Chapter

Capsule Endoscopy in Suspected and Established Small Bowel Crohn's Disease

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Abstract

Capsule endoscopy has recognized to be a very useful non-invasive tool for diagnosis and evaluation of the extension or the recurrence in Crohn's disease (CD) patients. It has the advantage of outstanding visualization of small-bowel lesions undetectable by conventional endoscopy or radiologic studies and has a good tolerability and safety in well-selected patients. In this chapter, we would like to evaluated the significant small bowel capsule endoscopy findings that can lead to better outcomes of diagnosis, classification, therapeutic management, and prognosis of patients with CD. Moreover, we would to discuss the specificity of the CE and to determine the place of the CE in the recurrence of CD and, for example, its role in monitoring drug response.

Keywords: capsule endoscopy, Crohn's disease, inflammatory bowel disease, small bowel investigation, medical devices

1. Introduction

Video capsule endoscopy (VCE) introduction and subsequent application in clinical practice almost 20 years ago [1], has revolutionized the management of a wide variety of small intestine diseases, allowing for the first time an extensive and high-quality examination of whole mucosal surface. VCE was minimally invasive, radiation-free and has an excellent safety profile. The most common indication for video capsule endoscopy is suspected a obscure gastrointestinal bleeding (OGIB), identification of small bowel malignant tumors, and follow-up of intestinal polyposis syndromes and the monitoring of mucosal inflammation in patients with active IBD in particular Crohn's disease (CD) as highlighted by several recent studies [2, 3]. VCE was able to detected even mildly inflammatory mucosal lesions, such as erythema, erosion, and small ulcers, which are rarely to highlight with radiological imaging modalities such as small bowel follow-through (SBFT), small bowel contrast ultrasound (SBCUS), CT enterography (CTE), and MR enterorrhaphy (MRE) [4, 5]. Yet, it lacks motion control and the possibility to perform biopsies or administer drugs. Hence the use of VCE has aided precision medicine-based diagnostic and therapeutic

decision-making, especially in patients with suspected or established Crohn's disease (CD) of the small intestine. Furthermore, in the last 20 years, its application has expanded allowing in patients with ulcerative colitis (UC), together with panenteric CD. This was made possible with the subsequent development of colonic capsule endoscopy (CCE), which allows visualization of both the small and large intestines [6, 7]. Therefore, the use of CE for the diagnosis and management of IBD is becoming more frequent and its implementation is considered a priority in the field of IBD. In this chapter, we would like to evaluated the significant small bowel capsule endoscopy findings that can lead to better outcomes of diagnosis, classification, therapeutic management, and prognosis of patients with CD. Moreover we would to discuss the specificity of the CE and to determine the place of the CE in the recurrence of CD and, for example, its role in monitoring drug response.

2. Video capsule endoscopy: type, technical and procedural aspects

Small bowel VCE was first introduced in 2000 as a noninvasive means of assessing the small bowel (SB) [1]. VCE, also known as wireless capsule endoscopy or video capsule endoscopy, is a gastrointestinal study that uses a pill camera to transmitted images of the intestinal lumen. The capsule was ingested orally, passed through passively via peristalsis and the images are downloaded from the data recorder to a computer for later review. The capsule was naturally eliminated from the body within 24 h, there was no need sedation or recovery time. At the present, several similar VCE systems are available worldwide, most of which wirelessly transmit and store images in an external recorder that patients carry during the recording. There are significant differences in the design of various CE systems (**Table 1**). Several small-bowel

	PillCam SB3 (Given Imaging Ltd., Israel).	**EndoCapsule System EC-1® (Olympus, Japan).**	**MiroCam® (IntroMedic, Korea).**	**OMOM (Chongqing Jinshan Science and Technology Group, China)**	**CapsoCam SV-1® (CapsoVision, Medical Innovations, US)**
Frame rate, fps	2–6	2	3	2	20 max
Dimension mm × mm	26.2 × 11.4	26 × 11	24.5 × 10.8	24.5 × 11	31 × 11
Battery life (h)	> 8	12	12	6–8	18–24 h
Transmission mode	RF	RF	RF	RF	USB
Field of view	156	145	160	140	360
Optical enanchament	FICE setting	Contrast setting	NA	NA	NA
FDA	Yes	Yes	Yes	No	No

Fps, frame per second; RF, radiofrequency; USB, universal serial bus; FICE, fujinon intelligent chromoendoscopy; NA, not applicable.
Given per Crohn (CE GINAm 2019).

Table 1.
Currently types of VCE available.

capsules (PillCam, Given Imaging, Yoqneam, Israel; EndoCapsule, Olympus, Tokyo, Japan; MiroCam, IntroMedic, Seoul, Korea; OMOM, Jinshan Science, Chongqing, China; CapsoCam, CapsoVision, Saratoga, CA, USA) are now available worldwide [8]. Capsule endoscope models with US FDA-approved capsule endoscope models include PillCam, EndoCapsule, and MiroCam. Although the various capsules are similar in size and shape, they differ in size, frame rate, runtime, field of view, image sensor, and optical enhancement. PillCam® is the original VCE and captures 2 frames per second. It has a "blood suspicious indicator" that can identify the site of bleeding. The third-generation capsule is about to be released, and almost all literature on VCE mentions PillCam. The EndoCapsule systems EC-1®, MiroCam® and OMOM are similar to the PillCam. The CapsoCam SV-1 is a new type of VCE with a 360 degree side view that does not require data loggers or sensors. Images are stored on the VCE itself, so the patient must remove the VCE from the stool. This VCE is then sent to the endoscope reader, which analyzes the data. It has a longer battery life of 18–24 h. Whether small bowel preparation is required for SBCE has been one of the most debated issues in capsule endoscopy science since the development of this diagnostic tool. The first manufacturer of small bowel capsule endoscopes recommended a low-fiber diet the day before surgery, drinking only water in the evening, followed by a 12-h fast, and advised against the use of laxatives before VCE. However, usually, 2 L polyethylene glycol (PEG) solution leads to improvement in small bowel visibility and diagnostic yield for SBCE [8]. Whether small bowel preparation is required for SBCE has been one of the most debated issues in capsule endoscopy science since the development of this diagnostic tool. The first manufacturer of small bowel capsule endoscopes recommended a low-fiber diet the day before surgery, drinking only water in the evening, followed by a 12-h fast, and advised against the use of laxatives before surgery. The choice of bowel preparation should be based on the patient's clinical situation. Patients should not take anything by mouth after midnight. On the morning of the capsule endoscopy, the patient should chew two simethicone tablets to reduce intraluminal air bubbles and improve visualization of the small bowel mucosa. The ideal dose of simethicone is yet to be defined and ranges between 80 and 200 mg [9]. After ingesting the video capsule, the patient needs to be nothing by mouth for at least 2 h. A clear liquid diet is allowed 2 h after capsule ingestion and light snack 4 h after capsule ingestion. Considering this evidence, the European Society of Gastrointestinal Endoscopy (ESGE) issued a technical review in 2018 recommending the use of purgative solutions prior to SBCE because the presence of residue in the small bowel lumen, limits observation, hampers interpretation, and may impair diagnostic accuracy [7]. Several meta-analyses confirmed that use of laxative solutions prior to SBCE improves small bowel cleansing but does not consensus has been reached regarding the optimal timing for purgative ingestion [10]. A meta-analysis of four randomized controlled trials (RCTs) highlighted that the use of prokinetics for capsule ingestion improves completion rate in SBCE [11]. Conversely, patients with incomplete SBCE studies were at increased risk (e.g., patients or subjects with one or more of the following: history of abdominal surgery, delayed gastric emptying, diabetic neuropathy, severe hypothyroidism, use psychotropic drugs, etc.) If the capsule remains in the stomach for more than 30–60 min, it may be affected by certain prokinetic drugs (metoclopramide or domperidone), as confirmed by real-time monitoring [12]. Probably the most relevant factor for attaining an adequate small bowel preparation is the timing and not the volume of the purgative solution. Many studies have now shown that factors other than the type of bowel preparation regime used, can influence the quality of bowel preparation among adult patients undergoing

colonoscopy. These factors can be generally categorized as either patient-related (age, gender, co-morbidity, socioeconomic status) or procedure-related (adherence to bowel preparation instructions, timing of bowel preparation administration) [13]. Several authors reported that SBCE diagnostic yield is related with small bowel transit time (SBTT), with positive correlation between the diagnostic yield and SBTT, indicating that the longer the SBTT, the higher the diagnostic yield [14]. Proximal small bowel has a faster transit time and therefore, SBCE has a higher rate of missed lesions in this segment (ESGE 2018). Even though VCE guidelines was established, there were no formal recommendations and only limited data on how to increase performance and obtain a consistent level of high-quality reporting to guide capsule endoscopists on how to read the many images collected in each SBCE [15, 16]. In the following paragraphs we will be discussed the best to approach for VCE reading skills according to the management CD disease.

2.1 Patency capsule

The patency capsule (PC) is a dissolvable diagnostic tool, safe, efficient, and accurate for the assessment of the small intestine functional patency. PC reduces the risk of retention and allows the safe administration of a capsule endoscope. Even if it does not provide direct visual information for the presence and location of strictures, masses or narrowing of the lumen of the small intestine, its safe passage, in a predefined period of time minimizes the risk of retention and allows safe administration of a capsule endoscope.

The manufacturer company for the PillCamSB has developed a revolutionary system dubbed the Given® M2A Patency System. Its Patency capsule comprises of two timer plugs whose dissolving process initiates earlier (a mere 30 h after ingestion) and continues even when lodged in a tight stricture [17]. The patented Given and Agile patency capsules differ in composition (lactose for the Given capsule and dissolvable compounds with a radio frequency identification tag detectable by X-ray for Agile), number of timer plugs (1 for Given and 2 for Agile), and dissolution start time (40–100 h for Given and 30 h for Agile) [18].

Nowadays, there are two different approaches regarding PC administration in established CD: the selective approach (administering the PC only in patients with obstructing symptoms) and the nonselective approach (in all CD patients). The selective approach was warranted by the real-life retention risk of patients with established CD is 2.5%, a significantly lower probability compared with preliminary observations [19]. On the other hand, routine administration in patients with a low retention risk, such as patients under investigation for suspected CD without obstructive symptoms, known stenosis, or prior surgery, is not justified. Actually, the benefit of PC evaluation in selected patients with known or suspected CD was clear. Patency Capsule multi-center clinical trials [20, 21] highlighted the decreased risk of video capsule retention in patients with known strictures emphasizing that it was a valid and safe tool to assess functional patency of the small intestine. PC can identify those patients who can safely undergo capsule endoscopy, despite clinical and radiographic evidence of small bowel obstruction. The risk of PC-related adverse events was low. Abdominal pain, symptomatic PC retention/impaction, intestinal ischemia, cellophane wall impaction and aspiration were the most common complication that in most patients resolves spontaneously even if some go to medical, endoscopic, or surgical intervention for their management.

2.1.1 PC vs. other modalities

PC was as accurate in identifying stricture as or better than standard radiological techniques and was at least comparable to cross-sectional imaging methods. Although it cannot produce direct information on small bowel mucosal abnormalities; it should therefore be considered a complementary method to radiographic diagnostic methods—in particular, magnetic resonance (MR) imaging, specifically MR enteroclysis and MR enterography, reformed the investigation of CD small bowel involvement and related complications [22]. MR enterography was shown to be superior to MR enteroclysis, especially in the identification of minor lesions. an interesting study underlined that MR enteroclysis was an accurate method for the identification of small bowel strictures, [23] while MR enterography was shown to be highly sensitive (>90%) but moderately specific (52–59%) in the prediction of small bowel stenosis causing PC retention [24]. This is due to the interpretation of the results subject to the experience of the observer, preparation before the exam and among others the optimal ability of MR enterography to detect strictures areas is largely in the area of the terminal ileum. Although the PC only allows for assessment of the gut functional patency by not being able to discriminate between fibrostenotic and inflammatory strictures, although some studies suggest that it may allow the distinction between rigid and inflammatory strictures flexible fibrotic strictures [25]. Therefore, MR enterography could be really helpful in distinguishing between these two situations and predicting the feasibility of further investigations with PC and SBCE. However, However, PC offers a better assessment of functional intestinal patency than other noninvasive diagnostic modalities, particularly in the pediatric population [26]. In conclusion, PC was accurate in identifying stenosis as good as or better than standard radiological techniques but it cannot offer direct visual information regarding small bowel mucosa abnormalities and should be considered as a complementary method to radiographic diagnostic methods.

3. Diagnostic implication of capsule endoscopy in IBD

Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic and immune-mediated inflammatory bowel diseases (IBD) with a highly heterogeneous presentation and characterized by relapsing and remitting mucosal inflammation which mainly affects the gastrointestinal (GI) tract that necessitates lifelong monitoring and treatment. Most patients exhibit an inflammatory phenotype at diagnosis, but over time more than 50% of affected patients develop more serious chronic complications including strictures, fistulas, and/or abscesses, which in turn often require major surgery [27, 28]. Approximately 5–15% of patients cannot be classified as a subtype of IBD and the disease does not suitable the characteristic diagnostic criteria specific to either UC or CD. In these patients, the condition is labeled indeterminate colitis (IC) and inflammatory bowel disease unclassified (IBDU) [29]. The general assumption is that the diagnosis is provisional [30] until a more definitive diagnosis of UC or MC can be made. Therefore, patients with suspected or proven CD and IBDU must be evaluated frequently to assess or rule out SB lesions and the potential need for escalated care. In addition, it is reasonable to perform SB in patients with establishing RCU if clinical presentation changes or CD diagnoses was suspected. However, despite the advances, the diagnosis and management of IBD remain

challenging. The establishment of new therapeutic goals, such as mucosal healing (MH) and the introduction of biologic therapies, based on tight monitoring and accelerated escalation of care, has created increasing demands and new indications for endoscopic assessment of disease activity [17–35]. These have been incorporated into the standard of care over the years, as are clinical guidelines developed by international societies such as the European Society for Gastrointestinal Endoscopy (ESGE) and the European Crohn's and Colitis Organization (ECCO) [28, 29]. In 2017, the American Gastroenterological Association (AGA) Institute Practice Guideline recommends SBCE for known, recurrent, or suspected Crohn's disease when active small bowel disease is suspected based on negative imaging studies and normal ileocolonoscopy.

Although these continue advance of novel indications, the SBCE was established to be principally a noninvasive instrument for the assessment of the SB mucosa that supports diagnosis and monitoring treatment of disease activity [36, 37], turning SBCE into a valuable decision-supporting tool.

3.1 Capsule endoscopy in suspected small bowel CD

Inflammatory disorders of the small bowel (SB) are frequently and can present in many different ways depending on the underlying cause such as Crohn disease, non-steroidal anti-inflammatory drug (NSAID) enteropathy, celiac disease, autoimmune enteropathy, radiation enteritis, infection and lymphoproliferative disorders.

CD was a chronic progressive inflammatory bowel disease that can affect any portion of the gastrointestinal tract, but affects the small intestine in up to 60% of cases [38].

Anyway, several SBCE findings are frequently associated with CD: aphthous lesions, serpiginous, linear or deep ulcerations, and mucosal edema (**Figure 1**). However, these findings are neither pathognomonic nonspecific to CD. Small-bowel

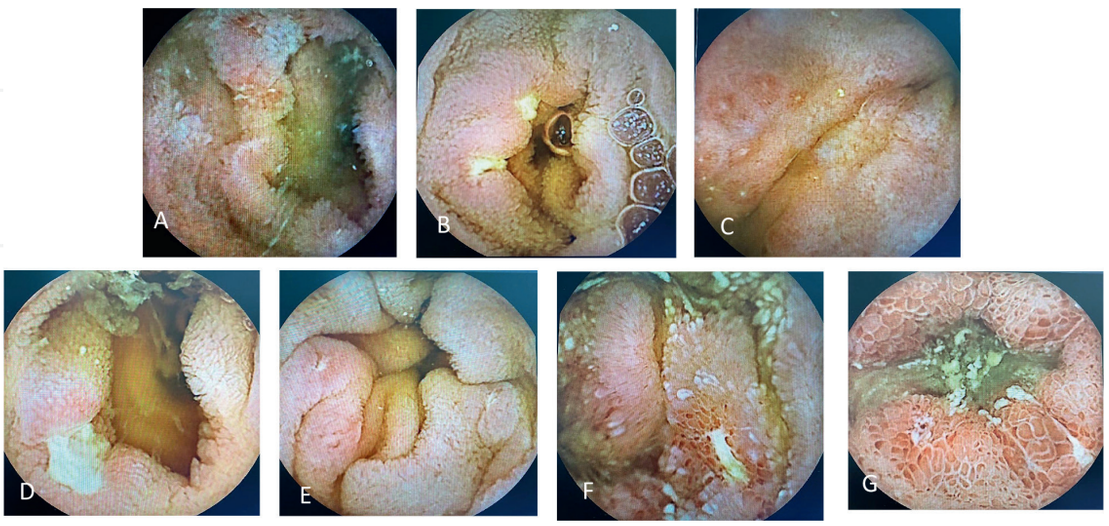

Figure 1.
Video capsule endoscopy for small bowel Crohn's disease. (A) Small and shallow aphtous ulcer in the duodenum were observered in suscpected CD patients, (B) small aphtous ulcer in the jejunum seen in suscpected CD patients, (C) apthous lesions in the distal jejunum were observed in suspected CD patients, (D) large ulcer in proximal ileal seen in established CD patients, (E) small erosion of the jejunum in established CD patients, (F) hiperemia, superficial ulceres and edematous mucosa in established CD patients and (G) edematous mucosa, hyperemia with extensive erosion and signs of bledding.

(SB) disease was involved in up to 80% of CD patients, while in about 30% of patients, the disease is limited to the SB exclusively [39, 40]. Small bowel CD was undervalued due to diagnostic limitations in visualizing the small bowel [41]. Small bowel CD is associated with serious complications such as strictures, abscesses, and obstruction. A gold standard for the diagnosis of CD is not available. CD has a multitude of phenotypes or presentations defined by the type, location, and disease severity. The diagnosis of Crohn's disease (CD) should be based on combined assessment of features of clinical history, symptoms, and evidence of intestinal inflammation based on imaging, endoscopy, histology, and biochemical parameters [42] Although ileocolonoscopy (IC) remains the primary modality for endoscopic evaluation in suspected cases [43].

3.1.1 Diagnostic yield and the clinical impact of SBCE

In Crohn's disease it is important to define the location of the disease.

Due to the length of the SB (average length of 575 cm at 20 years of age), the small bowel is difficult to examine directly and with conventional endoscopic equipment due to its complex loops and length [42]. Conventional endoscopic equipment can only be used to visualize the proximal jejunum and a small portion of the distal ileum. In particular SBCE could be appropriate to detect lesions outside the scope of conventional endoscopy because it seems to be more sensitive than imaging to detect a previously unrecognized disease location such as jejunal localization. Several studies have highlighted that jejunal disease was associated with an increased risk of structuring disease and abdominal surgeries as compared to either esophagogastroduodenal (EGD) or ileocolonic disease [44, 45]. Therefore, the CD distribution was crucial and upper gastrointestinal involvement was more frequent in children than in adults (30–80% vs 10–15%).

The Paris classification tried to avoid any ambiguity in the meaning of upper gastrointestinal lesions (L4) and further characterization of the L4 phenotype in the Montreal classification into three specific subgroups including L4-EGD, L4-jejunal, and L4-proximal ileal disease may be warranted [46]. A recent retrospective cohort study confirmed that L4 disease had a worse prognosis compared to non-L4 disease, and within L4 disease, the phenotype of L4-jejunal and L4-proximal ileal disease indicated a higher risk for intestinal surgery [47]. The most important comparative advantage of SBCE was considered its ability to visualize the small bowel and colonic mucosa directly and with higher sensitivity. Despite magnetic resonance enterography (MRE) has a good comparable diagnostic accuracy for small bowel disease, its presented a lower accuracy for mucosal inflammation. In the literature, SBCE has shown equal or higher diagnostic outcomes compared to MRE [48, 49]. Furthermore, SBCE was 50% diagnostic of CD when analyzed in a real setting [50]. Finally, the available magnetic resonance index of activity (MaRIA) has only been validated on the terminal ileum and colonic segments [51].

The role of SBCE for the detection of more proximal SB mucosal lesions is increasingly recognized. This is reflected in ECCO-ESGAR and ESGE guidelines and consensus statements [52]. A previous meta-analysis demonstrated that SBCE is a more sensitive method for the diagnosis of small bowel CD, with an incremental diagnostic yield 30% greater than other imaging modalities [48]. SBCE has a high sensitivity (93%) and a high negative predictive value (96%) for the diagnosis of small bowel CD [53, 54]. However, due to the high false positive rate and low specificity, SBCE should be used to exclude celiac disease rather than confirm it. Unfortunately, not all small

bowel lesions are from CD, even after excluding the use of NSAIDs. A previous study showed that 14% of healthy individuals with SBCE [55]. Although various diagnostic modalities contribute to the diagnosis of CD, histopathological examination plays a key role. "Histopathology is not everything, but without histopathology we have nothing" [56, 57]. The presence of structural changes or "chronicity," such as crypt deformation, basal lymphoplasmacytosis, and metaplastic Paneth cells or pyloric glands, has been considered a prerequisite for the diagnosis of IBD, although these chronic structural changes are not characteristic of IBD. Conventional VCE or SBCE lack tissue sampling capabilities, so they are not suitable as sole diagnostic tests for CD or IBD. However, the limited invasiveness of SBCE may make it an inexpensive screening or adjunct test, providing a roadmap for targeted biopsy via routine enteroscopy, balloon-assisted enteroscopy, or IC. In this regard, disease biomarkers such as fecal calprotectin (FCP) could be useful in selecting patients for SBCE in suspected CD, as it helps exclude non-inflammatory small bowel lesions. Although measurement of these biomarkers offers a preliminary assessment of disease activity and can guide treatment decision-making regardless of disease location. However, their role in diagnosis MH (endoscopic remission) or predict treatment response was yet to be clarified. One study demonstrated that both FCP and C-reactive protein (CRP) had low negative predictive values for small bowel where Pan-intestinal video capsule endoscopy (PCE) observed mucosal inflammation among patients with normal biomarker levels [58].

A recent metanalysis underlined that a FCP cut off of more than 100 _g/g has highest diagnostic accuracy (sensitivity and specificity 73% and diagnostic odd ratio 7.89) [59]. Thus FCP was a selection tool for small bowel capsule endoscopy in suspected IBD with prior negative bi-directional endoscopy [60]. Therefore, careful mucosal assessment with SBCE has become pivotal to the diagnostic approach in patients with suspected CD. In summary, CD remains a difficult and challenging entity to manage. The suspected CD patient cohort presents a tough clinical scenario even after negative initial routine endoscopic investigations. SBCE has proven a high diagnostic yield and is often the preferred initial diagnostic test in suspected CD, because its noninvasive quality, better tolerance, and ability to view the entire small bowel. SBCE role was still uncertainty. This ambiguity is partly because of variations in the parameters used to diagnose CD using SBCE and the lack of a gold standard. Anyway, SBCE has a high negative predictive value in patients with suspected CD, making it an excellent "rule-out" test [61].

3.1.2 Role for repeat capsule endoscopy

A repeat capsule endoscopy may be useful for the evaluation of rebleeding, and/or unexplained gastrointestinal pain after a negative or nondiagnostic capsule endoscopy result. Due to the high diagnostic yield and noninvasive nature of CE, repeat CE remains a reasonable option due to patient acceptability and ease of use before other types of small bowel Studies have reported an incremental diagnostic yield of 35–75% with repeat capsule endoscopy and alteration in management in 39–62.5% of patients [55, 62]. When there is a high clinical suspicion for a small bowel tumor, CTE and/or deep enteroscopy may be preferred over a repeat capsule endoscopy. Viazis et al. [63] reported on 76 patients with new evidence of overt bleeding or a decrease in hemoglobin who underwent a second-look CE procedure. There were positive findings in 37 patients (49%) on second CE, findings of uncertain significance in 22 patients (29%) and 17 patients had no findings. The study concluded that certain patients would benefit from a second-look CE procedure. An interesting study [64] supported the

hypothesis that repeat VCE is useful in equivocal and inconclusive studies where there is clinical suspicion of SB CD. The overall DY of CE recurrence in suspected SB-CD patients was 16.7% (3/18). However, patients without SB inflammation at the time of initial CE did not show any repeat CE indicates changes in CD (DY = 0). Patients with non-specific inflammation do not feel prompting CD in initial CE, DY in repeated CE was 33%. In addition, with higher fecal calprotectin results were more likely to provide evidences in support of a CD diagnosis in their repeat CE. In contrast, in patients whose initial CE showed no signs or evidence of SB inflammation, repeating the process does not seem to add much. Due to the high diagnostic yield and noninvasive nature of CE, repeat CE appears to be of benefit and should be considered for specific patients before other types of small bowel studies.

3.1.3 Role of pre-symptomatic and spondyloarthropathy patients

Spondyloarthritis (SpA) was a group of related chronic immune-mediated inflammatory disorders which share common genetic, pathophysiological and clinical features. IBD is a common extraintestinal manifestations in SpA patients, and around 8% of patients with ankylosing spondylitis develop clinically overt inflammatory bowel disease. Especially Crohn's disease percentage of 5–10% of patients with SpA that will develop inflammatory bowel disease and a much higher percentage, close to 60% of patients that have asymptomatic bowel inflammatory lesions [65]. Over 20 years ago, Mielants et al. [66] showed that a substantial number of these patients have subclinical ileal inflammation. Actually, approximately 50–60% of SpA patients display microscopic intestinal inflammation in biopsies of the ileum or colon, often reminiscent of Crohn's disease [67]. Since SpA and IBD patients share common genetic and immunopathogenic mechanisms [68], SpA patients have an up to four-fold increased risk of IBD compared to the general population. Different forms of SpA can be associated with variable frequencies of intestinal involvement, whereas articular involvement is frequently observed in IBD. Conventional endoscopic and radiological techniques are limited in their capacity to investigate the small bowel, thus often unable to detect CD mucosal lesions. CE uncovered SBI consistent with CD in 42.2% of patients with SpA, with a significant incremental yield over colonoscopy of 31% [69]. Significant small bowel findings (erythema, mucosal breaks, aphthous or linear ulcers, and erosions) were detected by capsule endoscopy in 30–80% of SpA patients [70]. Immunological link between SpA and IBD is still poorly understood. Even if there were relationship between the disease activity of SpA and the degree of gut inflammation [71]. A large percentage of SpA patients have subclinical gut inflammation without gastrointestinal symptoms and the presence of gut inflammation seems to be an important risk factor of progression of SpA [72]. Therefore in SpA patients when suspected IBD symptoms are present it's important to assessed the presence of small intestinal lesion using videocapsule endoscopy.

3.2 Capsule endoscopy in established CD

The management of IBD remains a challenge, indeed in the modern era of advanced biologic therapies. The need to differentiate between symptoms, endoscopic findings, and detecting of worsening disease activity at an early stage has set new goals in management. The approach to patients with suspected CD is different from the approach to patients with established CD. Although SBCE may have a limited role in the diagnosis of CD, it can be helpful in the assessment of a patient with known small bowel CD.

3.2.1 Diagnostic yield

SBVCE results impact clinical decision-making in a large cohort of patients with established CD. Previous studies have focused the definition of clinical impact in prognosis [73] and therapeutic changes [74, 75]. Although, the available scoring systems for quantification of SB inflammation (Lewis score and Capsule Endoscopy Crohn's Disease Activity Index) have not been extensively validated for the indication of monitoring of CD in large-scale clinical trials [76, 77]. Recent advances in the management of IBD have been a paradigm shift in treatment decisions for patients with established CD. In the past, the treatment was based mainly on the symptoms, but it is now known that symptoms were nonspecific for bowel inflammation. Actually, treatment strategies aim to treat beyond symptoms to normalization of objective markers of inflammation with the goal of mucosal healing. Mucosal healing at 1 year predicted an aggressive disease including the need for surgery.

Therefore, SBCE application in CD established can be regarded for assessment of disease activity, extent, severity, postoperative recurrence and mucosal healing once therapy was initiated.

Regarding mucosal healing, symptom assessment was a poor indicator of severity and extent of disease. In recent years, several studies have described the use of SBCE to monitor mucosal healing [78, 79] and postoperative recurrence [80].

Several studies have shown that SBCE can detect subtle mucosal abnormalities that other methods may miss.

SBCE can help identify CD missed by conventional endoscopy and assess the extent and severity of SB involvement [81]. Studies have also shown that the high diagnostic yield of SBCE affects disease management and clinical outcomes, thus hypothesizing that SBCE may play a role in assessing mucosal healing. In a prospective study of 28 patients with persistent symptoms, SBCE detected active inflammation in 82% of patients compared with ileocolonoscopy in only 49%, showing an incremental recovery of 33% [82].

Several recent studies evaluated the use of small bowel capsule endoscopy in the assessment of mucosal healing in patients diagnosed with Crohn's disease. Most of these studies did not evaluate a specific treatment, except for two studies, one of which focused on adalimumab and azathioprine [83] and the other that focused on certolizumab pegol [84]. In the other studies, there was no comparison between SBCE findings at baseline and during follow-up, because the most of patients in clinical remission had only one SBCE after treatment [85, 86]. Furthermore, according to these studies, the assessment of mucosal healing varies, although most of them are based on calculations of Lewis scores with normal values below 135. Overall, despite the high heterogeneity of these studies, the results suggest that mucosal healing can be assessed by SBCE to monitor the effect of drug therapy in CD patients, with a significant correlation between Lewis score and fecal calprotectin ($r = 0, 82$, $P < 0.0001$) [87], while there was no significant correlation between this score and clinical activity measured by CDAI [86].

Transmural healing (TH) is being increasingly recognized for reflecting deep remission in Crohn's disease. TH is an independent predictor of more favorable long-term outcomes than MH, suggesting that TH could become the potential treatment endpoint in CD [88]. In the future it will be important to evaluate transmural healing rather than MH, currently SBCE only detects MH so in the future to define disease remission SBCE will have to be integrated with the use of transversal imaging for established CD.

ECCO topical review (2018) recommends an appropriate reevaluation of disease activity considering clinical, biochemical, endoscopic and/or radiological techniques before withdrawing treatment of SBCE may play a key role in this regard. Mucosal healing in SBCE was the only independent factor predicting treatment downgrade in logistic regression. A remission as measured by the Harvey-Bradshaw index or inflammatory markers within this range, such as FCP or CRP, was not associated with discontinuation of treatment. Indeed, to assess remission endoscopic evaluation it was needs an endoscopic assessment for a appropriate risk evaluation and cannot rely on indirect parameters.

In patients with quiescent Crohn's disease involving the small bowel, fecal calprotectin predicts short term flare risk, whereas VCE predicts both short-term and long-term risk of disease exacerbation. In particular Shomron Ben-Horin et al. [89] underlined that VCE can identify patients who are at high risk of flare within 24 months, whereas fecal calprotectin can only identify patients who are at high risk of flare within 3 months. If supported by additional studies, protocols incorporating VCE could expand the scope of available methods for monitoring disease activity and predicting outcomes in small bowel Crohn's disease.

However, the definition of endoscopic remission as assessed by SBCE remains unknown because there is currently no consensus on the therapeutic objective to reach in luminal SB CD (normalization of SBCE or absence of deep or superficial ulcerations).

3.2.2 Comparison with other modalities

After CD is diagnosed, the extent of disease throughout the gastrointestinal tract should be determined.

Current practice uses MRE, which allows transmural visualization of the small bowel without exposing the patient to ionizing radiation and its potential future complications, or involving invasive procedures. However, SBCE can identify small bowel lesions that may not be detected by MRI. Although most guidelines do not recommend SBCE in patients with normal MRE or CTE [90], it can be considered for certain indications such as anemia, malnutrition and discrepancy between symptoms and instrumental investigations In patients with established CD, a meta-analysis of various modalities used in small bowel CD showed SBCE was superior to barium studies (small bowel follow-up or enema) (38%; 95% CI, 22–54%; P < 0.00001) and CTE (32%; 95% CI, 16–47%; P < 0.0001)) but not ileoscopy (13%; 95% CI, −1 to 26%; P 1/4 0.07) or MRE (−6%; 95% CI, −30% to 19%; P 1/4 0.65) [91]. It has been suggested that MRE may be superior to CTE in detecting strictures and strengthening of the ileal wall MRE and CTE have been shown to play an important role in established CD. Wall thickening and abnormal enhancement were sensitive indicators of CD, whereas abnormal T2 signal, mesenteric vascular prominence, and adenopathy were specific. It has been suggested that MRE may be superior to CTE in detecting strictures and strengthening of the ileal wall. Regarding MRE, a valid index based on wall thickness, relative contrast enhancement, edema, and ulceration has been developed, called Magnetic Resonance Activity Index (MaRIA) [92]. Recent advances in the management of IBD have been a paradigm shift in treatment decisions for patients with established CD. In the past, the treatment was based mainly on the symptoms, but it is now known that symptoms were nonspecific for bowel inflammation. There was still controversy about the most optimal way to evaluate SB inflammation.

In a prospective study [93] of patients with CD experiencing mild/no clinical symptoms, VCE was better tolerated compared to MRE and was preferred by 78% of patients due to less side effects. [94] VCE is also able to detect more cases of proximal SB CD than MRE.

In this case SBCE was helpful for prognostic purposes because proximal CD is associated with higher risk of stricture formation and need for surgical intervention.

Early identification of this high-risk group may allow for earlier aggressive therapy to reduce risk of CD complications. Besides, SBCE played a key role in persistent clinical suspicion despite negative ileocolonscopy and cross-sectional imaging. In a prospective study of patients with persistent perianal disease but negative standard work-up, VCE had an incremental diagnostic yield of 24% following negative ileocolonoscopy and radiology imaging [95].

Although the accuracy of SBCE in monitoring proximal SB-CD has not been formally compared with device-guided enteroscopy due to the invasive nature of the latter procedure, the mucosal changes in distal SB observed with CE appear to be comparable to those observed with ileocolonoscopy standard modality for evaluating changes in terminal ileum CD [96]. The diagnostic superiority of SBCE over radiography has also been demonstrated in patients with established CD. In earlier meta-analyses, CE vs. SB barium studies (71% vs. 36%; IY 5 38%; 95% CI, 22–54%) and CT enterography/bowel lavage (71% vs. 39%, IJ 5 32%, 95% CI, 16–47%), Although the accuracy of SBCE in monitoring proximal SB-CD has not been formally compared with device-guided enteroscopy due to the invasive nature of the latter procedure, the mucosal changes in distal SB observed with CE appear to be comparable to those observed with ileocolonoscopy. Consistent, reference standard, associated with terminal ileum CD [97]. The diagnostic superiority of SBCE over radiography has also been demonstrated in patients with established CD. In earlier meta-analyses, CE vs. SB barium studies (71% vs. 36%; IY 5 38%; 95% CI, 22–54%) and CT enterography/bowel lavage (71% vs. 39%, IJ 5 32%, 95% CI, 16–47%), but not when related with MR enteroclysis/enterography (70% vs. 79%; IY 5 6%; 95% CI, 30–19%) [98]. In a recent analysis of studies comparing SBCE diagnostic rates with radiological techniques, Kopylov and colleagues [99] underlined a modest correlation between SBCE and MRE-based quantitative indices of inflammation in patients with quiescent SB CD. Between-modality correlation was higher in patients with endoscopically severe disease.

Despite several modality-specific limitations, both SBCE and MRE provide an accurate and comprehensive assessment of SB and are capable of detecting persistent inflammation in most patients with clinically quiescent disease. The agreement between patterns was significantly better in patients with overt SB inflammation.

Therefore, SBCE and cross-sectional imaging (MRE and CT) are complementary diagnostic tools in CD established. In established non stricturing CD patients, SBCE was able to detect fine mucosal lesions especially in the proximal SB. Instead, cross-sectional imaging can detect more severe disease activity and better characterize the CD phenotype in terms of extraluminal involvement. Another retrospective study highlighted a significantly higher sensitivity of SBCE in detecting proximal and distal disease in the small bowel (jejunum and ileum) compared to MRE (76.6% vs. 44.7% $p = 0.001$) [5]. Compared with partial small bowel visualization endoscopy that occurs during endoscopy, SBCE exhibits high sensitivity to minor erosions or defects in the intestinal mucosa changes below the detection threshold of the imaging modality, and high sensitivity to small bowel length coverage.

However, if only one MRE or CE test can be performed during follow-up, there are limitations to the results each technique can provide. Therefore, it is necessary to recognize the advantages and disadvantages of these test methods. In particular, **Table 2** summarized and compared three diagnostic modalities.

3.2.3 Retention and management of retained capsule

VCE is a relatively safe and well-tolerated procedure. There are, however, a few limitations. However, certain complications arise as a result of the procedure, and they have been divided into clinical and technical complications (**Table 3**). The most important and common clinical complications was capsule retention in the gut lumen. Capsule retention can affect any area of the digestive system and remains undetected for a minimum of 2 weeks unless removed surgically or endoscopically. Most of the patients remain asymptomatic and in about one-third, the capsule is naturally excreted later than 15 days after ingestion [100, 101].

In a large multicenter retrospective study of CE-related adverse events, 61.5% of patients remained asymptomatic despite retention, 37.5% of events resolved spontaneously after a median of 42 days, and 19.2% of events passed after a median of 24 days medication resolved [93]. Nevertheless, in some patients acute obstruction or intestinal perforation has been reported [102–104]. This is a major worry not just for patients but also for physician. The overall incidence of capsule retention is low, approximately 1–2%. Thankfully, meta-analysis covering 227 publications and 22,840

	Capsule endoscopy	**MR enterography**	**CT enterography**
Advantage	Endoscopic view may detect subtle lesion Superior proximal SB lesion detection	Extraluminal finding	Extraluminal finding Widespread availability
Disadvantage	Risk of capsule retention and bowel obstruction Distal small bowel view may be obscured by debris	Long scan time in tight space (claustrophobia) Intravenous contrast Metal foreign object contraindicated Underdistention of bowel loops can compromise view	Ionizing radiation Intravenous contrast

Table 2.
Advantages and disadvantages of capsule endoscopy versus MR enterography versus CT enterography.

Clinical complications	Capsule retention Failure to reach the ileocecal valve—incomplete examination of the small bowel Swallowing disorders—inability to swallow and/or aspiration of the device.
Technical complications	Gaps in the recordings Short duration of capsule batteries Malfunction of battery pack Failure to activate the capsule Failure of localization software Failure of downloading Bowel preparation

Table 3.
Complications of capsule endoscopy.

capsule studies reported an overall retention rate of 1.4%, compared with the overall incidence retention rate of 2.6% for established CD [105]. This higher rate of retention can be attributed to the increased likelihood of intestinal strictures in CD. Risk of capsule retention can be stratified using cross-sectional imaging such as MRE/CTE or patency capsule, both of which have high negative predictive value, and can lower the overall risk of retention to 2.7% (95% CI, 1.1–6.4%) [21]. Nonselective use of patency capsule in all patients with established CD did not reduce the rate of capsule retention compared with a selective approach based on history of obstructive symptoms, previous obstruction, or previous abdominal surgery [106]. Symptomatic intestinal obstruction due to patency capsule is rare and usually managed conservatively [107]. The disadvantage of patency capsule testing is false positive rate which can be reduced by low dose, spot computed tomography, which can determine the exact location of capsule. False positive results are often due to colonic retention as a result of prolonged transit times. This can significantly reduce false positive patency tests. ESGE recommends that in asymptomatic patients without intestinal obstruction, capsule retention be initially treated conservatively with drugs (e.g., laxatives, prokinetics, steroids, immunomodulators, and biologics). If that fails, enteroscopy with a capsule retrieval device should be performed. If enteroscopy fails to recover the capsule; the next step is surgery (laparoscopy or open surgery with enterotomy) to remove the capsule (ESGE 2015). Another clinicals complication was the incomplete examination of the small bowel means that the capsule has not reached the cecum. Rodonotti et al. [108] in a retrospective analysis of 733 consecutive examinations underlined that failure to reach the ileocecal valve occurred approximatively in 15% of cases. In most cases the causes may be the failure to enter the duodenum with the capsule remaining in the stomach for the entire recording time, the delay in passing the pylorus and the retention of the capsule. These complications prevented or hindered the diagnosis in 38%. An increased risk of gastric retention and delayed gastric transit time should be suspected in patients who have diabetes, prior vagotomy, or scleroderma [109]. A prokinetic agent may be administered before the start of the examination to reduce the risk of this complication.

Swallowing disorders are a relative contraindication to capsule endoscopy. Possible complications related to swallowing the capsule include inability to swallow and/or aspiration of the device. Accidental Capsule endoscope aspiration into the respiratory tract is a rare complication of capsule endoscopy. The incidence of capsule aspiration in a large cohort of patients was very low. Rare case reports reported it may cause life threatening acute respiration distress, and over half of patients required bronchoscopy intervention after capsule aspiration [110, 111]. A meta-analysis study reported that aspiration was observed only in 2 out of 5.428 patients resulting in an incidence of 0.003% [112]. However, in some cases, induced shortness of breath necessitates removal of the aspirated capsule via bronchoscopy using general anesthesia. There is no established method to accurately predict and thus prevent capsule endoscope aspiration. Lack of symptoms associated with capsule inhalation can be dangerous as the capsule may remain in the airway until visualized on video, resulting in potentially life-threatening adverse event including respiratory failure [113]. Therefore, in elderly patients and in cases where capsule swallowing is difficult or symptomatic, post-capsule observation in real-time as possible is strongly recommended. Capsule aspiration should be considered an emergency. The presence of dysphagia is a relative contraindication to capsule endoscopy.

Most common technical complications were as short-life capsule batteries, downloading failure, failure of the localization software, recording gaps and inability

to activate the capsule. A review of 733 VCE studies underlined those technical limitations and failures were encountered in a small number of cases, mainly in the initial phase of capsule use and have been largely overcome with the use of improved equipment.

A more serious problem was the inability to download endoscopic images from the recorder to the workstation, hampering inspection and diagnosis of the records. Again, this problem occurred in only 5 cases (0.68%), limited to the early experience of each center. Overall, technical limitations prevented the diagnosis in 21/63 examinations (Rondotti 2005). Although the technology of capsule endoscopy has made significant progress, there are rare technical limitations and failures that hindered or prevented the diagnosis in a small number of cases.

One of the disadvantages of capsule endoscopy was the inability to maneuver the device and difficult to adjust the field of view as desired, stopping at a certain area for diagnostic or therapeutic purposes. It was also difficult to return to an area, re-observe, to accurately measure the lesion's size and to do biopsies. The overall miss rates of SBCE for small bowel tumors and ulcers were 18.9% and 0.5%, respectively [114]. These shortcomings can be overcome by adding the Magnetic assisted capsule endoscopy (MACE). MACE exanimated the gastrointestinal tract by control the location of the capsule endoscope swallowed by the patient using a magnetic field in real-time. The magnetic field generated outside the human body makes it possible to adjust a capsule endoscope equipped with a permanent magnet [115].

Finally, another limitation of using SBCE is the time it takes to read the results. Reliable and rapid reading of SBCE images remains a challenge, leading to missed lesions and inter-personal variability in interpreting results. Various software applications have been developed in recent years with the aim of reducing reading time by automatically selecting and interpreting images for diagnostic CDs (Quick view, top 100 images, Atlas). In addition, the use of artificial intelligence (AI) in medicine was rapidly progressing. In a recent review of AI applications in gastroenterology, various models have been analyzed in inflammatory lesions or gastrointestinal bleeding during wireless SBCE, demonstrating a high level of precision for disease detection [116]. This might represent a remarkable step forward in reducing the reading time. The efficacy of such technologies in IBD remains to be proven [51]. Therefore, the consideration reported in this carapter should be careful for further discussion and validation Despite these limitations, the NGT process is a valid method to systematically identify and prioritize ideas behind PCE for monitoring established CD. The role of SBCE for monitoring established CD in terms of target patient populations and benefits compared to other diagnostic modalities was undisputed. SBCE was an efficient method in a "treat-to-target" strategy for CD management and to prioritize efforts in further research needs. Future studies should focus on comparing the SBCE-guided approach to standard of care for all patients with established CD and involvement of both the colon and small bowel and should consider clinical, patient-reported, and economic outcomes.

4. Role in postoperative CD

In evaluating recurrence in patients with CD who underwent surgery, SBCE showed superior yield than ileocolonoscopy (62% vs. 25%), with the advantage of detecting proximal small bowel lesions. It is difficult to pass a surgical anastomosis

and observe the proximal part by ileocolonoscopy in patients who underwent side-to-side reconstitution of a neoiluem, which is why CE is more useful [117].

SBCE is also make use to diagnose recurrences of CD after surgery and VCE might increase diagnostic accuracy and impact therapeutic decisions.

After ileocolonic resection, clinical or surgical recurrence was frequently preceded by endoscopic recurrence of the neo terminal ileum in up to 70% of patients. Ileal lesions can be scored by Rutgreet's score at the first ileocolonoscopy (ideally at 6 months postoperatively) The Rutgeerts score (RS) was established to predict post operative recurrence and to lead medical therapy. However, this scoring system groups ileal and anastomotic injuries into the same category. A modified RS was developed to separate isolated anastomotic lesions and those in the neo-terminal ileum to further understand the role of anastomotic lesions in CD progression [80, 118]. Although ileo-colonoscopy was the standard method to diagnose postoperative CD recurrence, recent findings suggest that VCE was less sensitive in detecting recurrence in the neo-terminal ileum. However, VCE can identify two-thirds of the lesions that ileo-colonoscopy cannot reach [80]. Furthermore, studies indicated that ileal recurrence, rather than anastomotic recurrence, was a better predictor of CD's long-term outcomes [119]. As such in postoperative CD, VCE has the potential to improve clinical outcomes beyond the scope of ileo-colonoscopy.

5. Role in IBD unclassified

VCE plays a significant role in inflammatory bowel disease type unclassified (IBDU) since it provides visualization throughout the small bowel and contributes to its reclassification. A Lewis score of over 95% has a 90% sensitivity and 100% specificity in diagnosing CD [120].

In patients with IBDU, VCE can identify newly emerged small bowel lesions, which correspond to CD, in approximately 29–40% of cases [121]. This was particularly significant in pediatric IBD and can greatly influence treatment decisions [122]. Although VCE has high sensitivity to rule out small bowel involvement, up to 20% IBD-U patients with normal VCE can develop new small bowel lesions suggestive of CD on follow up.

Moreover, it is important to make a prompt diagnosis of IBD, it is equally important not to misdiagnose IBD. Since, there are many differential diagnoses which may have a similar presentation to IBD endoscopically, thus any significant findings on SBCE should be followed up with enteroscopy and biopsies according to ESGE Guideline (2023).

Furthermore, small bowel ruptures into the mucous membranes/lesions are common and asymptomatic and can lead to overdiagnosis of IBD. Besides, it is important to evaluate the role of SBCE on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU). An interesting retrospective study [123] including patients with IBDU undergoing SBCE was objectively assessed by determining the Lewis score (LS). SBCE lead to reclassification of disease from IBDU to definitive CD in 25% of cases. Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

The correct diagnosis of inflammatory bowel disease is extremely important to define prognosis, therapeutic orientation and surgical intervention.

6. Scoring systems

Nevertheless, there is a current lack of integrated evidence to guide optimal monitoring in terms of appropriate tools and timing Surveillance of established Crohn's disease through a "treat-to-target" strategy aimed at reducing and preventing long-term bowel damage and disability. Despite the availability of various monitoring techniques, comprehensive evidence for optimal monitoring in terms of appropriate tools and timing is currently lacking. In particular, whole-bowel video capsule endoscopy (PCE) allows noninvasive and direct visualization of the entire bowel, and its safety and efficacy have been demonstrated [51].

In this setting, SBCE may be particularly helpful in supporting decisions about escalating treatment for CD with persistent symptoms. In this case, a negative SBCE study indicates that symptoms are likely due to other non-inflammatory causes, such as IBD or bacterial overgrowth. If the test is positive, it is important to consider that the poor specificity and interobserver agreement of SBCE may lead to overtreatment of celiac disease in this setting. The Capsule Endoscopy Small Bowel CD Activity Index assessed inflammation, anatomic extent, and the presence of strictures was prospectively validated in a multicenter study. Finally, SBCE has also shown promise in postoperative recurrence monitoring, with excellent sensitivity but relatively low specificity compared with other modalities, including colon ultrasound and MRE [124]. Given the risks of capsule retention and the inability to obtain tissue samples, CE is unlikely to replace ileocolonoscopy as standard practice in patients undergoing ileocolectomy. However, it may still play a role in patients undergoing SB resection and entero-intestinal anastomosis inaccessible by standard endoscopy. An objective clinical activity score is recommended to assess disease severity, small bowel involvement, and response to drug therapy.

To determine disease severity, small bowel involvement and response to medical treatment, it's recommended to utilize objective clinical activity scores. It's important to note that while these scores can assess the type, location and severity of small bowel involvement, they cannot be utilized for diagnosing small bowel CD. The recent ESGE and ECCO guidelines supported the use of endoscopic activity scores for the classification of inflammatory activity in patients with CD undergoing SBCE, such as the Lewis score or the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) [52]. CECDAI, which evaluates inflammation severity, disease extent and stenosis, is a simpler alternative to LS and has been shown to be more reflective of active small bowel inflammation in comparative studies [125]. Although there's a strong correlation between LS and CECDAI, only moderate correlation was observed with stool biomarkers such as fecal calprotectin. A recent study found a LS range of 135–790 to be equivalent to a CECDAI score of 4.9–6.9.

The recent ESGE and ECCO guidelines supported the use of endoscopic activity scores for the classification of inflammatory activity in patients with CD undergoing SBCE, such as the Lewis score or the CECDAI. It is unclear whether these indexes are interchangeable for the evaluation of mucosal inflammation in established Crohn's disease.

The Lewis score (LS) was developed to differentiate between significant and nonsignificant inflammation of the intestine, as well as to assess inflammatory activity [126]. In particular, LS is based upon distribution and presence of ulcers villous edema and stenosis. The LS divided the small bowel into three equal tertiles (by small bowel transit time) and for each tertile, villous edema and ulcers are assessed based on its characteristics and extension. The final score results of the sum of the tertiles

with the highest score for villous edema and ulcers, plus the stenoses score rated for the whole examination It consists of dividing the SB into 3 equal parts (tertiles) based on SB capsule transit time and assigning a sub- score to each tertile based on the degree of edema or ulceration. The sum of the worst affected tertile is then added to a stenosis score (**Table 4**). LS score in the reading software for the automatic calculation has been incorporated into PillCam platfor. A score < 135 indicates normal or clinically insignificant mucosal inflammatory changes, 135–790 indicates mild inflammation, and a score ≥ 790 indicates moderate-to-severe inflammation. The application of LS ≥135 as the cutoff value for the presence of significant inflammatory activity in patients undergoing SBCE for suspected CD may be useful to establish the diagnosis of CD. Based on assessments of villous edema, ulcers, and stenosis, the LS classifies CD activity from mild to severe. The SBCE detects nonspecific lesions of CD, and the LS assesses the grade of inflammatory activity regardless of the etiology. In literature a series of study [127, 128] including patients with suspected CD submitted to SBCE and with a large period of follow-up after the capsule underlined that the application of LS ≥135 as the cutoff value for the presence of significant inflammatory activity in patients undergoing SBCE for suspected CD has a high sensitivity and specificity and may be useful to establish the diagnosis, when integrated with other relevant diagnostic elements.

The CECDAI or Niv score is another prospectively validated scoring system.

CECDAI assesses the severity of inflammation, stenosis, and the extent of disease (**Table 5**). In a comparison study, CECDAI emerged as a simpler and more accurate indicator of active small bowel inflammation than LS [55]. CECDAI was validated in multicenter prospective study of patients with isolated small-bowel CD [129], summing up the score in the proximal and distal portions of SB (based on transit time) across the three endoscopic parameters:: inflammation (A, 0 to 5 points), extent of disease (B, 0 to 3 points), and strictures (C, 0 to 3 points), both for the proximal and distal 10 segments of the small bowel based on the transit time of the capsule (**Table 3**). Even if no clear cut-off for inflammatory severity has been validated for the CECDAI score, the values of 3.8 and 5.8 correlate approximately to the 135 and

Parameters	**Number**	**Longitudinal extent**	**Descriptors**
Villous appearance	Normal—0	Short segment—8	Single—1
	Edematous—1	Long segment—12	Patchy—14
	>8	Whole tertile—20	Diffuse—17
Ulcer	None—0	Short segment—5	<1/4– 9
	Single—3	Long segment—10	1/4–1/2–12
	Few—5	Whole tertile—15	>1/2–18
	Multiple—10		
Stenosis (rated for the whole study)			
Stenosis	None—0	Ulcerated—24	Traversed—7
	Single—14	Non-ulcerated—2	Not traversed—10
	Multiple—20		

Lewis score = tertile with highest score (result of oedema and ulcers) plus score of stenosis for the entire small bowel.

Table 4.
Lewis score.

Parameters	Score
A. Inflammation score	0 = None
	1 = Oedema/hyperaemia/denudation (mild to moderate)
	2 = Oedema/hyperaemia/denudation (severe)
	3 = Bleeding, exudate, aphthae, erosion, ulcer <0.5 cm
	4 = Ulcer 0.5–2 cm, pseudopolyp
	5 = Large ulcer >2 cm
B. Extent of disease score	0 = No disease (normal examination)
	1 = Focal disease (single segment
	2 = Patchy disease (2–3 segments)
	3 = Diffuse disease (>3 segments)
C. Stricture score	None – 0
	1 = Single-passed
	2 = Multiple-passed
	3 = Obstruction (non-passage)
Segmental score (proximal or distal) = (A × B) + C	
Total score = **proximal** [(A × B) + C + **distal** (A × B) + C]	

Table 5.
CECDAI (Niv score) for capsule endoscopy.

790 cut-offs of the Lewis score, respectively. Lastly, measuring the extent and severity of inflammation is important in established small bowel CD as a "Treat to target" strategy based on mucosal healing can reduce disease related complications leading to surgery and hospitalization. SBCE could be useful for refining disease location and prognosis, assessing mucosal healing in patients receiving treatment, and monitoring patients in the post-operative setting.

7. Capsule endoscopy and artificial intelligence

An important limitation to the applicability of VCE in daily practice is the substantial time required to review images acquired during capsule endoscopy. Artificial intelligence (AI) is being tested to reduce review time and obtain accurate diagnoses without missing any lesions. Deep learning-based methods, especially convolutional neural networks (CNN), have been used in capsule endoscopy to detect bleeding, vasodilation, ulcers, cancer, and hookworms. The sensitivity and accuracy in detecting these lesions is close to 100% [125]. The AI model proved effective in detecting colorectal polyps or tumors, achieving high sensitivity of 47.4–98.1% and high specificity of 87.0%–96.3% in each frame analysis [130]. An evolution of AI research is capsule endoscopy (CE), with several publications evaluating the role of deep learning in automatic detection of inflammatory lesions, vascular lesions, [131–133] herniated and neoplastic lesions/mass, and assessment of bowel cleanliness [134]. However, many challenges remain to translate the impressive experimental capabilities of AI in CE into clinical practice. Some of these challenges include standardizing results, validating established endpoints, creating common datasets

and computational methods, and linking to clinical outcomes. These challenges are in part common to other areas of gastrointestinal endoscopy and general medicine [135]. In recent studies [136] all methods and study designs used were heterogeneous. Therefore, a formal meta-analysis of all literature studies could not be performed. Most studies have limited sample sizes and cannot test the performance of their AI models. Especially for research using machine learning or deep learning, a large fraction of CCE images is required to train the model, which limits the number of remaining images to test the model. Practical implementation of AI review of CCE-2 colon images was a critical step towards the applicability of CCE in daily clinical practice. In order to be able to fully assess the added value of the AI method, the study should always indicate the version of the capsule used and the accuracy of its model in terms of sensitivity and specificity. Furthermore, studies would be better off using only results from experienced CCE readers to test the performance of their AI methods, as the sensitivity and specificity of findings represent the ability of AI models to achieve the same level of performance as these readers. There is no doubt that AI has potential benefits for both physicians and patients, but applying it to clinical practice is challenging. While the U.S. Food and Drug Administration (FDA) has approved some assistive algorithms, there are currently no guidelines specific to AI's role in disability [137].

8. Conclusion

SBCE was safe, highly sensitive but not specific for detection of mucosal inflammation in small bowel CD [138]. SBCE played a pivotal role in suspected and established CD (**Figure 2**) and its was a useful tool for approaching therapeutic management in CD patients both for treatment escalation and de-escalation.

Therefore, in suspected CD with negative ileo-colonoscopy, SBCE was a reliable diagnostic tool for assessment in the absence stenotic lesions that prevent its passage and thus necessitate further invasive diagnostic modalities. Hence, fecal calprotectin

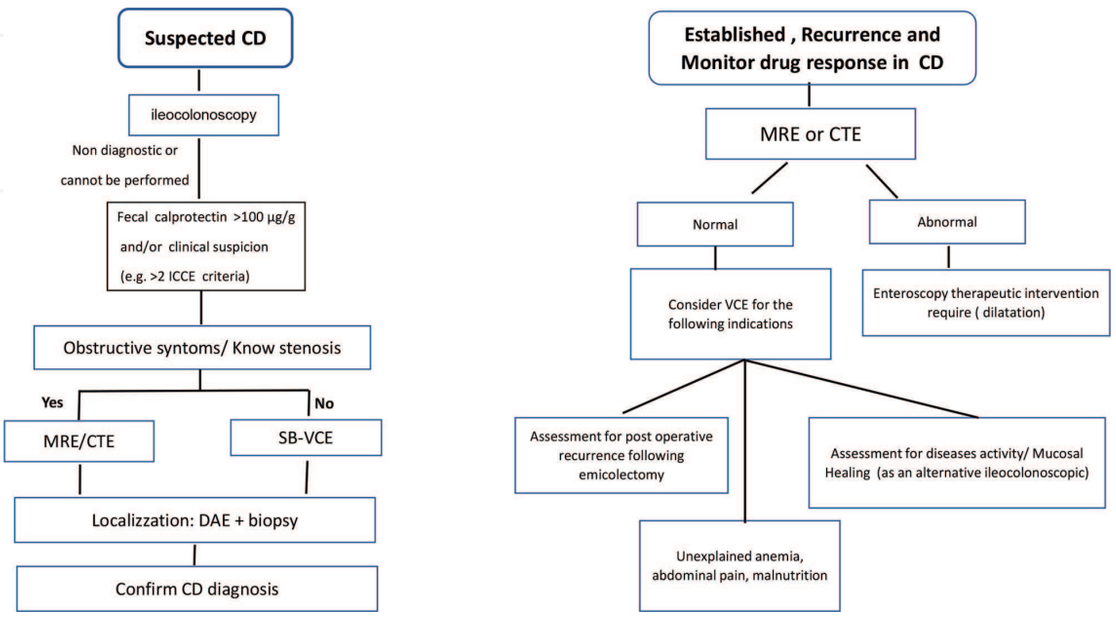

Figure 2.
Suggested diagnostic algorithm for the use of small bowel capsule endoscopy in CD.

can be used as a tool for selecting patients with suspected small bowel CD for SBCE. In the presence of obstructive symptoms or known stenosis, MRE/CTE should be preferred over VCE given the high risk of capsule retention.

In established CD, SBCE can help in detecting precise disease location, disease severity, monitoring response to therapy and mucosal healing. In post-operative SB disease, SBCE may be helpful to evaluate recurrence. After 20 years since its introduction, with all the above knowledge in mind, it is plausible to conclude that utilization of SBCE is safe if current indications are respected and it has significantly contributed to the knowledge of pathologies of the small bowel and to their therapy, through the production of a florid and large amount of scientific literature.

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