Chapter

Endoscopy in Small Bowel Crohn's Disease

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Abstract

Crohn's disease (CD) is a complex disorder with variable age of onset, disease location and behavior. It is characterized by a transmural inflammation that may involve any portion of the gastrointestinal tract. Ileocolonoscopy with biopsy is established as the first-line investigation for suspected CD. However, small bowel involvement is more difficult to assess by conventional endoscopy. Therefore, radiological imaging should also be performed to complement ileocolonoscopy in all patients with suspected CD. Recently, video capsule endoscopy and device-assisted enteroscopy have revolutionized the management of small bowel CD. In fact, video capsule endoscopy is a non-invasive test that provides the visualization of the entire small bowel mucosa, which can assist in the diagnosis of CD and assess the therapeutic response. On the other hand, device-assisted enteroscopy enables direct tissue sampling for histopathology confirmation when traditional endoscopy, video capsule endoscopy and cross-sectional imaging are inconclusive. Moreover, it allows therapeutic interventions such as balloon stricture dilation. In this chapter, we review the role of endoscopy in the diagnosis and management of patients with small bowel CD.

Keywords: Inflammatory bowel disease, Crohn's disease, endoscopy, small bowel

1. Introduction

Crohn's disease (CD) is an idiopathic inflammatory disorder with genetic, immunologic and environmental influences [1]. It is characterized by a transmural inflammation that may involve any portion of the luminal gastrointestinal tract, from the oral cavity to the perianal area. The diagnosis is based on the combination of clinical, biochemical, radiological, endoscopic and histological findings. CD is a chronic and progressive disease, marked by frequent relapses which usually require repeated investigations.

The most common symptoms of CD are diarrhea, abdominal pain and fatigue. However, clinical manifestations can be very heterogeneous, depending on the disease location and phenotype. Patients with CD often show laboratory evidence of inflammatory activity and anemia. In addition, fecal calprotectin and serum C-reactive protein are useful markers to detect and monitor inflammation. The endoscopic hallmark of CD is the patchy distribution of inflammation and mucosal biopsies usually show focal inflammation (rather than diffuse), crypt distortion and/or granulomas. Finally, cross-sectional imaging techniques provide information about the bowel wall and extra-enteric soft tissues and, therefore, can better classify disease phenotype and behavior.

Endoscopy has major implications not only for the diagnosis of CD but also for treatment and follow-up. Indeed, ileocolonoscopy and upper gastrointestinal endoscopy have well-established roles in assessing disease activity and therapeutic intervention. However, the small bowel is one of the most common areas affected in patients with CD, which is often inaccessible to conventional endoscopy. In addition, at the time of diagnosis, up to 30% of patients have only small bowel involvement, especially in the young ones [2, 3]. The advent of video capsule endoscopy and both balloon-assisted and spiral enteroscopy is revolutionizing the management of small bowel CD [4]. In fact, these techniques allowed direct visualization of the entire small bowel which can assist in the diagnosis of CD. Moreover, device-assisted enteroscopy enables direct tissue sampling and allows therapeutic interventions. In this chapter, we aim to review the role of small bowel endoscopy in the management of patients with CD.

2. Diagnosis

2.1 Ileocolonoscopy

Colonoscopy with intubation of the terminal ileum and multiple biopsies is recommended as part of the initial evaluation of patients with suspected CD [5]. It has been reported a successful ileal intubation rate as high as % when the cecum is reached [6]. A minimum of two biopsies from five different sites, including the rectum and the ileum, should be obtained for a reliable diagnosis of CD. Samples are preferably obtained both from areas which are involved by the disease and from uninvolved areas. Mucosal changes suggestive of CD include discontinuous segments of edema, friability, ulcerations, fistulous orifices and stenosis (**Figure 1**). With respect to the histological exam, macroscopic and microscopic features include discontinuous chronic inflammation, with lymphocytes and plasma cells, focal crypt distortion and granulomas. Although the presence of granulomatous inflammation is helpful, it is not required for diagnosis and is seen in only 33% of patients with CD [7].

Ileocolonoscopy is also helpful for the detection of stenosis, allowing tissue sampling for pathological diagnosis of dysplasia and cancer. Complementary radiological techniques to rule out additional stenotic lesions are necessary when the lesion is impassable with the endoscope.

Attempts to quantify the distribution and severity of mucosal involvement of the colon and the ileum in patients with CD have led to the development of multiple endoscopic scoring systems. Endoscopic scores that have been validated for ileocolonoscopy include both the Crohn's Disease Endoscopic Index of Severity (CDEIS) [8]

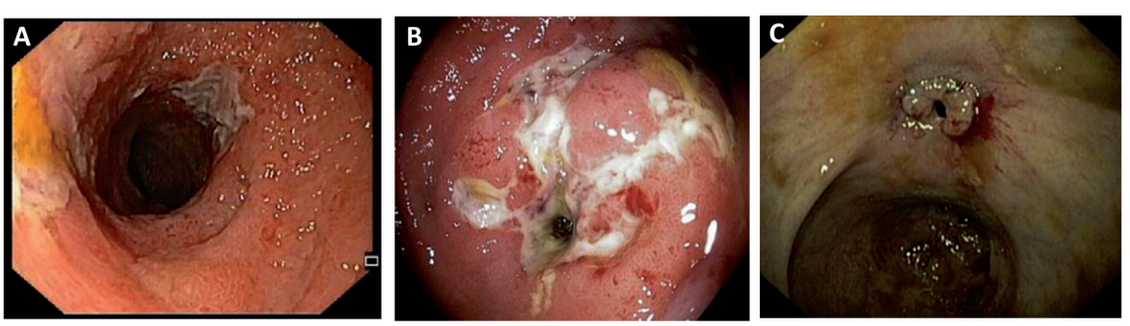

Figure 1.
Endoscopic appearance of Crohn's disease - discontinuous segments of edema, friability, ulcerations (A) and stenosis (B and C).

and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [9]. The CDEIS includes six endoscopic variables (presence of deep ulcers, superficial ulcers, nonulcerated stenosis, ulcerated stenosis, proportion of ulcerated surface and proportion of surface affected by disease), assessed in five bowel segments (terminal ileum, right colon, transverse, left colon and sigmoid, rectum) (**Table 1**). The CDEIS is complicated to use and requires training and experience. Therefore, it is used mainly in clinical trials. On the other hand, the SES-CD has been helpful to translate endoscopic activity into clinically meaningful and is easier to use and understand. The SES-CD includes four variables, each considered in five bowel segments (ulcer size, extent of ulcerated surface, extent of affected surface and stenosis) (**Table 2**).

	Ileum	**Right colon**	**Transverse colon**	**Left colon**	**Rectum**	**Sum**	
Deep ulceration (0 for none, 12 points if present)							Total 1
Superficial ulceration (0 for none, 6 points if present)							Total 2
Surface involved by disease (cm)							Total 3
Surface involved by ulceration (cm)							Total 4
Total 1 + 2 + 3 + 4							Total A
Number of segments totally or partially explored							n
Total A divided by n							Total B
Quote 3 if ulcerated stenosis anywhere							C
Quote 3 if nonulcerated stenosis anywhere							D
Total B + C + D							CDEIS

Table 1.
Crohn's disease endoscopic index of severity (CDEIS). CDEIS includes deep ulceration (no = 0, yes = 12), superficial ulceration (no = 0, yes = 6), surface involved by disease (0–10), ulcerated surface (0–10), and ulcerated or non-ulcerated stenosis (no = 0, yes = 3), each considered in five ileocolonic segments. Severe disease: CDEIS ≥12, moderate disease: CDEIS = 9–12, mild disease: CDEIS = 3–9, remission: CDEIS <3.

Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.2–0.5 cm)	Large ulcers (0.5-2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	None	<50%	50–75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Impassible

Table 2.
Simple endoscopic score for Crohn's disease (SES-CD). SES-CD = sum of all variables of each explored segment (ileum, right colon, transverse colon, left colon and rectum). Severe disease: SES-CD ≥16, moderate disease: SES-CD = 7–15, mild disease: SES-CD = 3–6, inactive disease: SES-CD <3.

It is important to note that up to 25% of patients have isolated proximal small bowel disease beyond the reach of even complete ileocolonoscopy [10]. Therefore, radiological imaging should be performed in all patients with suspected CD to complement ileocolonoscopy.

2.2 Upper gastrointestinal endoscopy

The presence of CD of the upper gastrointestinal tract, including the duodenum, is uncommon in adults, with most studies showing a prevalence range of 0.3–5% [11]. Moreover, the majority of patients are asymptomatic at the time of evaluation [12]. However, it is important to note that CD in the proximal gastrointestinal tract is associated with a worse prognosis and there is usually a low threshold to initiate therapy with anti-tumor necrosis factor (TNF).

CD involving the upper gastrointestinal tract is almost invariably accompanied by small or large bowel involvement [13]. Esophagogastroduodenoscopy is recommended in patients with upper gastrointestinal signs and symptoms, being still debated whether asymptomatic adult CD patients should routinely undergo upper endoscopy [6]. In fact, esophagogastroduodenoscopy may support the diagnosis when it is difficult to obtain a histological diagnosis of CD. In addition, a more recent prospective registry reported a higher prevalence of upper gastrointestinal involvement in asymptomatic patients than initially expected, suggesting a place for a standard gastroscopy to correctly evaluate disease extent at diagnosis [12].

Endoscopic features suggestive of upper gastrointestinal involvement include mucosal nodularity, aphthous ulcers, superficial erosions, antral thickening and duodenal strictures [1]. Histologic changes consistent with CD are granulomatous inflammation, focally enhanced gastritis and focal cryptitis of the duodenum.

In the presence of upper tract stenosis, balloon dilatation is recommended as first-line therapy, followed by proton pump inhibitors as second-line and steroids/thiopurines/surgery as third-line [14]. Currently, there is no credible evidence to support the best modality to assess response to treatment of upper gastrointestinal CD, therefore it must be primarily monitored by the reference standard endoscopy.

2.3 Video capsule endoscopy

Video capsule endoscopy is a method of endoluminal examination of the small bowel using a wireless capsule-shaped tool which is swallowed and then propelled through the gastrointestinal tract by gut motility [15]. Preparations for a video capsule endoscopy study usually include 8–12 hours' fasting and some method of bowel cleansing (e.g. polyethylene glycol preparation). During the battery life of the capsule, images of the small bowel are recorded and reformatted into a continuous video file. After 8–10 hours, the antenna and storage unit are removed and the images transferred to a computer with specially adapted software. Images are then downloaded, processed and examined by a trained gastroenterologist (**Figure 2**).

In addition to the small-bowel capsule, there are currently two more: the esophageal and the colon capsules [16]. The esophageal capsule is the same size as the small bowel capsule, but has lenses on both ends of the 'pill.' The capsule battery life is only 20 minutes (vs. 8–12 hours for small-bowel capsules), cameras are located on both ends of the capsule and take 18 frames per second (vs. 2–3 frames per second for small-bowel capsules). On the other hand, the second-generation colon capsule endoscope is equipped with two high-resolution cameras providing a viewing angle of 172° in front and back, senses the moving speed of the capsule endoscope and captures 4 to 35 images per second [17]. This capsule was primarily utilized

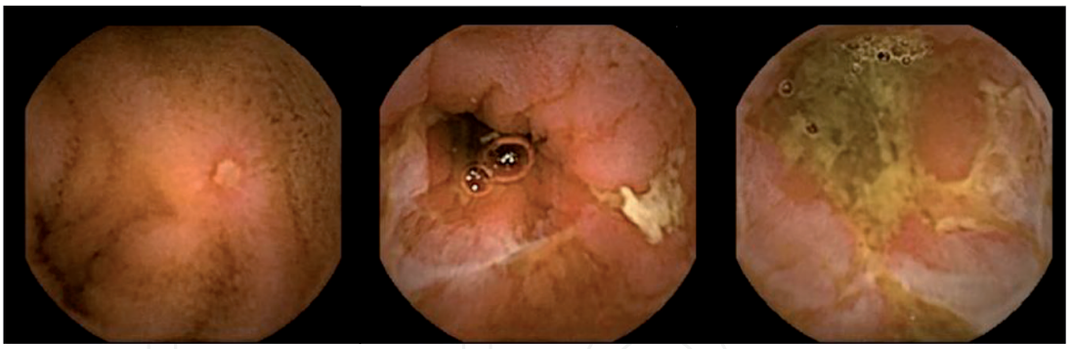

Figure 2.
Video capsule endoscopy images showing mucosal inflammation and ulcerations consistent with a diagnosis of Crohn's disease.

in screening for colonic neoplasia, particularly in situations such as incomplete colonoscopy. However, it can play a key role in the diagnosis and evaluation of CD extent, severity and prognosis, with treatment modifications based on data from capsule examination.

Video capsule endoscopy is a useful adjunct in the diagnosis of patients with small bowel CD since it allows for direct visualization of the mucosa of the entire small intestine. It is able to identify mucosal lesions compatible with CD in patients in whom conventional endoscopic and small bowel radiographic imaging modalities have been nondiagnostic, especially in the proximal small bowel [18]. Several meta-analyses have examined the diagnostic yield of video capsule endoscopy in the evaluation of patients with suspected CD and showed that it is superior to small bowel barium studies, computed tomography enterography and ileocolonoscopy, with an incremental yield of diagnosis of 32%, 47% and 22%, respectively [19]. Moreover, video capsule endoscopy has a negative predictive value of 96%, essentially ruling out small bowel CD [20]. On the other hand, a study examining the sensitivity and specificity of different endoscopic and radiologic exams showed that the specificity of video capsule endoscopy was significantly lower than the other tests [21]. In fact, detected lesions are nonspecific and cannot be distinguished from those seen in patients treated by nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, video capsule endoscopy should be reserved for cases in which ileocolonoscopy plus small bowel radiography is not diagnostic, but there is a high rate of CD suspicion.

Although there are no validated diagnostic criteria for the diagnosis of CD, the presence of more than three small bowel ulcerations, in the absence of NSAIDs ingestion for at least 1 month before the exam, constitutes the most commonly used diagnostic criterion in practice [22]. In addition, there are currently two validated indexes available, the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) [23] and the Lewis Score [24], which assess the disease location and activity of small bowel involvement. The CECDAI was validated in a multicenter prospective study of patients with isolated small bowel CD and evaluates the following three endoscopic parameters: inflammation, extent of disease and strictures for both the proximal and the distal segments of the small bowel, based on the transit time of the capsule (**Table 3**). The Lewis score is another scoring system based on the evaluation of three endoscopic parameters: villous appearance, ulcers and strictures (**Table 4**). The small bowel is divided into three equal parts and, for each tertile, a subscore is determined. The Lewis Score is the sum of the worst affected tertile plus the stenosis score. Both the scoring systems are incorporated into the software platform of the capsules and assists in the quantification of small bowel inflammatory burden and diagnosis of CD.

Parameter	Score and descriptor
A - Inflammation	0 - None 1 – Mild to moderate (edema, hyperemia or denudation) 2 – Severe (edema, hyperemia or denudation) 3 – Bleeding, exudate, erosion aphthae, ulcers <0.5 cm 4 – Pseudopolyp, ulcers 0.5-2 cm 5 – Ulcers >2 cm
B – Extent of disease	0 – None 1 – Sigle segment (focal disease) 2–2-3 segments (patchy disease) 3 - >3 segments (diffuse disease)
C - Stricture	0 – None 1 – Single-passed 2 – Multiple-passed 3 – Obstruction (non-passage)

Table 3.
Capsule endoscopy Crohn's disease activity index (CECDAI). CECDAI = proximal segment (A x B + C) + distal segment (A x B+C). Clinical or endoscopic remission: CEDAI <4.

Parameter	Descriptor or number	Longitudinal extent	Descriptor
Villous appearance	0- Normal 1- Edematous	8- Short-segment (<10%) 12- Long-segment (11–50%) 20- Whole tertile (>50%)	1- Single 14- Patchy 17- Diffuse
Ulcers	0- Normal 3- Single 5- Few (2–7) 10- Multiple (≥8)	5- Short-segment (<10%) 10- Long-segment (11–50%) 15- Whole tertile (>50%)	9- < ¼ 12- ¼ - ½ 18- > ½
Stenosis	0- None 14- Single 20- Multiple	2- Nonulcerated 24- Ulcerated	7- Transversed 10- Not transversed

Table 4.
Lewis score. Score total = worst-affected tertile villous appearance and ulcers plus stenosis score. Clinically insignificant inflammation: Lewis score <135, mild inflammation: Lewis score = 135–790, moderate to severe inflammation: Lewis score >790.

Video capsule endoscopy may also identify a site for directed visualization with other endoscopic techniques. In fact, it can be complementary to device-assisted endoscopy since findings may help direct the most effective route of intubation (oral versus anal), in order to obtain a histopathological diagnosis or therapeutic intervention.

In addition, video capsule endoscopy allows detection of subtle small bowel lesions, which may affect the therapeutic management. Because of the high sensitivity of video capsule endoscopy, it has a potential role in the assessment of mucosal healing after drug therapy and can be used in the follow-up of treated patients. In fact, video capsule endoscopy has a significant impact on disease management and is associated with earlier escalation of therapy. In the largest retrospective series of patients with established CD that were evaluated with video capsule endoscopy, a change in management was suggested in 40–52% of individuals [25, 26].

The main advantage of video capsule endoscopy is the ability to visualize all of the small bowel with minimal discomfort for the patient. However, it lacks therapeutic capabilities and there is some risk of impaction due to possible strictures.

The capsule retention rate in patients with suspected CD is 1.5–5.4% but can reach 13% in those with established CD, particularly if there are known intestinal stenosis [27, 28]. Therefore, those with obstructive symptoms or established CD of the small bowel should always have small bowel imaging and/or patency capsule evaluation before video capsule endoscopy to decrease the risk of capsule retention. Video capsule endoscopy is considered safe if the patency capsule is excreted before 30 hours, an intact capsule is excreted after 30 hours or passage to the colon of an intact patency capsule has been radiologically confirmed. Another disadvantage of video capsule endoscopy is that the quality of images is not comparable to the view achieved at conventional endoscopy with gas insufflation. In addition, it has been reported that the caecum is not reached in 8–40% of video capsule endoscopy studies [22, 29]. Finally, the most serious complication reported with video capsule endoscopy is perforation, which has been exceedingly rare [30].

2.4 Device-assisted endoscopy

Device-assisted endoscopy is a generic term for any endoscopic technique that includes assisted progression (i.e. balloons and overtubes) and comprises double-balloon enteroscopy, single-balloon enteroscopy and spiral enteroscopy [31]. Device-assisted endoscopy allows direct mucosal visualization of the entire small bowel as well as tissue sampling and therapeutic intervention (**Figure 3**). However, it is technically challenging and may require a bi-directional approach, deep sedation or general anesthesia.

Double-balloon enteroscopy was introduced in 2001 as the first method for device-assisted enteroscopy [32]. It allows deep intubation of the small bowel by pleating the bowel onto a long and flexible endoscope fitted with an overtube. The endoscope and the accompanying overtube have balloons at their distal end. By intermittent inflation and deflation of these two balloons, combined with instrument insertion and retraction, large portions of the small bowel can be visualized directly. Oral and anal routes are used to achieve a complete small bowel examination.

Single-balloon enteroscopy is able to achieve a complete examination of the small bowel using principles similar to double-balloon enteroscopy. However, in contrast to double-balloon enteroscopy, this exam has only one balloon at the distal end of the overtube, which simplifies the preparation of the scope before starting the procedure. Single-balloon enteroscopy uses scope tip angulation and suction instead of balloon inflation to maintain a stable position while advancing the overtube.

Spiral enteroscopy is based on a completely different concept, by pleating of the bowel on the instrumentation shaft by active rotation instead of applying pushing force. The distal end of the overtube harbors a flexible spiral thread for pleating the small intestine over the overtube. By manually rotating the overtube, the spiral engages the small bowel which is thus pleated onto or unpleated from the overtube, respectively, depending on the direction of the spiral rotation. Spiral assisted endoscopy has been approved for both anterograde and retrograde enteroscopy.

The Motorized Spiral Enteroscope is a new technology with an incorporated user-controlled motor contained in the handle of the endoscope [33]. This would offer the possibility to accelerate the procedure, facilitate insertion and simplify the technique with a single operator. Recently, Beyna et al. demonstrated that the Motorized Spiral Enteroscope is effective for diagnostic and therapeutic antegrade enteroscopy and may compare favorably with traditional methods of deep enteroscopy in ease of use and procedural duration [34].

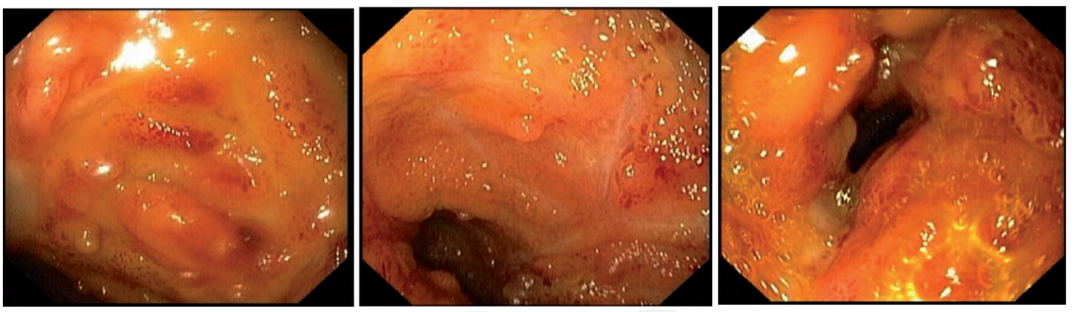

Figure 3.
Device-assisted endoscopy images showing mucosal inflammation and ulcerations consistent with a diagnosis of Crohn's disease.

Device-assisted endoscopy is not part of routine diagnostic testing in patients with suspected CD and should not be the first-line procedure in the evaluation of small bowel [1]. However, it may provide additional information when it is required biopsy of small bowel tissue to histological corroboration. Indeed, compared with video capsule endoscopy and small bowel imaging techniques, the advantages of device-assisted endoscopy include the evaluation of atypical lesions, the ability to obtain biopsies for histopathology and the potential for therapeutic intervention.

Device-assisted endoscopy studies in individuals with suspected CD have not included large numbers of patients but report a diagnostic yield as high as 80% [35]. In fact, device-assisted endoscopy is more sensitive in detecting lesions in patients with suspected CD than multiple radiographic imaging techniques. Nevertheless, because of the invasive and potentially time-consuming nature of the exam, it should be reserved for patients with high clinical suspicion of CD despite negative conventional studies (including ileocolonoscopy, video capsule endoscopy and radiographic imaging), particularly if endoscopic and histologic finding would alter disease management or potential therapeutic intervention is required [36]. In a prospective trial, positive findings at device-assisted enteroscopy led to a step-up of medical therapy in 74% of patients, leading to clinical remission in 88% [37]. In addition, device-assisted endoscopy may be preferable to video capsule endoscopy if there is a clinical suspicion of obstruction because it may allow therapeutic intervention and be safer, simply by avoiding capsule retention.

In patients with established CD, device-assisted endoscopy is indicated when endoscopic visualization and biopsies are necessary from areas of the small bowel inaccessible to conventional endoscopy [1]. Usually, previous video capsule endoscopy provides information on the optimal route of approach (oral or rectal) and lesion location. Adhesions may limit examination by device-assisted endoscopy and, in these circumstances, double-balloon enteroscopy may be preferred to single-balloon enteroscopy. In addition, device-assisted endoscopy has the capacity for endoscopic therapy, including dilation of small bowel strictures, removal of impacted capsules and treatment of bleeding lesions (*vide infra*).

Overall, diagnostic device-assisted endoscopy is safe, with few reports of complications (<1%) [38]. However, there appears to be an increased risk of complications in the case of active CD or previous intestinal surgery. The risk of perforation is 0.12% without therapeutic intervention and 1.74% with therapeutic intervention, the majority of which occurred after stricture dilatation [39]. Bleeding occurs in approximately 2.5%. In addition, device-assisted endoscopy involves risks related to sedation, in contrast to video capsule endoscopy where no sedation is required.

3. Treatment

3.1 Treatment of intestinal strictures

Strictures in CD develop during the course of the disease or as the presenting feature and are believed to result from partial healing and localized fibrosis. In addition, almost one-third of CD patients develop an anastomotic stricture after ileocecal resection/right hemicolectomy [40]. As a progressive disease, anastomotic strictures will be more likely over time.

Immunomodulators and biologic agents have been widely used for the treatment of CD, however endoscopic dilatation is a preferred technique for the management of symptomatic and mild to moderate stenosing disease [41]. Indeed, medical therapy for stricture management is limited due to fibrotic nature. Endoscopic dilatation may prevent or delay the need for surgical resection or strictureplasty. Moreover, endoscopic balloon dilation should be performed to access the mucosa proximal to strictures and evaluate disease activity, that otherwise may be missed if we only relied on symptoms or biochemical markers [42]. Thus, it can provide adequate endoscopic therapy and adjust or optimize medical therapy.

Endoscopic balloon dilation may be used in Crohn's strictures of the gastric outlet, duodenum, colon, ileocolonic anastomosis and of the small bowel, if accessible [43]. It is performed using a through-the-scope balloon catheter, which is a simple and safe procedure (**Figure 4**). The dilation procedure is performed with monitoring of the pressure of the inflated balloon using a dilator with or without X-ray guidance. When performing endoscopic balloon dilation, forcible dilation to achieve a larger dilation diameter or pressure is not recommended, as it could lead to intestinal perforation. The length of the balloons for inflation is about 5 cm; therefore, stenoses longer than 5 cm are considered unsuitable for endoscopic balloon dilation. Moreover, intestinal strictures with deep ulcers and fistulous complications are contraindications for endoscopic dilatation. In case of long or inflammatory strictures, balloon dilation may significantly increase the risk of perforation [44]. Hence, inflammatory and ulcerative strictures should be primarily treated with medical therapy.

Over the last years, there is increasing evidence for endoscopic balloon dilation as a safe and minimally invasive effective method for the treatment of stricturing disease. In a retrospective single tertiary center study, Lopes et al. evaluated the long-term efficacy and safety of endoscopic balloon dilation in ileocolonic

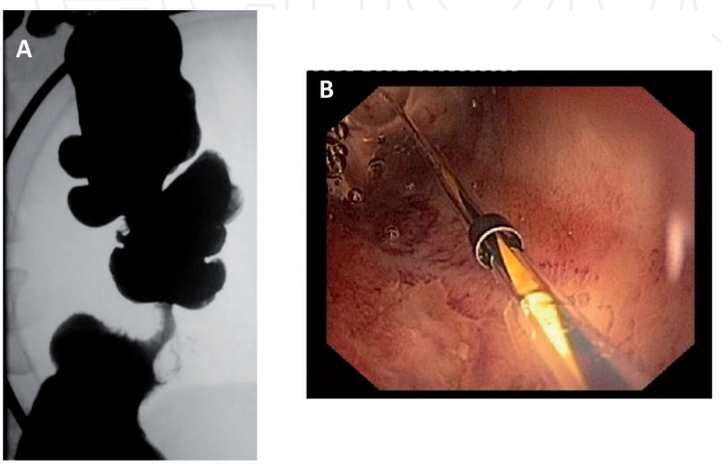

Figure 4.
A segment of short stenosis is delineated using injection of contrast via a catheter (A). A guide wire is inserted through the stenosis and a balloon is then advanced over the wire and carefully inflated (B).

strictures. The authors reported a technical success rate of 97.7% to anastomotic strictures and similar to non-anastomotic strictures (100%) without major adverse events (major bleeding and perforation) [40]. Endoscopic dilatation using balloon-assisted enteroscopy for small bowel strictures is almost the same as for ileocolonic strictures in terms of procedure and technique. However, there are some technical difficulties. In fact, it is not easy to stabilize the tip of the scope and to maintain a good visual field because of the limited space available, severe angulation, motility and adhesion in the small intestine. Nevertheless, the reported technical success rate is over 85% with a perforation rate of 1% [45, 46].

A key concern of endoscopic dilatation is the long-term outcome. Indeed, a recent study showed that 63% of patients with anastomotic strictures and 41% of those with non-anastomotic strictures required additional dilation over a 4.4-year period [40]. However, Sunada et al. reported that the surgery-free rate in 321 patients with CD who underwent endoscopic dilatation for small intestinal strictures was 87% and 78% at 1 and 3 years, respectively [47]. Similarly, a systematic review assessed the role of device-assisted enteroscopy in 581 small bowel dilatations, showing an 80% long-term success rate without the need for surgery during follow-up (2.5 years per patient) [48].

In conclusion, endoscopic balloon dilation is a feasible, simple, effective and safe procedure and an appropriate option for either delaying or preventing surgery, with the possibility of being repeated as needed.

To have a persistent effect over time and avoid the high risk of recurrence, a self-expanding metallic stent has been proposed [49]. Stenting appeared to be an effective technique in treating symptomatic CD intestinal strictures, however the procedure was associated with a high rate of spontaneous migrations and complications. More recently, an anti-migration, removable and shaped self-expandable metal stent is available. Attar et al. performed a real-life study to describe short- and long-term results of the removable anti-migration stent [50]. The authors showed that it was safe and effective in about half of patients and had an extremely low migration rate, with no perforation reported. In addition, the high success rate was close to that obtained with endoscopic balloon dilation, but without complications. Taking this into account, the placement of a transient metallic stent is a new minimally invasive alternative to the management of refractory anastomotic stricture of less than 5 cm, before considering a new surgery. The use of biodegradable instead of metal stents was recently evaluated in intestinal and colonic CD strictures. Although it was technically feasible, premature stent failure occurred in all of the patients, as well as side effects such as mucosal overgrowth and stent collapse [51].

3.2 Removal of impacted capsules

One problem of video capsule endoscopy in patients with suspected or known CD is the risk of impaction due to previously undiagnosed stenoses. One effort to overcome this difficulty was the development of the patency capsule. However, the successful passage of the patency capsule does not absolutely guarantee that intestinal obstruction will not occur during the passage of the video capsule. Similarly, some stenoses may not be detected by prior radiographic methods. Therefore, capsule impaction can occur.

A retained capsule, in general, does not cause obstruction. In fact, the capsule can remain in the small bowel for several months without causing symptoms. Thus, unless malignancy is strongly suspected, conservative or pharmaceutical intervention, namely with corticosteroids, are justified therapeutic options in the majority of cases [52].

When patients develop obstructive symptoms, they may have to undergo device-assisted enteroscopy or surgery. Push-and-pull enteroscopy using the double-balloon technique has proven to be extremely effective (90–100% of cases) and is considered the method of choice [53]. Surgery is an alternative procedure for removing impacted capsules, especially in those cases in which investigations unequivocally suggest the presence of neoplastic disease. The surgical intervention allows the removal of both the capsule and the pathology that caused capsule retention. In addition, intra-operative enteroscopy can be a useful tool to establish intra-luminal pathology like ulceration as a cause of retained endoscopic capsule.

Besides some cases of acute intestinal obstruction, there are only a few more complications reported in the literature due to a retained capsule. In fact, bowel perforation and capsule disintegration have already been reported, but only in case reports [54, 55].

3.3 Treatment of bleeding lesions

CD may be associated with mild gastrointestinal bleeding while major hemorrhage is a rare complication. In addition, a definitive bleeding site is not identified in most patients. In fact, hemorrhage is frequently attributed to diffuse areas of active inflammation [56]. The majority of bleeds originate from the ileum and colon and only a small number of episodes have been attributed to a jejunal or upper gastrointestinal source.

Initial management of major hemorrhage should always include primary resuscitation, as in any individual with a significant gastrointestinal bleed [57]. Once a patient is stabilized, diagnostic maneuvers are of primary importance. The site of bleeding can be identified by endoscopy, angiography or labeled red blood cell scans. However, clinicians should be aware that identifying a precise source of bleeding is difficult and salvage surgery may be necessary.

In the context of CD, urgent device-assisted enteroscopy for large-volume bleeding should be performed via the retrograde route, given the propensity of these conditions to involve the distal small bowel [52]. When it is identified, the source of bleeding is more commonly described as a deep ulcer eroding into a blood vessel and therapy may be attempted [56]. Endoscopy therapy includes thermocoagulation alone or a combination of epinephrine injection and bipolar coagulation [58]. Application of hemoclips may be compromised in the presence of inflamed and friable mucosa. On rare occasions, a large pseudopolyp in the ileum or colon has been identified as the source of bleeding; polypectomy should be performed in these cases. Although endoscopic therapy can stop acute bleeding, it does not promote mucosal healing and therefore cannot prevent rebleeding. In fact, the risk of rebleeding associated with endoscopic hemostasis is about 50% [56]. Thus, therapies that can induce and maintain mucosal healing are necessary to prevent rebleeding, such as anti-TNF agents.

Intraoperative enteroscopy may be the most reliable method to achieve a complete small bowel evaluation. It involves evaluation of the small bowel at laparotomy and may be performed orally, rectally or via an enterotomy. Upper endoscopes, colonoscopes, push enteroscopes and balloon-assisted scopes have all been used. Although it is highly invasive and associated with major complications, it may help in the identification of the bleeding source and in planning the optimal therapeutic intervention [59].

When CD is complicated by obscure bleeding, video capsule endoscopy and device-assisted endoscopy may identify and treat the bleeding source beyond the reach of standard endoscopes [1]. In fact, video capsule endoscopy has a fundamental role in diagnosing obscure gastrointestinal bleeding in patients with CD. It

has been found to be superior to push enteroscopy and small bowel radiography. Video capsule endoscopy should be performed immediately after a negative upper and lower endoscopy as a screening method. The results of video capsule endoscopy should guide the use of device-assisted endoscopy, which aims at both the confirmation and treatment of the detected lesions.

3.4 Intralesional injection

Although local injection of immunomodulatory drugs like corticosteroids and infliximab CD stricture may look like an attractive therapeutic strategy [60], the available evidence is inconsistent. Some studies have shown benefit of intralesional injection of triamcinolone [61] and infliximab [62] at the time of balloon dilatation of CD. On the other hand, East et al. compared local quadrantic injection of triamcinolone after endoscopic balloon dilatation of Crohn's ileocolonic anastomotic strictures vs. saline placebo and showed that a single treatment of intrastricture triamcinolone injection did not reduce the time to redilatation [63]. Moreover, there was a trend toward a worse outcome. Similarly, Atreja et al. reported that intralesional steroid or biologics injection did not decrease the need for re-intervention or surgery for either primary or anastomotic strictures [64]. Until now, there is no strong evidence supporting the injection of drugs at the site of strictures and larger series are needed to evaluate the real effectiveness of these techniques in the treatment of patients with obstructive strictures.

4. Postoperative recurrence

In the natural history of CD, intestinal resection is unavoidable in a significant proportion of patients. The majority of individuals will develop disease recurrence at or above the anastomosis, which usually occurs within a few weeks to months after ileocolonic resection [65].

Diagnosis of postoperative recurrence is based on clinical symptoms, serum and fecal markers, radiological and endoscopic findings. Nevertheless, ileocolonoscopy remains the gold standard, by defining the presence and severity of morphological recurrence [41]. It is recommended within the first 6 to 12 months after surgery, when treatment decisions may be affected. In fact, endoscopic recurrence usually precedes clinical recurrence and severe endoscopic recurrence predicts a poor prognosis. Rutgeerts et al. developed an endoscopic scoring system to assess postoperative recurrence in patients having ileocolonic resection [66]. The patients were stratified into five groups according to the endoscopic severity (**Table 5**). An

Rutgeerts´ score	Endoscopic description of findings
i0	No lesions
i1	≤5 aphthous ulcers
i2	>5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions or lesions confined to ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, nodules and/or narrowing

Table 5.
Rutgeerts´ score. Postoperative recurrence: Rutgeerts score = i2-i4.

endoscopic score of i0 or i1 correlated with a low risk of endoscopic progression and had clinical recurrence rates of less than 10% over 10 years. An endoscopic score of i2 or above suggests mucosal inflammation and should prompt considered treatment escalation [14]. However, it is important to note that the i2 category, including aphthous lesions in the terminal ileum as well as ileocolonic anastomosis lesions, had a heterogeneous recurrence risk. Therefore, a modified Rutgeerts' score has recently emerged in which i2 is subdivided into i2a for lesions confined to the ileocolonic anastomosis, including anastomotic stenosis, and i2b for more than 5 aphthous ulcers or larger lesions, with normal mucosa in between, in the neoterminal ileum, with or without anastomotic lesions [67]. With this modified score, stenosis and/or ulceration of the anastomosis, which might simply be related to ischemia or staples, do not define recurrent disease and have no prognostic or therapeutic implications [68]. Thus, possible confounding factors for recurrent disease are overcome with this score.

Video capsule endoscopy can also be used to assess postoperative recurrence of CD and should be considered if ileocolonoscopy is contraindicated or unsuccessful. Video capsule endoscopy may identify lesions in the small bowel that have not been detected by ileocolonoscopy after ileocolic resection. An important advantage of capsule endoscopy is the ability to detect proximal small bowel recurrence. However, patency capsule evaluation is recommended before capsule endoscopy to minimize the risk of retention.

5. Small bowel malignancy

Patients with CD are at an increased risk of developing malignancy, which is more frequent in the CD-affected colon. However, those with small bowel involvement may also develop cancer, which can be difficult to diagnose. In fact, compared with an age-matched population, patients with CD have an 18-fold increased incidence of small bowel malignancy and only a minority are detected at an early stage [69]. Adenocarcinoma is the most common form of all small bowel cancer. Prognosis of small bowel adenocarcinoma is poor and the mortality at 1 and 2 years ranges from 30–60% dependent on the stage of cancer [70].

Early detection of small bowel carcinoma remains a problem. Radiological imaging and video capsule endoscopy could potentially detect malignancies at an early stage. However, differentiation between inflammatory stenosis and cancer is difficult. In these cases, device-assisted enteroscopy should be performed to direct visualization and tissue sampling. Furthermore, these procedures are not routinely used for screening asymptomatic individuals. Therefore, every patient who has a change of symptoms should perform further exams as this might be an indicator of malignancy [69]. Moreover, most of the small bowel carcinoma in CD is located in strictures, so the endoscopist should have a low threshold for taking biopsies before endoscopic balloon dilatation [71].

6. Conclusions

Endoscopy has major implications for diagnosis, classification, therapeutic decision and prognosis of CD. Ileocolonoscopy with biopsy is the first-line exam for suspected CD. However, the small bowel is one of the most affected areas by inflammation, which may skip the terminal ileum and not be detected by ileoscopy. In fact, small intestine involvement is more difficult to assess by conventional endoscopy. In addition, radiological examinations, including both magnetic

resonance imaging and computed tomography, may not detect disease of the small bowel, especially in mild lesions.

Until a decade ago, mucosal visualization of the small intestine was limited to the reach of the push enteroscope. The advent of video capsule endoscopy and device-assisted endoscopy is revolutionizing small bowel CD diagnosis and treatment. In fact, these techniques allowed direct visualization of the entire small intestine, which would alter patient management, especially in those with inconclusive results from conventional studies. Device-assisted endoscopy has also the ability to obtain biopsies for histopathology and the potential for therapeutic intervention. Finally, video capsule endoscopy and device-assisted endoscopy play an important role in assessing response to therapy.

Conflict of interest

The authors declare no conflict of interest.

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