diagnosis has implications in terms of medical and surgical therapy, as well as clinical outcome.

The term 'indeterminate colitis', coined by Ashley Price in 1978 [89] to describe colectomy specimens that could not be confidently classified as Crohn's disease or ulcerative colitis, became widely adopted to describe IBD any patient in whom it was impossible to reach a definitive diagnosis, whether or not the patient had undergone surgery [90]. This changed in 2006 when an international working group [91] confirmed that the term 'indeterminate colitis' would be reserved for those cases where colectomy had been performed, but a definite diagnosis could not be reached histologically. Colonic inflammatory bowel disease, without small-bowel involvement, for whom a definite diagnosis of either Crohn's disease or ulcerative colitis could not be made after ileocolonoscopy, biopsies, and small-bowel radiology would be defined as colonic IBD, type unclassified (IBDU).

4.2 SBCE in patients with IBDU

4.2.1 Indications for SBCE in patients with IBDU

Statement 4A

- In patients with IBDU, SBCE can be helpful in identifying those with mucosal lesions compatible with Crohn's disease. A negative SBCE does not exclude a future diagnosis of Crohn's disease [**EL3b, RG C**]

There is limited evidence for the role of SBCE in patients with IBDU. The three full papers published [19,92,93] and eight abstracts or letters [94–101] reporting the impact of capsule endoscopy (SBCE) on patients with IBDU are all retrospective and involve small numbers of patients (each study has ≤ 31 patients). SBCE demonstrates small-bowel lesions compatible with Crohn's disease in 17%–70% of patients with IBDU or indeterminate colitis, but their clinical significance is unclear. Most studies used diagnostic criteria for small-bowel Crohn's disease proposed by Mow and colleagues (more than 3 ulcers seen on SBCE [19]). These criteria, however, are both arbitrary and unvalidated (Section 2.2.1). Conversely, a negative SBCE does not exclude a future diagnosis of Crohn's disease [102–104]. In one study [92], 5 of 25 patients with negative SBCE were eventually diagnosed with Crohn's disease at follow-up.

4.2.2 How does SBCE compare with other imaging modalities in patients with suspected Crohn's disease?

4.2.2.1 SBCE compared with SBFT/enteroclysis

Statement 4B

- In patients with IBDU, SBCE is better than SBFT or enteroclysis at identifying mucosal lesions consistent with Crohn's disease [**EL3b, RG C**]; in this subset of patients there are no data comparing SBCE and either CTE or MR enteroclysis

Controlled trials in this patient group are lacking. Two out of three published studies included patients who have had a negative SBFT [19,92].

4.2.2.2 SBCE compared with CTE

In patients with suspected or established Crohn's disease, SBCE revealed more inflammatory lesions in the proximal and mid-small bowel when compared with CTE, but their clinical significance is not known [21,43]. Currently there are no published data comparing these two modalities in patients with IBDU.

4.2.2.3 SBCE compared with MR enteroclysis

Similarly there is no evidence to suggest which one of these modalities is superior in patients with IBDU. SBCE demonstrated more inflammatory lesions in the small bowel compared with MR enteroclysis, but their clinical significance is unclear [25].

4.3 DAE in patients with IBDU

4.3.1 Indications for DAE in patients with IBD-unclassified (IBDU)

Statement 4C

- DAE includes promising diagnostic tools, but at the present time there are no data supporting the use of these techniques in patients with IBDU [**EG5, RG D**]

Evidence for the use of these techniques in patients with IBDU is lacking. DAE allows direct mucosal inspection of the small bowel and allows mucosal biopsy, which may facilitate diagnosis, but this needs to be balanced against potential risks of the procedure.

4.3.2 How does DAE compare with other imaging modalities in patients with IBDU?

There are currently no studies comparing DAE with radiographic imaging modalities (SBFT, CT or MR enterography) in patients with IBDU.

SECTION 5
Ulcerative colitis (including ileal pouch–anal anastomosis [IPAA])

▼

5.1 Introduction

Although ulcerative colitis is ultimately curable by colectomy, many patients with the disease are managed medically for years and undergo investigations to define the extent of the disease, assess the severity of relapse, or identify complications. Differentiation of Crohn's disease from ulcerative colitis lies in being able to show upper gastrointestinal tract or small-bowel involvement in Crohn's disease. This is occasionally necessary in patients with established ulcerative colitis, when the diagnosis is questioned, especially before surgery: indications and evidence for small-bowel investigations in patients with ulcerative colitis and ileal pouch–anal anastomosis (IPAA) are reviewed.

5.2 SBCE in patients with ulcerative colitis

5.2.1 Indications for SBCE in patients with ulcerative colitis

Statement 5A

- The diagnosis of ulcerative colitis does not require SBCE [**EL5, RG D**]

The diagnosis of ulcerative colitis is made using a combination of medical history, clinical evaluation, and typical endoscopic appearances, confirmed by histopathology. Small-bowel radiology is not routinely recommended [3], although some experts advise small-bowel imaging to exclude Crohn's disease prior to elective colectomy for medically refractory ulcerative colitis.

Statement 5B

- SBCE or DAE in a patient with a diagnosis of ulcerative colitis may be indicated if anaemia or abdominal symptoms are unexplained despite conventional imaging [**EL5, RG D**]

Around 10% of patients with an initial diagnosis of ulcerative colitis will be reclassified as having either Crohn's disease or IBDU at follow-up. In one retrospective study [93], 19/120 (16%) patients had SBCE findings (defined as the presence of three or more ulcerations [19]) consistent with Crohn's disease. After excluding 8 patients with prior use of NSAIDs, the proportion of patients with small-bowel lesions was significantly lower in those without a colectomy (12%) compared with those with a history of colectomy (33%) ($P = 0.04$) [93].

Statement 5C

- SBCE can detect mucosal lesions in ulcerative colitis patients with atypical or refractory symptoms, especially after IPAA, but the clinical significance is unclear. The presence of such lesions does not predict the outcome after IPAA for ulcerative colitis [**EL3b, RG C**]

Of 21 patients who had undergone colectomy for a presumed diagnosis of ulcerative colitis, 13 (62%) had documented pouchitis on follow-up pouchoscopy, and six of those (46%) had SBCE findings consistent with Crohn's disease, defined as the presence of 3 or more ulcers. In a study [105] evaluating the utility of preoperative SBCE in predicting long-term outcome of IPAA, 8 out of 20 patients with ulcerative colitis and IBDU had abnormal findings on SBCE. Of these, only 1 (13%) presented with pouchitis at follow-up compared with 4/12 (33%) patients who had a normal preoperative SBCE. These data suggest that the presence of small-bowel lesions prior to colectomy does not predict the post-colectomy outcome.

In 17 ulcerative colitis patients with iron-deficiency anaemia after IPAA, a combination of upper gastrointestinal endoscopy, pouchoscopy with mucosal biopsy and histopathology, SBCE, and coeliac disease serology, revealed a cause of anaemia in 5 (arteriovenous malformation [AVM] in 1 patient, findings compatible with Crohn's disease in 3, and coeliac disease in 1) [106]. Anaemia after IPAA is therefore a reasonable indication for SBCE.

5.2.2 How does SBCE compare with other imaging modalities in patients with ulcerative colitis?

5.2.2.1 SBCE compared with SBFT/enteroclysis

There is some evidence to suggest that the diagnostic yield of SBCE is greater than that of SBFT/enteroclysis when an established diagnosis of ulcerative colitis is questioned. In one study [19], SBCE revealed lesions compatible with Crohn's disease in 11/18 ulcerative colitis patients (including 6 with IPAA), 8 of which were confirmed by histopathology. Of these, 5 had a normal SBFT previously. In 7 patients with an abnormal SBFT, Crohn's disease was confirmed in 4 patients. These results suggest that information provided by SBCE may affect the evaluation and management of patients thought or suspected to have ulcerative colitis, particularly those with negative conventional small-bowel imaging.

In a retrospective study of 120 patients with a diagnosis of highly suspected ulcerative colitis who underwent an SBCE [93], 19/120 patients had positive findings at SBCE and 18 of these (95%) had a previously normal SBFT study, suggesting a higher diagnostic yield of SBCE compared with SBFT. A proportion of ulcerative colitis patients with atypical symptoms (about 10%), medically refractory disease (about 9%), or prior colectomy and new symptoms (about 33%) could be reclassified as having Crohn's disease if the diagnostic criterion of 3 or more ulcers at SBCE was applied [93]. Data on outcome after long-term follow up are lacking.

A case–control study [107] evaluated the use of SBCE for small-bowel assessment in 16 patients with chronic refractory pouchitis and 8 controls. SBCE demonstrated inflammatory changes in all 16 patients with pouchitis compared with SBFT, which was abnormal in only 2/16 patients. SBCE has a superior diagnostic yield to SBFT, although the clinical significance of the small-bowel lesions detected is unclear.

5.2.2.2 SBCE compared with CTE

5.2.2.3 SBCE compared with MR enterography/enteroclysis

There are no objective data comparing SBCE with CTE or MR enterography/enteroclysis in patients with ulcerative colitis. The majority of the Consensus participants considered that data on imaging techniques from patients with suspected or established Crohn's disease could be extrapolated to patients with ulcerative colitis. The clinical significance of the small-bowel lesions detected is not certain.

5.3 DAE in patients with ulcerative colitis

5.3.1 Indications for DAE in patients with ulcerative colitis

There are currently no data regarding the use of DAE in patients with ulcerative colitis, so no recommendations regarding indications for its use can be made.

5.3.2 How does DAE compare with other imaging modalities in patients with ulcerative colitis?

As with IBDU (Section 4.3.2) the lack of data make it impossible to make recommendations; however, the direct mucosal visualization and biopsy capability of DAE could be seen as an advantage, most probably when elucidating abnormalities identified by other imaging techniques.

SECTION 6
Paediatric practice

▼

6.1 Introduction

IBD starts at age <18 years in approximately 10% – 15% of cases. Among paediatric IBD cases seen in most areas of North America and Europe, Crohn's disease is far more common than ulcerative colitis. The endoscopic assessment of the small bowel beyond the ligament of Treitz and proximal to a short segment of the distal ileum has been a major challenge for paediatric and adult gastroenterologists alike. Advances in SBCE and DAE, in addition to improved imaging by CT and MR enterography, have improved the ability to diagnose small-bowel pathology, but paediatric data remain limited.

6.2 SBCE in paediatric patients

6.2.1 Indications for SBCE in paediatric patients

Statement 6A

- Gastroduodenoscopy with biopsies is necessary in all paediatric patients suspected of having IBD [**EL4, RG C**]

Statement 6B

- **SBCE** can be helpful in identifying mucosal lesions compatible with Crohn's disease in paediatric patients [**EL3b, RG C**]

US Food and Drug Administration (FDA) approval was granted in 2003 for SBCE use in children aged 10 years and over, on the basis of the first controlled paediatric study [108] using the PillCam SB capsule (Given Imaging Ltd, Yoqneam, Israel). The European Society of Gastrointestinal Endoscopy [109] and the American Society for Gastrointestinal Endoscopy [110] make no definitive statement on the indications for SBCE in children, so current practice refers largely to adult data and individual experience. There are still few studies on the role of SBCE for the detection, classification, or management of paediatric IBD.

Ten peer-reviewed paediatric studies published in English (case series and comparative studies) have included 311 children with a mean age of 12.8 years (minimum 16 months). SBCE was completed in 92% of procedures and significant clinical findings (defined as a definite diagnosis, or change in diagnosis or clinical management) were demonstrated by SBCE in 67%. The average capsule excretion time (3 studies) was 42 hours, with a range of 6 hours to 30 days.

In the paediatric age group, the most commonly reported indication for SBCE was the investigation of suspected IBD (n = 145). Other indications included obscure or occult gastrointestinal bleeding with or without iron-deficiency anaemia (n = 66), hereditary polyposis syndromes (n = 58), chronic abdominal pain (n = 22), protein-losing enteropathy (n = 7), or growth failure (n = 5). Other, less common indications included investigation of idiopathic malabsorption or other undiagnosed enteropathies [108, 111 – 119]. SBCE can be considered in children with an established diagnosis of Crohn's disease who have unexplained symptoms despite negative conventional endoscopy. In such cases, a negative SBCE in combination with a normal ileocolonoscopy would favour a diagnosis other than IBD to explain the symptoms. Other potential indications for SBCE include assessment of postoperative recurrence of Crohn's disease and small-bowel mucosal healing following medical therapy, but there is no evidence from paediatric practice.

Statement 6C

- SBCE should be performed in children or adolescents with a high suspicion of Crohn's disease, when conventional endoscopy and small-bowel imaging are normal [**EL3b, RG C**]

Suspected small-bowel Crohn's disease is the main indication for SBCE in the paediatric age group. In the first controlled prospective study [108], SBCE had a high diagnostic yield, with a diagnosis of Crohn's disease or eosinophilic gastroenteropathy made by SBCE in 60% of the 20 cases studied, compared with 0% using conventional imaging techniques (SBFT and ileocolonoscopy). It is again worth noting that the diagnosis of Crohn's disease was made using the criterion proposed by Mow et al. (3 or more ulcers in the small bowel [19]), which has not been validated, and has uncertain clinical significance. A further study in adolescents yielded similar results (58% vs 0%) for establishing a diagnosis of Crohn's disease missed by conventional imaging [117].

Statement 6D

- SBCE can be helpful in identifying mucosal lesions compatible with Crohn's disease in paediatric patients with ulcerative colitis or IBDU, although the clinical significance of these lesions remains unclear [**EL4, RG C**]

In up to 10% of adults with IBD involving only the colon, it is not possible to distinguish Crohn's disease from ulcerative colitis (Section 4), but this increases to up to 30% in children [120]. In the most recent study [112], 5 out of 7 children had their diagnosis changed from ulcerative colitis or IBDU to Crohn's disease on the basis of SBCE findings.

6.2.2 How does SBCE compare with other imaging modalities in paediatric patients?

6.2.2.1 SBCE compared with SBFT/enteroclysis

SBFT and small-bowel enteroclysis have been the most common diagnostic modalities used to investigate the small bowel in children because of their accessibility, diagnostic value and cost-effectiveness [121 – 124]. However, a retrospective analysis of 164 children revealed a diagnostic sensitivity of only 45% (17/37) for small-bowel radiography compared with ileocolonoscopy [125]. A major disadvantage of small-bowel radiography, especially in children, is the radiation exposure, particularly if fluoroscopy

time is not kept to a minimum [126]. The mean relative effective doses of radiation in children are: plain abdominal X-ray (AXR), 0.5 milliSievert (mSv); SBFT, 2 mSv; and multidetector CT (MDCT), 3.5 mSV.

There are few paediatric publications directly comparing SBCE and SBFT/small-bowel enteroclysis. Most SBCE studies included patients who had negative colonoscopies and SBFT [108, 117]. Thomson et al. [114] showed that SBCE is more sensitive for small-bowel pathology than SBFT (out of 19 children who had abnormalities on SBCE, only 5 had abnormal results at SBFT) and than upper intestinal endoscopy with ileocolonoscopy (only 10 had endoscopic findings compared with 23 at SBCE). Data from paediatric case series suggests that SBCE is superior to SBFT/SBE for detecting small-bowel pathology. Clinically relevant pathology was detected by SBCE, but not by SBFT/SBE in 10 of 20 children in another study [115].

6.2.2.2 SBCE compared with CTE

CTE allows intra- and extraluminal assessment of the small bowel and colon but is associated with significant radiation exposure. There are no paediatric studies comparing SBCE and CTE.

CTE has been compared with small-bowel contrast studies. In a study of 18 children, a multidetector CTE was more acceptable to patients than SBFT and yielded additional clinically relevant findings [127]. White blood cell (WBC) scintigraphy and CTE were compared with colonoscopy in a study where 99mTc-WBC scintigraphy was more sensitive than CTE for detecting inflammation of the bowel wall in children [128].

6.2.2.3 SBCE compared with MRE

Magnetic resonance imaging (MRI) also allows intra- and extraluminal assessment of the small bowel and colon, but without radiation exposure. There are no studies comparing the diagnostic value of SBCE with MRI in children with IBD.

Initial studies suggested MRI without contrast was insufficiently reliable to investigate the small bowel in children with suspected IBD [129]. However, the use of gadolinium and enteral contrast solutions (e.g., polyethylene glycol [PEG], mannitol), resulted in a high correlation with ileoscopy, histology and the Paediatric Crohn's Disease Activity Index (PCDAI) [130, 131]. A sensitivity of 96% and specificity of 92% was obtained with gadolinium-enhanced MRI for confirming an established histopathological diagnosis of either ulcerative colitis or Crohn's disease in a study of 58 patients [132]. Studies in adults suggest the superiority of MR enteroclysis/enterography over conventional SB enteroclysis for detection of mesenteric findings [133].

6.3 DAE in paediatric patients

6.3.1 Indications for DAE in paediatric patients

Statement 6E

- Advanced enteroscopic techniques (DAE) are promising diagnostic tools, but at the present time there are no data supporting the use of these techniques in paediatric patients with known or suspected IBD [**EL5, RG D**]

There are few data on the use of advanced enteroscopy (push enteroscopy, BAE, or DAE) in children.

Although push enteroscopy provides access to the small intestine distal to the duodenum, its range is limited. Push enteroscopy can, at best, reach 120 – 180 cm of small bowel beyond the ligament of Treitz, although biopsy and therapeutic interventions can be performed [134]. The yield, safety, and efficacy of push enteroscopy in 44 children has been reviewed [135]. Indications were suspected small-bowel disease after radiological imaging and/or gastrointestinal bleeding. Among 37 children with intestinal pathology (not all IBD), lesions in only 9 were within reach of a conventional endoscope. Enteroscopy led to a modification of management in 34/44 patients. The procedure was not significantly more time-consuming compared with upper endoscopy, and no complications were reported.

There are no published studies on the use of DAE in children with IBD. DBE was performed in 13 children for various indications including occult gastrointestinal bleeding, iron-deficiency anaemia and diarrhoea. The diagnostic yield was 86%, with no major complications [136].

6.3.2 How does DAE compare with other imaging modalities in paediatric patients?

There are no studies comparing DAE with SBCE, SBFT, CT or MR enterography/enteroclysis in paediatric patients.

6.4 SBCE: safety and prior investigations

Statement 6F

- Although extensive data about the safety of SBCE in paediatric patients are lacking, it seems to be a safe procedure
- In paediatric patients with established Crohn's disease, it is essential to attempt to exclude small-bowel strictures by a thorough clinical history before SBCE. A patency (biodegradable, 'dummy') capsule should be used to reduce the risk of retention, or MR enterography should be performed if available
- There is no available evidence to support a particular bowel preparation for children undergoing SBCE [**EL5, RG D**]

Available data suggest that SBCE is a useful diagnostic tool in the paediatric age group. Certain considerations prior to the procedure apply to both children and adults. Because of the nature and length of the procedure, SBCE is not an emergency investigation. No tissue sampling is yet possible, and diagnoses based on macroscopic appearances alone should be made with caution [137]. NSAIDs commonly cause mucosal injury, including ulcerations that mimic those seen in Crohn's disease, but the use of such anti-inflammatory drugs is far less common in children. Histopathological confirmation of specific diagnoses suggested by SBCE should be obtained, where feasible.

Small children require specific consideration and two factors need to be considered – the ability to swallow the capsule and the ability to pass the capsule. Limiting factors should be weight- and not age-based. A capsule should pass the pylorus if a child weighs more than 17 kg. In some cases, prior training with sweets or candy may avoid the need for endoscopic insertion of the capsule. In published studies, the majority of children swallowed the wireless capsules voluntarily. Only 7% required endoscopic placement to the duodenum rather than the stomach, although this may simply reflect recruitment bias in these initial studies. Capsule retention is the most important adverse effect and can occur in either the stomach or strictured small bowel and require endoscopic or surgical removal. In 4% – 5% of paediatric cases, the capsule was retained in the stomach and required endoscopic removal [115]. In a recent paediatric series [108], cap-

sule retention occurred in 1/28 known cases of IBD. In the paediatric literature there are reports of only three cases of capsule retention in strictured small bowel that did not respond to corticosteroids and required surgical intervention [108, 111, 115]. Use of a patency capsule can decrease the risk of capsule retention and has been used in paediatric patients with good effect [64].

Visualization of the small bowel by SBCE may be impaired by intestinal contents. Results from studies in adults that assessed the value of bowel preparation are conflicting [138–140]. One randomized, single-blind study in 90 adult patients showed best mucosal visibility in patients who, prior to SBCE, had ingested 2 L of PEG (72% visualization) compared with 1 L of PEG (52% visualization), but either was superior to a clear liquid diet and overnight fast (25% visualization) [138]. Although mucosal visualization was improved, it did not affect the diagnostic yield. There are currently no data on the choice of bowel preparation in children. Most paediatric studies use only an 8–12-hour overnight fast. Bowel preparation can be traumatic for children and may require nasogastric tube insertion.

SECTION 7
Complications and unresolved questions

7.1 Introduction

Unlike SBCE, which has been used for a decade, DAE is a relatively new modality and the true rate of adverse events is difficult to establish. This section addresses the complications of SBCE and DAE reported in literature as well as their management. Key unresolved questions and areas for further research are discussed.

7.2 Complications

7.2.1 SBCE

Statement 7A

- In patients with suspected Crohn's disease the risk of small-bowel capsule retention is low and comparable to that when the indication for SBCE is bleeding [**EL3a, RG C**]

Statement 7B

- In patients with an established diagnosis of Crohn's disease the risk of small-bowel capsule retention is increased, particularly in those with known intestinal stenosis [**EL3b, RG C**]

Statement 7C

- In patients with established Crohn's disease of the small bowel, it is essential to attempt to exclude small-bowel strictures by a thorough clinical history and radiographic imaging before SBCE. However, normal radiographic studies cannot entirely exclude the potential for small-bowel capsule retention [**EL4, RG C**].
- A patency (biodegradable, 'dummy') capsule to reduce the risk of retention should be considered, or DAE, if strictures are identified

Capsule retention in the small bowel is the most frequent complication, observed in 1.8%–5.8% of investigations in large series where bleeding was the principal indication for the procedure [141–145] (**Table 3**; bleeding was also the predominant indication in those series shown as having 'Various' indications). The retention rate seems to be similarly low in patients with suspected Crohn's disease (without symptoms or clinical findings suggestive of intestinal obstruction), but can be up to 13% in patients with an established diagnosis [22, 44, 141]. A capsule may be retained despite a normal radiographic study [144, 146]. In large series including healthy volunteers taking NSAIDs for a short period, no cases of retained capsule were documented [29–31, 147].

Table 3 Rates of retention in small-bowel capsule endoscopy (SBCE).

	Indication	Patients, n	Retention, n (%)
Sears et al. 2004 [164]	Bleeding	52	3 (5.8)
Pennazio et al. 2004 [181]	Bleeding	100	5 (5)
Rondonotti et al. 2005 [144]	Various	733	14 (1.9)
Cheifetz et al. 2006 [142]	Various	568	19 (3.3)
Sturniolo et al. 2006 [145]	Various	304	4 (1.3)
Cheon et al. 2007 [143]	Various	1291	32 (2.5)
Sachdev et al. 2007 [73]	Various	115	3 (2.6)
Li et al. 2008 [182]	Various	1000	14 (1.4)

Statement 7D

- There is no evidence that pacemakers or implantable cardioversion devices cause complications in patients undergoing SBCE, or vice versa [**EL4, RG C**]. Individual capsule systems have to be tested for safety in this regard [**EL5, RG D**]

Clinical observation of patients with pacemakers or implantable cardioversion devices undergoing PillCam SBCE [148] could not demonstrate any relevant interaction. Neither simulation tests with Given capsule systems held close to pacemakers [149] nor in vitro experiments with Given and Olympus capsules [150] showed important effects on pacemakers.

7.2.2 Push enteroscopy

Statement 7E

- Diagnostic push enteroscopy has a low complication rate that may be increased when an overtube is used [**EL3b, RG C**]

Complications of push enteroscopy are more frequent than for standard upper endoscopy. Complications include mucosal stripping [151], perforation [152, 153], and pharyngeal tear [154]. Such adverse events may have been related to use of an overtube [155] during the procedure; these are no longer used for push enteroscopy in the majority of centres.

7.2.3 Balloon-assisted enteroscopy (BAE)

Statement 7F
- Diagnostic DBE has a low complication rate, although active Crohn's disease or previous intestinal surgery may increase the risk of perforation [**EL3b, RG C**]

Statement 7G
- DAE involves risk related to sedation, in contrast to SBCE where no sedation is required [**EL4, RG C**]

Statement 7H
- Hydrostatic balloon dilation of short fibrotic strictures in patients with small-bowel Crohn's disease has a small, but definable risk of perforation [**EL4, RG C**]

With the development of DAE, intraoperative enteroscopy is performed less frequently. Morbidity associated with intraoperative enteroscopy has been reported in 3%–42% of cases, including serosal tears (some requiring resection), avulsion of the superior mesenteric vein, anastomotic leakage, abscess, or prolonged ileus [156].

Diagnostic DBE is accompanied by complications in < 1% of cases. Hyperamylasaemia has been documented in up to 50% of patients [157], but clinically significant pancreatitis occurs in only 1%, almost exclusively after use of the oral insertion route [158, 159]. Therapeutic balloon enteroscopy with balloon dilation of strictures has a reported perforation risk of 0%–3%, which is comparable to dilation of colonic Crohn's strictures [160, 161]. Complications related to sedation during DBE led to termination of the procedure in 11 of 3894 examinations [161]. Safety data on SBE are still scarce, but may be comparable to those of DBE [11].

7.3 Management of complications

7.3.1 Capsule retention

Statement 7I
- Passage of an intact patency capsule predicts safe transit of a small-bowel capsule of identical or lesser size. A patency capsule may itself cause obstruction at tight strictures, but this is usually transient [**EL4, RG C**]
  A retained small-bowel capsule can often be retrieved by DAE [**EL4, RG C**]

Retained capsules in general do not cause obstruction and can remain intact for up to 4 years [19, 144, 146, 162–164]. However, single cases of acute obstruction have been reported [165]. In one case, a fracture of a retained capsule was observed [166] and one case of small-bowel perforation [167]. Removal of retained capsule may require surgery, although removal by DBE may be an option [77, 168, 169]. Use of a patency (biodegradable, 'dummy') capsule may help avoid capsule retention [66, 170–172], but rare adverse events including acute small-bowel obstruction have occurred with the device itself [64].

Statement 7J
- Nonvisualization of the colon at SBCE should raise the suspicion of capsule retention. Follow-up until self-report of capsule excretion or a plain abdominal radiograph after 2 weeks is advisable [**EL5, RG D**]

Only about a third of patients notice the passage of the SBCE, and both capsule retention and small-bowel pathology may be overlooked [173]. Visualization of the caecum seems to be a reliable measure of excluding retained capsule, although long-term follow-up is lacking.

7.4 What are the principal questions that remain to be resolved?

7.4.1 Can Crohn's disease be differentiated from other pathologies on the basis of endoscopic findings?

Statement 7K
- Endoscopic differentiation of small-bowel Crohn's disease from drug-induced lesions or other diseases is unreliable. [**EL3b, RG C**] Findings have to be interpreted with the results of clinical symptoms, cross-sectional imaging, histopathology, and biochemical markers [**EL5, RG D**]

Crohn's disease, tuberculosis, cytomegalovirus infection, Behçet's disease, vasculitis, ischaemia and ingestion of NSAIDs are some of the causes of ulcerating lesions in the small bowel. Their differentiation appears impossible based on endoscopic images alone. Within 2 weeks of taking NSAIDs, up to 75% of patients may have small-bowel lesions [29, 30]. Selective COX2-inhibitors cause fewer small-bowel lesions [31].

7.4.2 Are there criteria that can be used to select patients for SBCE?

Statement 7L
- Weight loss, anaemia, thrombocytosis, biochemical, or faecal markers of inflammation, and serological markers can be used to select patients for SBCE when Crohn's disease is suspected and conventional endoscopy and radiographic imaging are normal or inconclusive [**EL3b, RG C**]

Predictive markers for detection of small-bowel lesions suggestive of Crohn's disease have been described, although not validated in prospective studies. These include biochemical markers of inflammation such as raised C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) [174], thrombocytosis [175], anaemia, faecal markers of inflammation (e.g., calprotectin, lactoferrin), and symptoms of abdominal pain, diarrhoea [176], or weight loss [177]. Recurrent abdominal pain without other findings exceptionally rarely results in detection of clinically relevant lesions in the small bowel [178, 179], little different from colonoscopy for isolated abdominal pain. This simply reflects the fact that endoscopy (of any sort) examines the mucosal lining and not the wall of the intestine, wherein lie the enteric nerves. The long-term outcome of patients found to have superficial small-bowel lesions is currently not known.

7.4.3 What scoring methods are appropriate for the diagnosis and assessment of the severity of the disease?

Statement 7M

- Prospective studies are required to define diagnostic criteria by SBCE for Crohn's disease [**EL5, RG D**]

There are currently no validated SBCE diagnostic criteria for Crohn's disease, ulcerative colitis or IBDU. Criteria proposed by Mow et al [19] are arbitrary and not validated (see Section 2.2.1).

Statement 7N

- Scores for diagnosis and for assessing the activity or severity of Crohn's disease by SBCE or DAE are desirable and should be validated prospectively [**EL5, RG D**]

There are also no validated scores for either diagnosis or the assessment of severity of small-bowel Crohn's disease at SBCE or DAE. Existing endoscopic scores for Crohn's disease, such as the CDEIS [32] or SES-Crohn's disease [33], are only validated for ileocolonoscopy, or apply to the postoperative neoterminal ileum (Rutgeerts' score, [34]). SBCE scores that have been proposed are based on the degree of villous oedema, mucosal ulceration, and stenosis [35], or inflammation, extent of disease, and strictures [36], but they have yet to be validated prospectively. Diagnostic scoring needs to be validated in patients with suspected Crohn's disease and assessment scores in patients with established Crohn's disease.

7.4.4 What is the evidence behind new technology?

Statement 7O

- Improved visualization of the mucosa is achieved with high-resolution and magnification endoscopy. Small-bowel spectral light selection, endoscopic ultrasound, and confocal laser microscopy via miniprobes have yet to prove their value in clinical practice. Modified procedures such as spiral or balloon-guided enteroscopy have to be evaluated in comparison with established techniques [**EL5, RG D**]

Spiral enteroscopy [16] could shorten the procedure time, as the enteroscope is propelled through the small bowel using a rotating spiral, like an overtube. A single-use double-balloon spiral overtube is available that can be mounted on most of the standard endoscopes, thus enabling push-and-pull manoeuvres [180]. Recent advances in endoscopic design include high definition imaging and optical or electronic structure enhancement of images, facilitating detection of subtle mucosal changes. Miniprobes for endosonography and confocal laser microscopy can be used in the small bowel, although their clinical value in the diagnosis of Crohn's disease has not yet been established. Endoscopic ultrasound has the potential to provide information on bowel wall thickness and thereby evaluate the true transmural inflammatory process.

Acknowledgments

The authors are delighted to acknowledge Professor Tony Axon (President of OMED) for initiating the idea and Kristen Hartley of OMED for expert administrative support. The initiative was conceived and driven entirely by OMED and ECCO. We greatly appreciate the unrestricted educational grants to support the process from Abbott, Centocor, Given Imaging, Olympus, Pentax and Schering Plough, and Fujifilm who also respected the necessity for no other involvement.

Competing interests: None

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