


Review

# Endoscopic Evaluation and Therapeutic Considerations of Small Bowel Crohn's Disease

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**Abstract:** Small bowel evaluation is warranted in all newly diagnosed cases of Crohn's disease (CD) as small bowel is involved in two-thirds of CD patients at diagnosis and the involvement can be discontinuous. Endoscopic evaluation of the small bowel in suspected or established CD can be done by video capsule endoscopy (VCE), device assisted enteroscopy (DAE) (which includes single and double balloon enteroscopy, novel motorized spiral enteroscopy (NMSE) and balloon guided endoscopy (BGE)) and intra-operative enteroscopy (IOE). In suspected CD with a negative ileo-colonoscopy, VCE is the preferred initial diagnostic modality in the absence of obstructive symptoms or known stenosis. VCE should be preceded by cross-sectional imaging or patency capsule testing if obstruction is suspected given with high retention risk. In established cases, small bowel cross-sectional imaging (magnetic resonance or computed tomography enterography) is preferred over VCE as it can assess transmural and extra-luminal involvement. VCE is indicated subsequently if necessary to assess disease extent, unexplained symptoms (e.g., anemia, malnutrition) or mucosal healing. Pan-enteric capsule endoscopy (PCE) and the use of artificial intelligence are the recent developments with VCE. DAE with small bowel biopsy can provide definitive evidence of CD including the extent and severity. A final diagnosis of CD is based on the constellation of clinical, radiologic, histologic and endoscopic features. Newer technologies like NMSE and BGE can help with deeper and faster small bowel evaluation. DAE has also allowed endoscopic treatment of small bowel strictures, small bowel bleeding and retrieval of retained capsule or foreign bodies. Endoscopic balloon dilation (EBD), endoscopic electro-incision, strictureplasty and stenting have shown promising results in CD related small bowel strictures. In conclusion, endoscopic evaluation of the small bowel is rapidly evolving field that has a major role in diagnosis and management of small bowel CD and can alter treatment outcomes in properly selected patients.

**Keywords:** Crohn's disease; capsule endoscopy; device assisted enteroscopy; small bowel endoscopy; endoscopic balloon dilation



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## 1. Introduction

Crohn's disease (CD) is a chronic idiopathic, inflammatory bowel disease that can involve any part of the gastrointestinal tract. It is characterized by mucosal and transmural inflammation and even extra-mural involvement in the form of abscess and fistula [1]. Therefore, apart from cross-sectional imaging modalities, gastrointestinal mucosal assessment is necessary. This is traditionally done by ileo-colonoscopy as the terminal ileum is the most common site involved. Upper gastrointestinal endoscopy is warranted if upper GI symptoms are present. However, CD can affect the intestine in a discontinuous manner and isolated involvement of proximal small intestine can occur in up to one third of cases. A negative ileo-colonoscopy thus does not rule out CD and the small bowel should be assessed in both suspected and established CD [2].

There are various modalities of small bowel assessment that are evolving rapidly. Traditionally, this was done by radiological imaging that has evolved from small bowel follow through (SBFT) to dedicated cross sectional imaging modalities like computed tomography (CT) enterography/enteroclysis and more recently magnetic resonance enterography (MRE).

Direct endoscopic visualization of small bowel mucosa has today shifted the paradigm of diagnosis providing histopathologic evidence to rule out infective and neoplastic causes of small bowel ulcerations. This can be done by flexible endoscopes that are advanced through the small intestine assisted by balloon (single balloon enteroscopy (SBE) and double balloon enteroscopy (DBE)) and more recently, balloon guided enteroscopy (BGE) and motorized spiral enteroscopy (NMSE) [3–5]. Faster and deeper small bowel endoscopic assessment can now be done by new and evolving advances in small bowel endoscopy with an increase in therapeutic enteroscopy [6]. Video Capsule Endoscopy (VCE) enables visualization of the entire small bowel mucosa less invasively than flexible endoscopes. With the evolution of technology, pan-enteric capsule endoscopy (PCE), which can enable visualization of both small and large bowel mucosa, can become the ideal noninvasive diagnostic tool. However, careful patient selection and cross-sectional imaging or patency capsule testing is warranted before proceeding to VCE in case of suspected or established CD given the higher risk of capsule retention than in the general population [7].

In fact, with the advent of VCE and dedicated small bowel cross-sectional imaging (CTE/MRE), the role of small bowel enteroscopy in suspected or established CD is primarily histological confirmation and therapeutic interventions. In this review, we have critically evaluated the current role of the various small bowel endoscopic modalities for evaluation and management of suspected or established small bowel CD. This review comprehensively sums up the existing, emerging, and ever-expanding literature in this field and highlights areas of future study.

## 2. Endoscopic Evaluation of Small Bowel Crohn's Disease

### 2.1. Indications of Small Bowel Endoscopy in CD

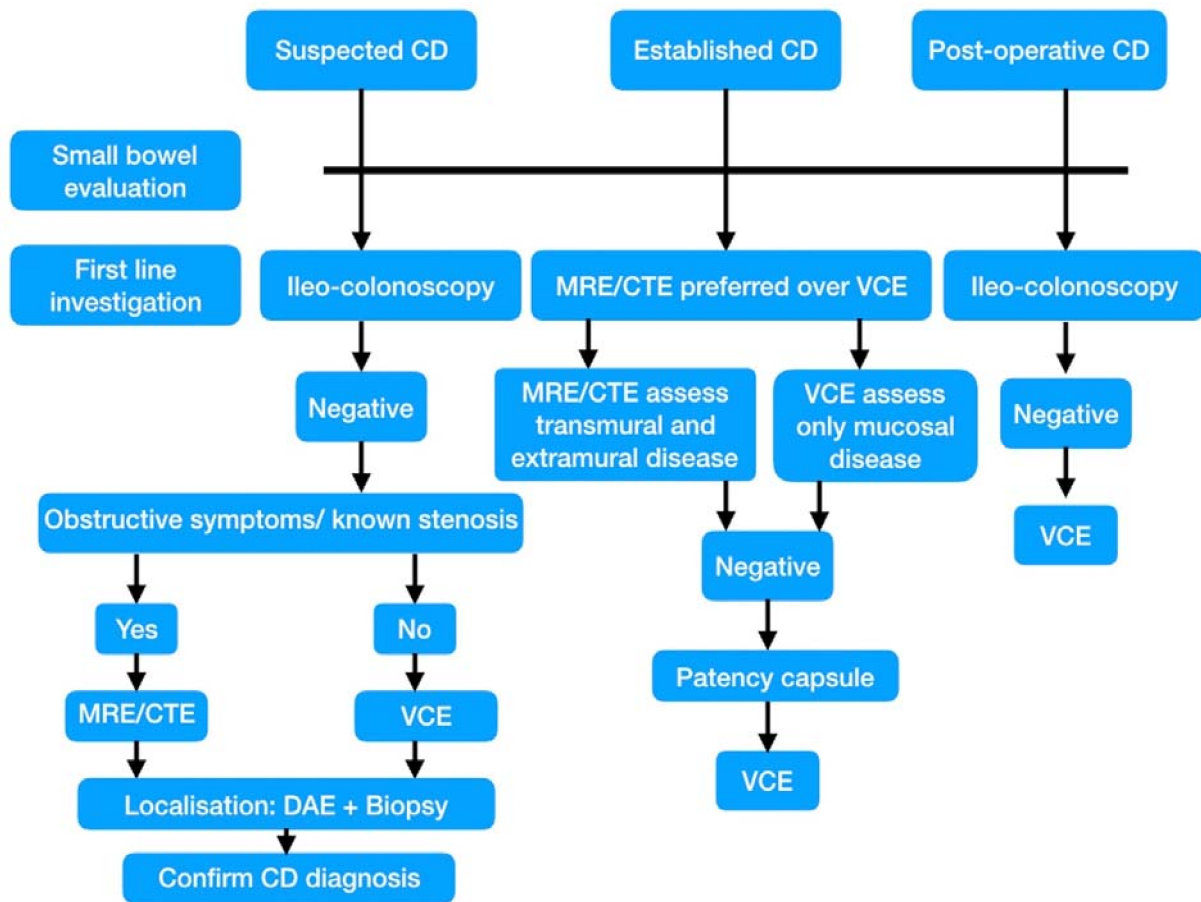
- (1) Suspected isolated small bowel CD [8];
- (2) Small bowel evaluation in patients with confirmed CD [9];
- (3) Assessment for post-operative CD recurrence in small bowel after ileo-colonic resection [10];
- (4) Small bowel evaluation in IBD-unclassified and disease reclassification [8];
- (5) Therapeutic interventions in small bowel CD (stricture dilatation, retained capsule or foreign body retrieval, hemostasis for small bowel bleed) [8].

### 2.2. Role of Small Bowel Endoscopy in Suspected and Established CD

Small bowel involvement is seen in two thirds of CD patients and among them 90% have the involvement of terminal ileum [11]. Hence, in suspected small bowel CD, ileo-colonoscopy is the first line of investigation [12]. VCE is the next diagnostic modality in cases with suspected CD and negative ileo-colonoscopy in the absence of obstructive symptoms or known stenosis (Figure 1). In the presence of obstructive symptoms or known stenosis, MRE/CTE should be preferred over VCE given the high risk of capsule retention. In isolated small bowel involvement in suspected CD on VCE or MRE/CTE, DAE with a small bowel biopsy can provide definitive evidence of CD. This is particularly important in resource limited countries where infections (e.g., tuberculosis) still predominate and need to be excluded prior to initiation of therapy [13].

Small bowel evaluation is warranted in every case of established CD, as the small bowel is involved in two thirds of CD, which can be discontinuous. In established CD, CTE/MRE is preferred over VCE due to its potential to assess transmural and extra-luminal disease. VCE is indicated subsequently if cross-sectional imaging is non-contributory preferably after patency capsule testing. VCE can better evaluate mucosal healing, unexplained pain/anemia, malabsorption and early post-operative recurrence compared to cross-sectional imaging, especially in non-stricturing CD [8]. In established CD, DAE is indi-

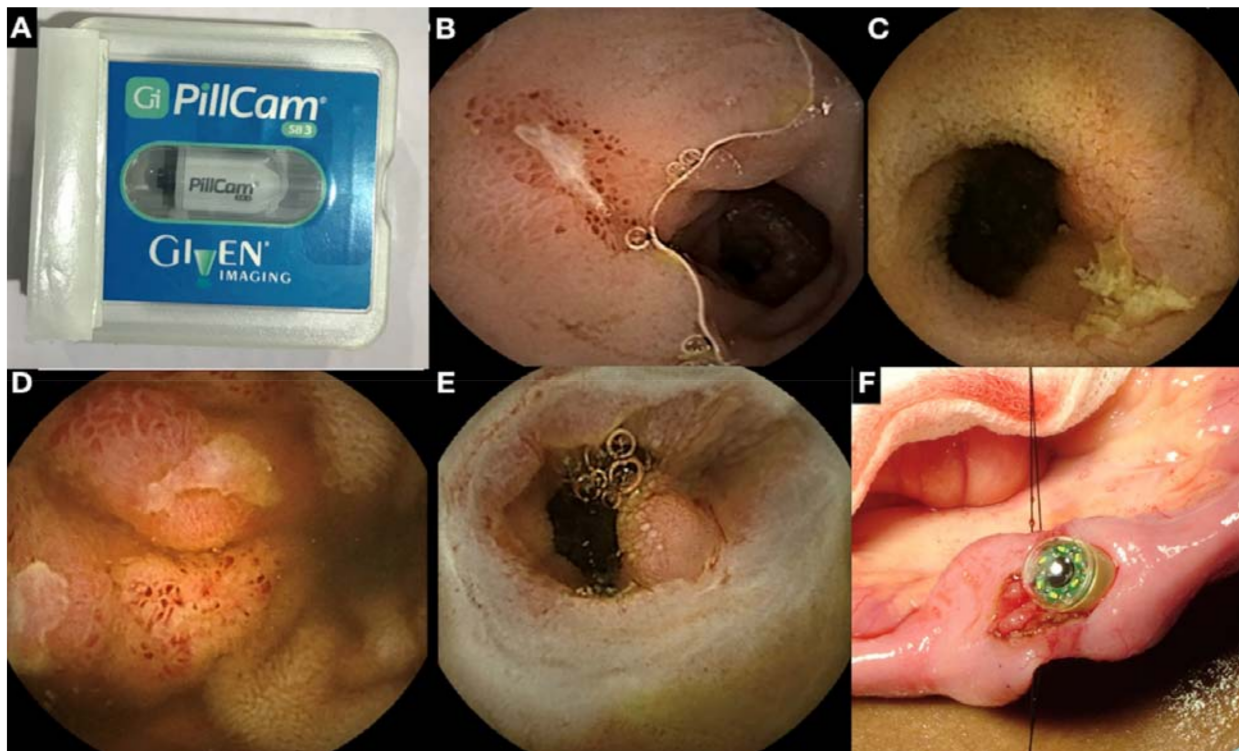
cated for endoscopic treatment of small bowel strictures (balloon dilatation, stricturoplasty and stenting), small bowel bleed and foreign bodies/retained capsule retrieval [9].



**Figure 1.** Algorithm for small bowel evaluation in a suspected, established and post-operative Crohn's disease (CD). DAE—Device assisted enteroscopy, MRE—Magnetic resonance enteroclysis, CTE—computed tomography enteroclysis, VCE—video capsule endoscopy.

### 2.3. VCE in Small Bowel CD

VCE is highly sensitive but not specific for detection of mucosal inflammation in small bowel CD (Figure 2). Hence, in suspected CD, VCE is useful in ruling out the diagnosis especially if ileo-colonoscopy and cross-sectional imaging are negative. In established CD, VCE can help in detecting precise disease location, disease severity and monitoring response to therapy [7]. VCE can better detect subtle mucosal abnormalities in both suspected and established CD (Figure 2B–E) [14]. The major drawback of VCE in small bowel CD are false positive diagnosis and high risk of capsule retention (Figure 2F). The later can be reduced by prior cross-sectional imaging and use of patency capsule [7].



**Figure 2.** Video capsule endoscopy (VCE) for small bowel Crohn's disease (CD). (A) Video capsule endoscope for small bowel (PillCam, Given imaging Ltd., Yokneam Illit, Israel); (B) Aphthous ulcer seen on VCE in a case of suspected small bowel CD; (C) Small ulcer seen on VCE in CD; (D) Hyperemia, superficial ulcers and edematous mucosa on VCE in a case of CD. (E) Ulcerated stricture in CD; (F) Retained capsule removed at laparotomy.

### 2.3.1. Comparison of VCE with Other Diagnostic Modalities

VCE has a distinct advantage over cross-sectional imaging (CTE/MRE) in small bowel CD as it directly visualizes the small bowel mucosa and can detect subtle mucosal abnormalities [7]. In a meta-analysis of 12 studies including more than 400 patients, VCE had better diagnostic yield compared to small bowel radiology, CTE and ileo-colonoscopy in suspected CD and was a better diagnostic modality in established CD as well [14]. However, the majority of this incremental diagnostic yield could be attributed to false positives in VCE as the positive predictive value of positive VCE findings such as "more than 3 ulcers" reported to be only 50% at 12 months [15]. Moreover, these studies have significant selection bias. The only prospective blinded study comparing these modalities showed that diagnostic yield of VCE (83%) was not different from others including CTE (83%). The specificity of VCE was quite low (53%) [16]. This, combined with need for prior small bowel cross-sectional imaging, precluded the use of VCE as a first line diagnostic test in suspected CD. In a retrospective study comparing MRE and VCE, VCE detected more small bowel lesions compared to MRE, especially proximal and superficial lesions [17]. Meta-analyses have shown that VCE, MRE and small intestinal contrast ultrasound (SICUS) have similar diagnostic yield, except in the proximal bowel where VCE performs better than MRE. However, risk of capsule retention should be kept in mind [18]. In a prospective blinded study of 93 patients, the sensitivity and specificity of VCE (100% and 91%) were higher than that of CTE (76% and 85%) and MRE (81% and 86%). Proximal small bowel lesions were detected in 16 patients in VCE compared to only two patients with MRE/CTE. Only two patients had additional small bowel stenosis who did not have obstructive symptoms and underwent complete ileo-colonoscopy [19]. Therefore, it was concluded that CE is the first line modality for detecting small bowel CD in the absence of clinical suspicion of stenosis.

### 2.3.2. VCE in Suspected Small Bowel CD

VCE has high sensitivity (93%) for the diagnosis of small bowel CD with a high negative predictive value (96%) [20,21]. However, due to high false positive rates and consequent low specificity, VCE should be used for exclusion of CD rather than for confirmation of diagnosis [7]. Non-steroidal anti-inflammatory drugs (NSAIDs) and other drug induced enteropathy, infections (e.g., small intestinal tuberculosis), autoimmune enteropathy, radiation enteritis and immunodeficiency can mimic CD on VCE [22,23]. Hence, NSAIDs should be discontinued for at least 4 weeks prior to VCE. In this regard, disease biomarkers such as fecal calprotectin could be useful in selecting patients for CE in suspected CD, as it helps exclude non-inflammatory small bowel lesions. A recent meta-analysis has identified that a fecal calprotectin cut off of more than 100 µg/g has highest diagnostic accuracy (sensitivity and specificity 73% and diagnostic odd ratio 7.89) [24]. Hence, fecal calprotectin can be used as a tool for selecting patients with suspected small bowel CD for VCE. Therefore, in suspected CD with negative ileo-colonoscopy, VCE is indicated in the absence of obstructive symptoms and known stenosis [25].

### 2.3.3. VCE in Established Small Bowel CD

#### Assessing Distribution and Monitoring Disease Activity: The VCE Scores

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 [26]. Criteria of more than three ulcers proposed by Mow et al. has modest positive predictive value of 50–70% to diagnose small bowel CD but does not give any idea on the extent and severity of mucosal inflammation [27]. The Lewis score (LS) and capsule endoscopy Crohn’s disease activity index (CECDAI) assess the disease extent, severity of mucosal inflammation and presence of stenosis (Tables 1 and 2) [28,29]. The scores are based on a similar principle but differ in the way they are measured. CECDAI is simpler to use and was shown to be more reflective of small bowel inflammation, according to a comparative study [30]. There is strong correlation between the two scores as an LS of 135–790 was shown to be equivalent to a CECDAI score of 4.9–6.9 [30,31]. There is moderate correlation with biomarkers such as fecal calprotectin. Although incorporation of these scores in clinical practice can improve clinical outcomes and larger prospective, validation is warranted [7].

VCE can be useful for detecting occult small bowel inflammation in patients with irritable bowel syndrome (IBS) type symptoms in CD with normal ileo-colonoscopy and cross-sectional imaging [32,33]. Fecal calprotectin as a measure of small bowel inflammatory activity is uncertain in this regard [34]. However, the potential of VCE to over diagnose CD should be borne in mind.

VCE have been shown to diagnose jejunal lesions in more than half of the patients with CD. Jejunal lesions were associated with relapsing disease [35].

Although proximal and superficial small bowel lesions are better identified by VCE than MRE, the risk of capsule retention especially in presence of strictures and frequent incomplete bowel examinations should be kept in mind [36].

**Table 1.** Lewis Score for the assessment of small bowel lesions using small bowel capsule endoscopy.

Parameters	Number	Longitudinal Extent	Descriptors
First tertile			
Villous appearance	Normal—0	Short segment—8	Single—1
	Edematous—1	Long segment—12	Patchy—14
		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		

Table 1. Cont.

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

**Table 2.** The capsule endoscopy Crohn's disease activity index (CECDAI) for the assessment of small bowel lesions using video Capsule Endoscopy.

CECDAI Scoring System		
CECDAI	Proximal	Distal
A. Inflammation score		
0 = None		
1 = Mild to moderate edema/hyperemia/denudation		
2 = Severe edema/hyperemia/denudation		
3 = Bleeding, exudate, aphthae, erosion, small ulcer ( $\leq 0.5$ cm)		
4 = Moderate ulcer (0.5–2 cm), pseudopolyp		
5 = Large ulcer (2 cm)		
B. Extent of disease score		
0 = None		
1 = Focal disease (single segment)		
2 = Patchy disease (multiple segments)		
3 = Diffuse disease		
C. Narrowing (stricture)		
0 = None		
1 = Single-passed		
2 = Multiple-passed		
<b>Segmental score = (A × B) + C</b>		
<b>Total score = ((A1 × B1 + C1) + (A2 × B2 + C2))</b>		

### Mucosal Healing and Treat to Target

As mentioned above, mucosal healing as treatment target in small bowel CD can improve long term outcomes. A sequential capsule endoscopy study in CD has shown a poor correlation between endoscopic mucosal healing and clinical disease activity scores/inflammatory markers [37]. Deep remission rates of 42% can be achieved with anti-tumor necrosis factor (TNF) therapy or thiopurines, which is comparable to deep remission rates in colon and terminal ileum [38]. There is insufficient information on the temporal relationship and differences between healing of colonic and small bowel lesions. Incomplete VCE examinations, risk of capsule retention especially in the presence of strictures and routine requirement of prior patency capsule testing are the drawbacks of VCE in monitoring small bowel disease [36]. Capsule endoscopes with longer battery life and pan-enteric capsules can overcome the existing drawbacks. Nevertheless, VCE is an emerging tool for surveillance of small bowel CD.

### Evaluation of Unexplained Anemia or Obscure GI Bleed in CD

Meta-analysis has shown that VCE has highest diagnostic yield while investigating obscure GI bleed compared to small bowel radiology, CTE and push enteroscopy [39].

### Assessment of Postoperative CD Recurrence

Bowel resection is eventually required in 75% of CD patients over 20 years of follow up. On the other hand, post-resection recurrent CD affects 70% patients 20 years post-surgery. Ileo-colonoscopy is the test of choice to diagnose post-operative recurrence of CD. The sensitivity of VCE is lower than ileo-colonoscopy in detecting recurrence in the neo-terminal ileum. Two thirds of the lesions beyond the reach of ileo-colonoscopy can be detected by VCE [40]. Emerging data shows that VCE have incremental diagnostic yield compared to ileo-colonoscopy especially for proximal lesions and can lead to a change in management in more than half of the patients [41]. According to a recent study, ileal recurrence is more likely to predict long term outcomes in CD compared to anastomotic recurrence [42]. Hence, VCE could have the potential to improve clinical outcomes in postoperative CD beyond the scope of ileo-colonoscopy. Moreover, patient acceptance is usually better for VCE than ileo-colonoscopy in this regard due to its non-invasiveness.

### Classification of IBD-Unclassified (IBD-U)

IBD-U refers to inflammatory colitis that cannot be classified into UC or Crohn's colitis. This is important as surgical management differs between the two. Small, uncontrolled studies have demonstrated that VCE can detect new small bowel lesions compatible with CD in 29–40% patients of IBD-U [43,44]. This can impact management especially in pediatric IBD [45]. 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 [46].

### Mimics of Crohn Disease on Capsule Endoscopy

NSAID induced enteropathy is the most common CD mimic on VCE. On VCE, the most common finding is mucosal breaks, and presence of diaphragms (circumferential thin membrane) is characteristic. Most of the cases are asymptomatic but iron deficiency anemia due to acute and chronic gastrointestinal hemorrhage and intestinal obstruction are the main complications. Other presentations are protein losing enteropathy and malabsorption syndrome. Risk of capsule retention is high in NSAID induced enteropathy. Treatment with enteroscopy guided dilation carries a low risk of perforation as the diaphragms do not include muscularis propria [47].

Differentiating small bowel tuberculosis (SBTB) from small bowel CD could be a diagnostic challenge in a tuberculosis endemic area. In prospective study on VCE, ileocecal valve involvement was more common in SBTB whereas aphthous ulcers were less

frequent compared to CD. Proximal small bowel involvement was seen only in SBTB, although it was not statistically significant [48].

Cryptogenic multifocal ulcerating stenosing enteropathy (CMUSE) presents with chronic abdominal pain and GI blood loss due to idiopathic strictures in the absence of systemic inflammation. VCE carries very high risk of retention and small bowel endoscopy shows shallow, superficial ulcers. Biopsy shows non-specific inflammation limited to submucosa. Although termed cryptogenic, genetic defects in prostaglandin function (e.g., solute carrier organic anion transporter family, member 2A1-SLCO2A1 gene) have been identified [49].

Radiation enteritis presenting with chronic abdominal pain, anemia and VCE showing erythema and mucosal enema can resemble small bowel CD. History of radiation and histology could be helpful in differentiation [50]. Eosinophilic enteritis can show ulcerations and even strictures mimicking CD, which can be differentiated on histology [51]. Autoimmune enteropathy presenting with sprue like diarrhea and malabsorption without dietary triggers can show villous blunting and scalloping on VCE and the histopathology is diagnostic [52]. Behcet's disease and malignancy of the small bowel (e.g., lymphoma, adenocarcinoma) can also present as small bowel strictures [53].

#### Capsule Retention

Risk of capsule retention in the general population, suspected CD and established CD are 1–2.5%, 2.6% and 13%, respectively, in the pre-patency capsule era [54]. Current meta-analysis reports retention rates of 2.45% and 4.63% in suspected and established CD, respectively. The retention rates are 2.32% and 2.68%, respectively, when prior cross-sectional imaging and patency capsule testing has been done [55].

Retained capsule should be treated with an observant, conservative approach followed by medical therapy with steroids and biologics failing which endoscopic retrieval or surgery should be attempted [56].

#### Patency Capsule

Patients with suspected CD at risk of capsule retention (obstructive symptoms or known stenosis) and all patients with established CD should undergo either cross-sectional imaging or patency capsule testing prior to VCE [57]. The two currently available patency capsules (Given and Agile) differ in the number of timer plugs (Given 1 and Agile 2), dissolution start time (Given 40–100 h and Agile 30 h) and composition (Given capsule: lactose, Agile capsules: dissolvable compounds surrounding radio frequency identification tag detectable by X-ray) [58]. Symptomatic intestinal obstruction due to patency capsule is rare and mostly managed conservatively [59]. Drawbacks of patency capsule testing is false positive rates that can be reduced by low dose, spot computed tomography (CT), which determines precise location of capsule. False positive results are common due to colonic retention as a result of prolonged transit time. This can markedly reduce false positive patency testing [60].

#### Pan-Enteric Capsules

Pan-enteric capsules can evaluate both small bowel and colon. Better diagnostic yield than ileo-colonoscopy (69.7%) have been reported with pan-enteric capsule endoscopy (83.3%) [61]. In pediatric CD, pan-enteric capsules can have comparable sensitivity to ileo-colonoscopy and MRE according to preliminary data [62].

#### Application of Deep Learning Technology for VCE in CD

Substantial progress has been made in the application of deep learning technology using an artificial neural network for VCE in CD. Automated, fast detection of CD related ulcers and strictures have been reported with high accuracy in recent studies [63,64]. Convolutional neural networks for grading CD ulcerations have shown high accuracy in grading of CD ulcers specifically identifying severe CD related ulcers [65].



#### 2.4. Enteroscopy in CD

Device assisted enteroscopy (DAE) techniques include double balloon enteroscopy (DBE), single balloon enteroscopy (SBE), balloon guided enteroscopy (BGE) and novel motorized spiral enteroscopy (NMSE).

##### 2.4.1. SBE/DBE

SBE is technically easier due to the absence of any balloon at the tip of the enteroscope, unlike DBE. However, DBE has relatively higher depth of insertion, advantageous in presence of adhesions and is less prone to backward slippage during retrograde enteroscopy than SBE [66]. The majority of the studies on DAE in CD are based on DBE than SBE.

##### 2.4.2. BGE

Balloon guided enteroscopy (BGE) is a novel through the scope (TTS), on-demand balloon assisted enteroscopy performed by the push pull technique with the help of a disposable advancing balloon through the working channel (diameter 3.7 mm) of a colonoscope. Therapeutic procedures can be performed through the working channel after removing the balloon. Shorter procedure time, easier learning curve and obviating need for enteroscope and over-tube are the advantages while a relative lack of stability is the disadvantage. This was circumvented by integration of a latex free balloon at the bending section of the colonoscope. The safety and feasibility has been proven in adults as well as in a pediatric group [4,67]. Depth of insertion from trans-oral and trans-anal routes were 158 cm (50–350 cm) and 89 cm (20–150 cm), respectively, and the average procedure time was 15.5 min in adult multi-center study [67]. In the pediatric population, reported depth of insertion were 138 cm (range 100–190 cm) and 143 cm (range 100–170 cm) via antegrade and retrograde routes, respectively. Average procedure time was very low (21.9 min and 12.8 min in the antegrade and retrograde routes, respectively) [4].

##### 2.4.3. NMSE

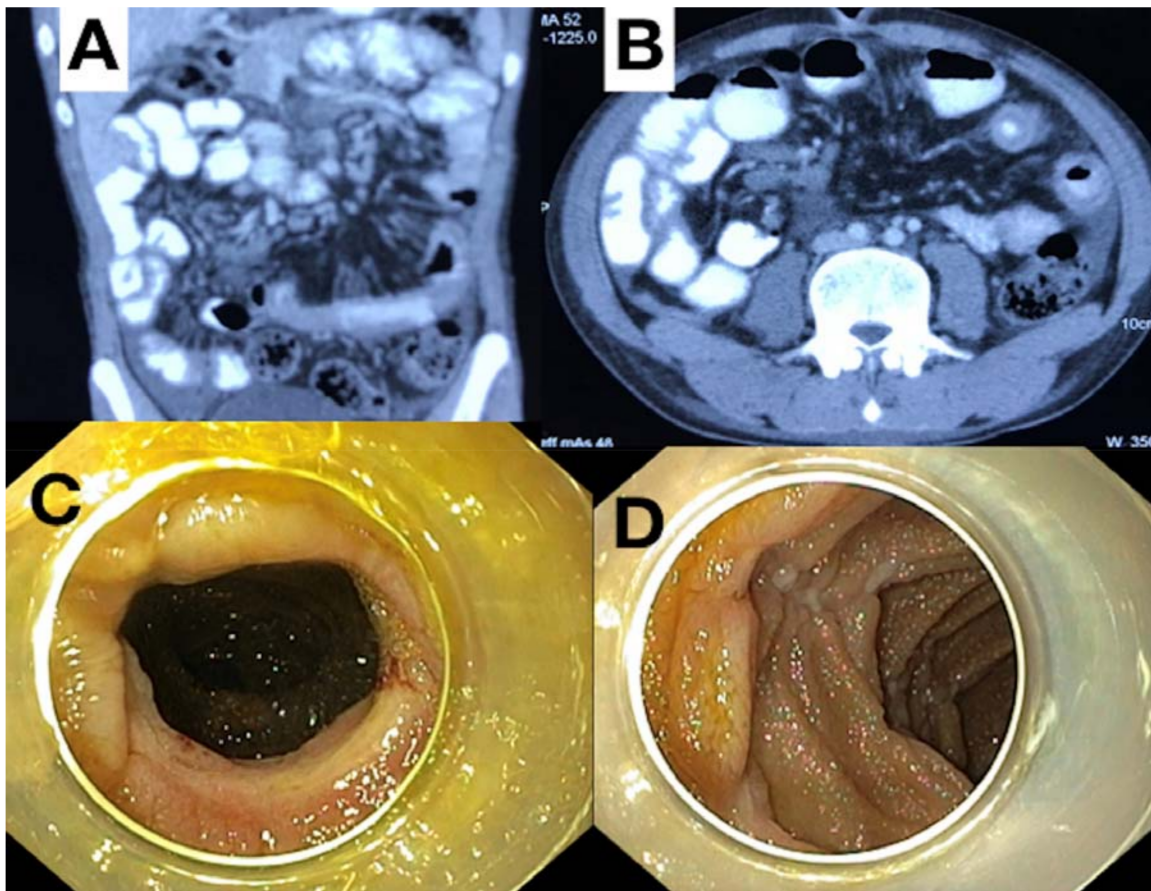
Conventional spiral enteroscopy uses over-tube with raised spiral edges that is rotated clockwise for advancement of enteroscope pleating small bowel loops. NMSE is composed of a reusable endoscope with an integrated motor, which permits rotation of a short spiral over-tube in the insertion tube portion of the endoscope. Short procedure time, larger working channel (3.2 mm), high diagnostic yield (>80%), greater depth of insertion and higher total enteroscopy rates (>60% with combined antegrade and retrograde approach) are the advantages of NMSE [5].

In a recent large, single center, retrospective study, out of 61 cases of NMSE, the majority were inflammatory lesions (41%) including CD, TB and CMUSE. Therapeutic interventions were done in one quarter of patients, which included stricture dilatation and retrieval of retained capsule [5,68]. NMSE is not suitable in pediatric patients due to large diameter of the over-tube and is technically difficult in post-operative patients due to adhesions.

##### 2.4.4. DAE in Suspected CD

DAE is indicated for confirmation of diagnosis when CD is suspected based on cross sectional imaging (Figure 3A–D) or VCE (Table 3). DAE not only helps in diagnosing CD, it also helps in excluding CD, diagnosing alternate conditions such as NSAID enteropathy leading to NSAID discontinuation and making a surgical decision if a tight stricture is found [69]. The prevalence of new diagnosis of CD in patients with suspected CD varied from 25–75% [4,69–78]. This wide range is due to variable pre-DAE investigations done in various studies. When CD was suspected based on both MRE and VCE, the prevalence of CD was as high as 75% [78]. Hence, proper patient selection is the key to higher diagnostic yield with DAE. Diagnostic yield for DAE in suspected CD is based on the likelihood that DAE provides information on establishing or refuting a diagnosis. Only

a few studies addressed this issue in the true sense. Two studies are worth mentioning in this regard [69,71].



**Figure 3.** Cross sectional imaging and enteroscopic images in small bowel Crohn's disease (CD). (A) Computed tomography (CT) enterography coronal section image showing long segment jejunal thickening with prominent vasa recta in a suspected case of CD; (B) CT enterography image of the same patient showing wall thickening in axial section; (C) Single balloon enteroscopy (SBE) done trans-orally showing a stricture with features of mild inflammation, (D) SBE image of the same patient showing linear ulcers with skip areas in jejunum.

Rahman et al. studied 43 patients with suspected CD, 39.5% were diagnosed as new CD. Diagnostic yield was 79%. DAE altered existing management in 77%. In 17% cases, DBE failed to reach target lesion. Only 1% had perforation. Although CD was diagnosed based on endoscopy and histology, precise histopathological findings were not mentioned [69]. This was addressed in a larger retrospective study of 100 patients with suspected CD by Tun et al. that included follow up data as well. In that study, the proportion of new CD was 38% and diagnostic yield was 71%. Histology was diagnostic in 8%, suggestive in 15%, but in total 45% was initiated on CD treatment based on clinical, VCE and DAE findings. On median follow up of 27 months, 38% were finally diagnosed to have CD. Additionally, two patients each were diagnosed to have small bowel malignancy and tuberculosis on DAE guided biopsy. Two patients with normal DBE developed CD on follow up. This result suggests that histological yield of DAE guided biopsy is low and treatment based on macroscopic findings on DAE can help initiate CD treatment in a substantial number of patients. Moreover, alternate diagnosis of TB and small bowel malignancy can be made on histology [71].

Therefore, DAE is helpful in establishing diagnosis of small bowel CD whereas VCE is more useful in ruling out small bowel CD. Cross sectional imaging like MRE is better

for assessment of transmural and extra-luminal disease, whereas luminal disease is better assessed by DAE with additional advantage of histologic sampling [79].

**Table 3.** Summary of studies based on device assisted enteroscopy (DAE) in suspected Crohn's disease (CD) [4,69–78].

Author	DAE System	Patient Subgroup	Study Design	Suspected CD (n)	Proportion with CD (%)	Diagnostic Yield (%)	Impact on Management: Suspected CD (%)	Histology Suggestive or Confirmatory of CD
Broide et al., 2020, [4]	BGE	Pediatric IBD	Prospective	15 (IBD)	3/15 (20%)	15/15 (100%)		
Holleran et al., 2018, [70]	SBE	Adult CD	Retrospective	13	4/13 (31%)	8/13 (61.5%)		
Tun et al., 2016, [71]	DBE	Adult CD	Retrospective	100	38/100 (38%)	71/100 (71%)	71/100 (71%)	23/100 (23%, 8% diagnostic, 15% supportive)
Christian et al., 2016, [72]	Retrograde SBE	Adult CD	Retrospective	29	12/29 (38%)			
Rahman et al., 2015, [69]	DBE	Adult CD	Retrospective	43	17/43 (39.5%)	34/43 (79%)	33/43 (77%)	
Navaneethan et al., 2014, [73]	SBE or DBE	Adult CD	Retrospective	22	6/22 (27%)	22/22 (100%)		
Schulz et al., 2014, [74]	DBE	Adult CD	Retrospective	16		7/16 (44%)		3/16 (19%)
Urs et al., 2014, [75]	DBE	Pediatric CD	Prospective	3	2/3 (66%)	3/3 (100%)		2/3 (66%)
Uchida et al., 2012, [76]	DBE	Pediatric CD	Prospective	8	2/8 (25%)	7/8 (87.5%)		2/8 (25%)
De Riddler et al., 2012, [77]	SBE	Pediatric CD	Prospective	14	8/14 (57%)	14/14 (100%)		
Di Nardo, 2012, [78]	SBE	Pediatric CD	Prospective	16	12/16 (75%)	16/16 (100%)		

#### 2.4.5. AE in Established CD

DAE can be helpful in established CD to diagnose active small bowel disease that is suspected based on cross-sectional imaging (CTE/MRE) or VCE (Table 4), alteration in medical management, assess requirement of surgical intervention and direct therapeutic interventions like endoscopic therapy for small bowel strictures/bleed and retrieval of retained capsule/foreign body [69]. In a study by Mensink et al., therapy adjustment based on DBE resulted in a decrease in the Crohn's disease activity index (CDAI) score on follow up [80].

DAE could be important in evaluation of small bowel activity in CD as VCE and cross-sectional imaging have their own drawbacks in this regard. Incomplete small bowel examination, risk of capsule retention, requirement of patency capsule testing, inability to take biopsy and poor correlation with enteroscopic findings are drawbacks of VCE. VCE is otherwise relatively non-invasive and better tolerated. Nearly one third of patients with abnormal VCE findings had normal DBE results and one fourth with abnormal VCE had different lesions in a study by Rahman et al. Therefore, results of VCE should be interpreted with caution. DAE can also be useful to evaluate small bowel mass in the small bowel CD for ruling out adenocarcinoma on DAE guided biopsy and may obviate the need for laparotomy [69].

The diagnostic yield of DAE for established CD is higher (77–100%) than in cases of suspected CD (25–75%) [75–82]. However, DAE can be technically difficult leading to inability to reach target lesion in up to 17% cases. Fixation of a mobile small bowel due to active CD or adhesions from stricture or previous surgery can hinder deep enteroscopy. Moreover, complications like transient pain, bleeding and perforation can occur [69].

There is increasing evidence that small bowel mucosal healing may not correspond to colonic mucosal healing. In a post hoc analysis of CD patients treated with anti-TNF, small bowel ulcers detected by DAE were more difficult to heal (36%) than colonic ulcers (79%) and were associated with complicated CD [83]. In a retrospective study, endoscopic

evaluation of the deep small bowel was an independent predictor of relapse in CD on clinical remission whereas evaluation of terminal ileum was not. This highlights the importance of deep small bowel evaluation in CD even if in clinical remission to prevent future relapses [84].

**Table 4.** Summary of studies based on device assisted enteroscopy (DAE) in established Crohn's disease (CD) [4,69,70,75–78,80].

Author	DAE System	Patient Subgroup	Study Design	Known CD (n)	Diagnostic Yield Confirmed CD (%)	Impact on Management: Confirmed CD (%)	Therapeutic Intervention (Endoscopic)
Broide et al., 2020, [4]	BGE	Pediatric IBD	Prospective	9	9/9 (100%)		
Holleran et al., 2018, [70]	SBE	Adult CD	Retrospective	39	30/39 (77%)	33/39 (85%)	13/39 (33.3%)
Rahman et al., 2015, [69]	DBE	Adult CD	Retrospective	38	33/38 (87%)	31/38 (82%)	3/38 (8%)
Navaneethan et al., 2014, [73]	SBE or DBE	Adult CD	Retrospective	43	41/43 (95.3%)	23/43 (53%)	
Urs et al., 2014, [75]	DBE	Pediatric CD	Prospective	5	5/5 (100%)	5/5 (100%)	
Uchida et al., 2012, [76]	DBE	Pediatric CD	Prospective	4	4/4 (100%)	3/4 (75%)	1/4 (25%)
De Riddler et al., 2012, [77]	SBE	Pediatric CD	Prospective	6	5/6 (83%)	5/6 (83%)	
Di Nardo, 2012, [78]	SBE	Pediatric CD	Prospective	14	14/14 (100%)	14/14 (100%)	3/14 (21%)
Kondo et al., 2010, [81]	DBE	Adult CD	Retrospective	50	48% (percentage of active lesions among all enteroscopy sessions)	53% (overall impact including new cases of CD)	
Mensink et al., 2009, [80]	DBE	Adult CD	Retrospective	40	24/60 (40%)	18/40 (45%)	2/40 (5%)

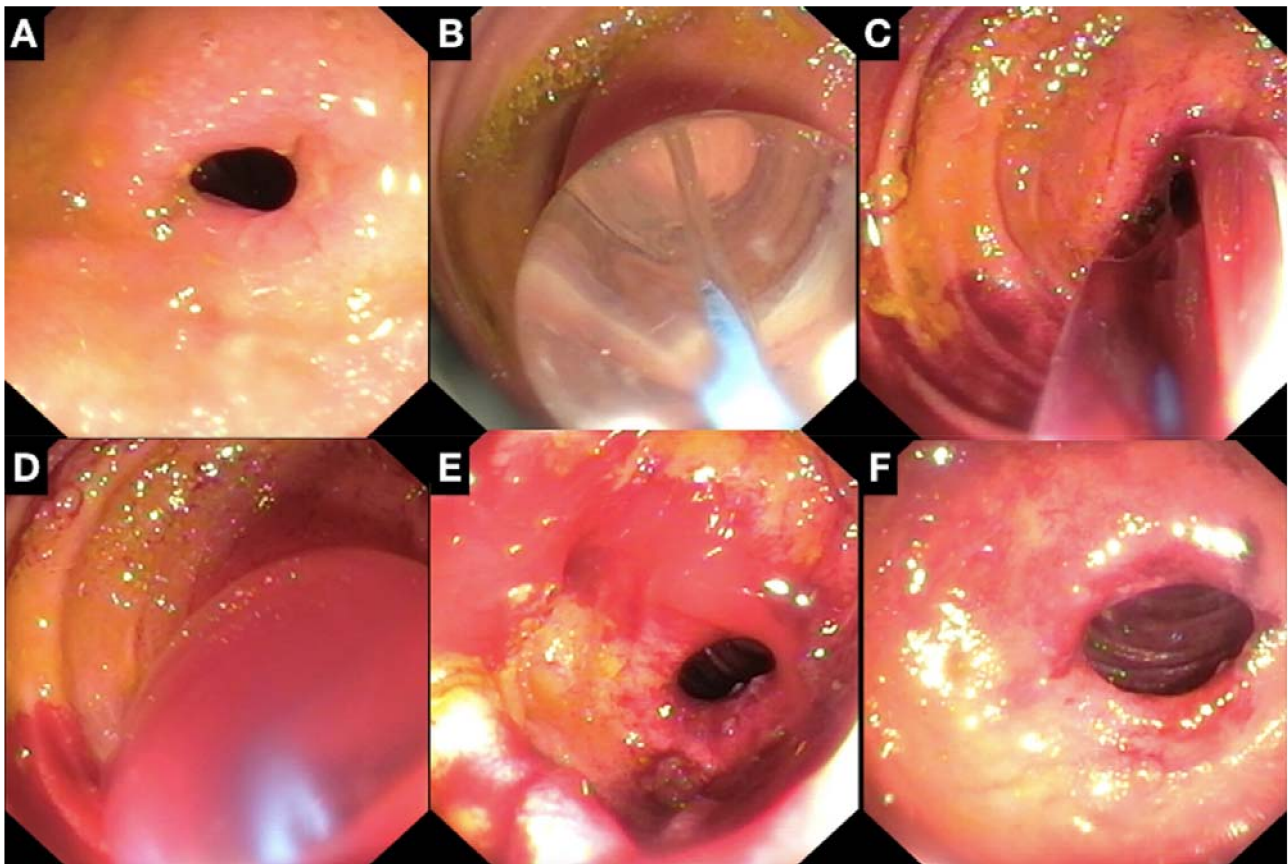
#### 2.4.6. DAE Guided Therapeutic Intervention

##### Small Bowel Strictures

Treatment of small bowel strictures is challenging. Treatment with anti-inflammatory drugs improve obstructive symptoms in symptomatic small bowel strictures but 40% require surgery/EBD within 1 year and 50% require surgery in 4 years [85]. Most of the data on EBD for CD strictures is on ileal and anastomotic strictures is done with ileocolonoscopy; however, data on EBD for small bowel strictures with DAE is limited [86].

##### Endoscopic Balloon Dilatation (EBD)

EBD is recommended for symptomatic, de novo or anastomotic, small bowel strictures (less than four closely situated strictures) less than 5 cm in size with minimal inflammatory activity (Figure 4). For asymptomatic small bowel strictures, risk of complications with EBD should be balanced with the benefits of halting progression of asymptomatic stenosis. Cross-sectional imaging (CTE/MRE), or more recently small bowel ultrasound, is being used for evaluation of stricture prior to EBD. Wall thickening, luminal narrowing and pre-stenotic dilatation should be noted prior to EBD using these modalities [87]. Monitored/general anesthesia, fluoroscopic guidance and in-patient admission are not mandatory but should be used if complex strictures and a long procedure time is contemplated in a patient with significant co-morbidity. Carbon dioxide insufflation and prophylactic antibiotics are recommended and warfarin/thienopyridines should be discontinued for 5 days (aspirin could be continued).



**Figure 4.** Endoscopic balloon dilation (EBD) of fibrotic proximal jejunal stricture done. (A) Symptomatic proximal jejunal stricture detected on single balloon enteroscopy reached by pediatric colonoscope; (B) Graded dilatation was done with controlled radial expansion (CRE) balloon up to 13.5 mm, direct through the balloon visualization done to detect endoscopic tearing during balloon dilation; (C) Post dilatation bleeding noted at dilation site; (D) Mechanical pressure applied by balloon tamponade with CRE balloon. (E) Post balloon tamponade, mild ooze noted from structure; (F) Complete hemostasis achieved after hypertonic glucose spray at dilation site with no delayed bleed on follow up, remains asymptomatic for 6 months post dilation.

#### Outcomes of EBD for Small Bowel Strictures

The most common therapeutic intervention in small bowel Crohn's disease is endoscopic balloon dilatation (EBD). Table 5 summarizes the published literature on EBD for small bowel strictures in CD. In a recent meta-analysis, data of 218 patients and 384 EBD were analyzed. It showed high technical success rate (95%) that is comparable to that for ileo-cecal (90%) and gastroduodenal (100%) strictures. Short term clinical efficacy (82.3%) was also comparable to clinical success rates of EBD for ileo-cecal (80.8%) and gastroduodenal (87%) strictures. Recurrent symptoms were seen in half of the patients (48.3%) compared to recurrence rate of 47.5% and 70.5% for ileo-cal and gastro-duodenal strictures over 2 years follow up. Repeat dilatation or surgery were required in 38.8% and 27.4% patients, respectively [88]. Surgery rates in ileo-cecal and gastroduodenal strictures post EBD were 28.6% and 30.8%, respectively. Although a technical success, clinical success and long term success were similar to other strictures, complication rates of small bowel stricture was higher (5.3%) compared to ileo-cecal (2.8%) and gastroduodenal (2.9%) strictures [89,90]. This finding is due to the technically challenging procedure with DAE compared to that with endoscope or colonoscope.

Intra-procedural bleed (Figure 4C–F) with hemodynamic instability and post-procedure bleeding requiring hospitalization or blood transfusion should be tried with volume resuscitation and rescue endoscopy and hemostasis with clips/mechanical pressure/epinephrine

injection or hypertonic glucose spraying failing which angiographic embolization or surgery may be required in rare instances. For intra-procedural perforation, endoscopic closure could be attempted failing which surgical intervention is warranted.

#### Factors Predicting Outcomes of EBD

According to the meta-analysis, fibrotic strictures, absence of inflammatory disease elsewhere, higher body mass index (BMI) and use of anti-inflammatory drugs lower the risk of re-intervention following EBD [88]. Deep ulcers in a strictured segment increases risk of bleeding and perforation; however, superficial ulcers should not preclude EBD [91]. Concomitant use of steroids (prednisolone  $\geq 20$  mg/day) but not biologics is associated with increased risk of complications with EBD [89]. Advanced disease usually leads to weight loss that could be the explanation of better outcome in patients with a high BMI. Pre-stenotic dilatation signifying long standing disease and stricture length  $> 5$  cm were significant risk factors for failure of EBD and future surgery. Every 1 cm increase in stricture size increases the risk of future surgery by 8% [90]. Adjacent abscess and fistula are contraindications to EBD [91]. De novo CD strictures have low short-term clinical efficacy compared to anastomotic strictures, although long term outcomes are not different. EBD is safe and effective for less than four strictures in close proximity to each other compared to more than equal to four strictures located far away [91]. Asian ethnicity was associated with low short term clinical efficacy, lower recurrence and a higher risk of surgery that could be related to protocol for EBD, different disease phenotype and a lower threshold for surgery. Disease located in jejunum or proximal ileum were associated with higher risk of re-dilatation or surgery [88]. Concurrent intra-lesional steroid injection is not recommended and there is no definite benefit of intra-lesional anti-TNF therapy [91].

#### Graded Versus One Step Dilatation

It is not clear whether a graded dilatation is better than one time dilatation, although generally graded dilatation is recommended to reduce chances of bleeding and perforation. Usually, graded dilatation is done up to 18–20 mm, but smaller balloon sizes are preferred for small bowel strictures [91]. Graded dilatation was associated with higher short term efficacy but 65% higher risk of recurrent symptoms. Although complication rates (3.2%) were higher with graded dilatation compared to one-step dilatation (0.7%), it was not statistically significant due to overall low complication rates. Balloon size (15.8 mm) was lower with graded compared to one-step dilatation (17.2 mm) [88]. Future studies are warranted in this regard.

**Table 5.** Summary of published literature on endoscopic balloon dilatation (EBD) for small bowel strictures in Crohn’s disease with device assisted enteroscopy (DAE); SBE—single balloon enteroscopy, DBE—double balloon enteroscopy, BGE—balloon guided enteroscopy [70,73,81,91–101].

Author	DAE System	Study Design	CD/no of Strictures (n)	Total Number of Dilations (Per Patient Mean)	Dilation Diameter: Mean (Range) (mm)	Technical Success (%)	Short Term Clinical Efficacy (%)	Major Complications (%)	Follow up (Months)	Recurrence of Symptoms	Re-Dilatation on Follow up	Surgery on Follow up
Hirai et al., 2018, [92]	SBE or DBE	Prospective	95		15 (8–20)	94%	69.5	5%	24			
Holleran et al., 2018, [70]	SBE	Retrospective	13	14 (1)	13 (12–15)	100	80	0	8	24	7.7	0
Nishida et al. 2017, [93]	DBE	Retrospective	37	72				8.1	27.1			48.6
Sunada et al., 2016, [94]	DBE	Retrospective	85	473	12.4 (8–20)		87	5.9	41.9		75.3	24.7 (5 years)
Navaneethan et al., 2014, [73]	SBE or DBE	Retrospective	8	10		75		16			66.6	
Hirai et al., 2014, [95]	DBE	Retrospective	65	105	NA	80	80	4.6	40.3	36.5	50	26.2
Gill et al., 2014, [96]	DBE	Retrospective	10	18	13.3	100	80	20	16	40	40	30
Hirai et al., 2010, [97]	DBE	Retrospective	25	55	NA	72	72	8	11.4	22.2	22.2	28
Kondo et al., 2010, [81]	DBE	Retrospective	8	18 (1.5)		100	87.5	0				
Despott et al., 2009, [98]	DBE	Prospective	11	18 (2)	15.4 (12–20)	81.8	72.7	9.1	20.5	22.2	22.2	9.1
Ohmiya et al., 2009, [99]	DBE	Retrospective	16	18	NA (8–20)	96	100	0	16	31	12.5	18.8
Pohl et al., 2007, [100]	Push enteroscopy	NA	10	15 (1.5)	17 (12–20)	80	60	0	10		50	40
Fukumoto et al., 2007, [101]	DBE	Prospective	23	35 (1.52)	NA	100	74	0	12	26.1	17.1	8.7

### Endoscopic Techniques Other Than EBD for Small Bowel Strictures

Endoscopic stricturotomy (horizontal or radial incision in strictures) and stricturectomy (endoscopic electro-incision along with clip placement) can be used as rescue therapies for CD related short strictures (<3 cm) where EBD has failed. Delayed bleeding may occur in a higher frequency than in EBD although the risk of perforation is lower. Full covered removal metal stents have been used successfully as rescue therapy for terminal ileal and ileo-colonic short, fibrostenotic stricture [91]. However, data is scarce on the effect of these modalities in small bowel strictures. Risk of migration, perforation and fistula formation are drawbacks of metal stents, which can be circumvented in future by biodegradable stents specifically designed for CD [102,103]. In the recent meta-analysis of EBD of small bowel strictures, 0.54% and 2.7% patients were treated with electro-incision and stents, respectively [88].

#### 2.4.7. DAE in Pediatric Patients

DAE is technically difficult in children due to small abdominal cavity, thin abdominal wall and narrow lumen. DAE is feasible in children more than 3 years old and with a body weight of more than 14 kg. Single or double balloon enteroscopy and balloon guided enteroscopy have been used extensively in pediatric CD (Tables 3 and 4). IBD-U reclassification is more relevant for pediatric population. DAE is safe according to large DBE and SBE series [75–77,104,105]. Currently available motorized spiral enteroscopy is not feasible in children due to the large diameter of the scope.

#### 2.5. Intra-Operative Enteroscopy (IOE) in CD

Although the role of IOE is becoming limited with current advances in small bowel endoscopy, IOE has been shown to be useful in surgical decision of small bowel CD. IOE can help in assessment of severity of stricture (severe strictures do not allow passage of enteroscope) and deciding the extent of surgical resection. Supposedly mild stricture on inspection and palpation at laparotomy could turn out to be severe, non-passable stricture on IOE altering surgical extent [106,107].

### 3. Conclusions

Direct endoscopic evaluation of the small bowel has revolutionized diagnostic and therapeutic management of small bowel CD. Small bowel endoscopy is useful for diagnosing small bowel CD with normal ileo-colonoscopy. In this scenario, VCE in the absence of known stenosis or obstructive symptoms carries low risk of capsule retention. DAE with endoscopic biopsy may help rule out mimics of small bowel CD; however, histological yield is poor in small bowel CD. Small bowel endoscopy could also be helpful in IBD-U. In post-operative small bowel disease, VCE may be helpful to evaluate recurrence. In established CD, small bowel disease extent, severity and mucosal healing can be assessed by both VCE and DAE. VCE has high risk of retention in established CD and hence should be preceded by cross sectional imaging or patency capsule testing. The indications of small bowel therapeutic enteroscopy are expanding and include treatment of small bowel stricture/bleeding and removal of retained capsule or foreign body. EBD has been extensively used in treatment of small bowel stricture. Newer techniques for treatment of strictures in CD like electro-incision, stricturoplasty and stenting need to be evaluated in small bowel strictures.

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**Informed Consent Statement:** Informed consent was taken from all the subjects involved in the study for use of anonymized images of small bowel endoscopy.

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