

Review

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Review

Endoscopic Management of Strictures in Crohn's Disease: An Unsolved Case

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Abstract: Crohn's disease (CD) is a chronic inflammatory disease associated with a significant burden in terms of quality of life and health care costs and is frequently associated with several complications, including the development of intestinal strictures. Stricturing CD requires a careful multidisciplinary approach involving medical therapy and surgery, still posing a continuous management challenge; in this context, endoscopic treatment represents a valuable, in-between opportunity as a minimally invasive strategy, endorsed by extensive yet heterogeneous evidence and evolving research and techniques. This review summarizes current knowledge on the role of therapeutic endoscopy in stricturing CD, focusing on evidence gaps, recent updates, and novel techniques intended for optimizing efficacy, safety, and tailoring of this approach in the view of precision endoscopy.

Keywords: Crohn's disease; Crohn; stricture; balloon dilation; EBD; stricturotomy; intestinal stent; fibrosis; nanoparticles

1. Introduction

Crohn's disease (CD) is a chronic inflammatory condition that can affect all gastrointestinal tract segments, with an intermittent and chronic course and increasing incidence [1]. Intestinal strictures represent one of the most frequent complications of CD, resulting from sustained transmural inflammation and abnormal extracellular matrix deposition, and affecting approximately one-third of CD patients [2]. Two types of stricture can be identified: primary (de novo) and secondary (post-operative, anastomotic) strictures: primary strictures can develop in all segments affected by the disease, with the ileum being the most frequent site of onset, given the higher prevalence of disease-related inflammation in this segment and its smaller diameter compared to the colon [3,4].

Prompt multidisciplinary management of stricturing CD is required, considering the risk of bowel obstruction, the neoplastic potential [5], and the need to monitor upstream disease activity hidden proximally to the stricture. In this scenario, advanced therapy with biologics and small molecules may delay or reduce the need for repeated surgery in an organ-sparing perspective [6]); endoscopy stands out between medical therapy and surgery as a feasible, minimally invasive tool in selected cases, with an established role and still growing evidence in managing stricturing CD. Endoscopic balloon dilation (EBD) is the most extensively employed endoscopic procedure, being associated with a technical success rate exceeding 90% in most studies and a favorable safety profile for the treatment of short intestinal strictures [7]. Beyond EBD, in the last two decades, a wide range of alternative procedures have been gathering attention [8], with still limited data and a lack of standardization both in techniques and study designs [9]. In the era of precision endoscopy in inflammatory bowel disease (IBD), there is growing interest in advanced imaging techniques and

artificial intelligence tools to aid inflammation and dysplasia recognition and discriminate molecular patterns to target [10,11]; likewise, both the established and the potential therapeutic endoscopic tools promise to lead the management of stricturing CD to an increasingly minimally invasive and personalized approach, with still several dark spots to be addressed and groundbreaking roads to be taken.

Our review aims to build on established knowledge of endoscopic treatment of CD-associated strictures, identify evidence gaps, and highlight the latest advancements in the most intriguing techniques in development (Figure 1).

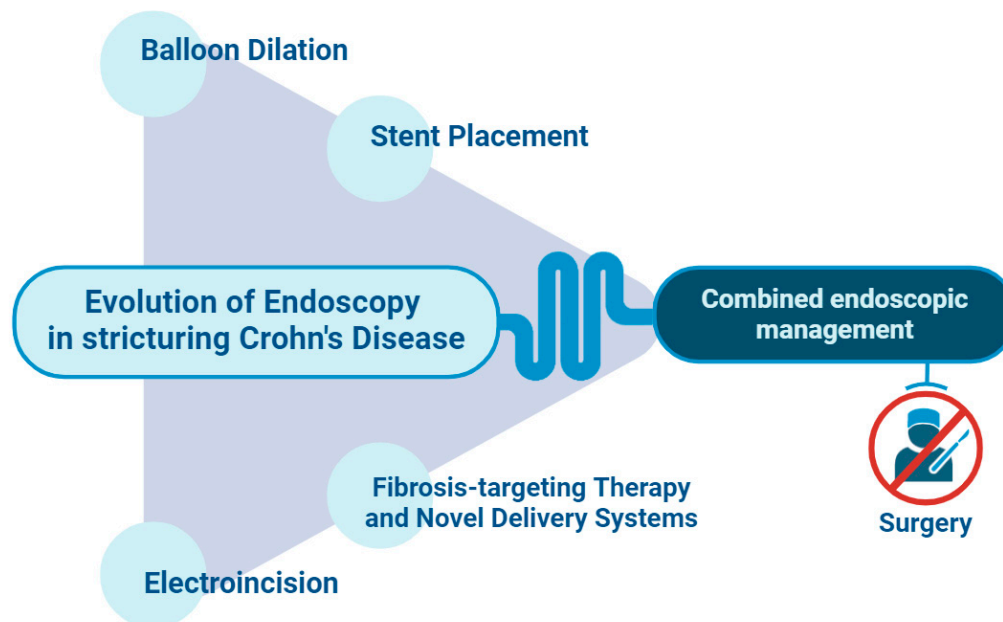


Figure 1. Evolution of endoscopy in structuring Crohn's Disease. The improvement of the known techniques alongside with the development of new technologies paves the way for an increasingly less invasive, combined endoscopic approach, with a view to tailored management, organ-sparing strategy, and better quality of life.

2. Endoscopic Balloon Dilation

2.1. Endoscopic Balloon Dilation as the Standard Endoscopic Procedure for Short Strictures in Crohn's Disease

EBD is the first described endoscopic treatment for intestinal strictures [12]. Since 1986, EBD has been applied for a wide range of gastrointestinal strictures and has been shown to be a straightforward, effective, and safe procedure, rapidly developing into the most used endoscopic treatment in stricturing CD upon proper selection of the patient, setting, and stricture type. Although extensive data is available, the heterogeneity of techniques and study designs made the adequate standardization and generalization of results challenging.

The definition of the efficacy outcomes and the procedure technique widely vary both in study settings and clinical practice. According to the recent practical guidelines on endoscopic management of stricturing CD [9], a standardization of efficacy outcomes is advisable, in particular technical success (post-procedural resistance-free passage of the endoscope through the stricture, specifying the type of endoscope used), clinical efficacy (relief from occlusive symptoms at 6 months), and long-term efficacy (surgery-free survival at 1-year follow up), still taking into account the limits of these definitions; in fact, symptoms of CD-associated strictures may not reflect objective findings and the threshold for surgical intervention varies based on the patient and the surgeon's preferences; moreover, the severity of the stricture and the persistence of symptoms might influence the need for an additional EBD [9]. Regarding the procedure technique, graded inflation has proved to reduce the risk of intestinal perforation and bleeding, allowing proper inspection of the dilated tract after each

controlled expansion, with gradually increasing diameters [13] and each dilation step varying from 20 seconds to 3 minutes in the available studies [12]. In a pooled analysis by Reutemann et al, no association between balloon size and surgery-free survival was found. Notably, patients undergoing dilations greater than 18 mm had an increased risk of surgery compared with 14 to 18 mm sizes, possibly due to the refractoriness of the disease in patients treated with larger balloons [14]; whether all strictures can tolerate the same degree of dilation in a single episode, or instead, if features exist to stratify the dilation capacity of individual stenoses, remains to be clarified. In a systematic review including 33 studies from 1991 to 2013, with 1463 CD patients who underwent 3213 EBD procedures (62% anastomotic, 38% de novo strictures), Betterworth et al. conducted a pooled analysis after collecting the individual data of 676 patients, showing that a length <5 cm was associated with a longer surgery-free interval after EBD; the rate of technical success was 89.1% and EBD resulted in clinical efficacy (remission of obstructive symptoms) in 80.9% of all patients, with no statistical difference between anastomotic and de novo strictures. However, at 2-year follow-up, 73.5% and 42.9% of patients underwent redilation and resective surgery respectively. A stricture length of <5 cm was associated with a surgery-free outcome with (HR 2.5; 95% CI 1.4–4.4; P=0.002) and without (HR 2.4; 95% CI 1.3–4.2; P=0.003) correction for stricture location, type of strictures, balloon caliber, steroid injection, and accessory endoscopic therapy. A cutoff for stricture length of <5 cm also showed a strong tendency to be associated with a redilation-free outcome (P=0.06); however, no specific cut-off value for balloon size could be definitively recommended, although a larger balloon diameter was identified as a predictive factor for greater technical success [15]. Major complications, like perforation, bleeding, or surgery after dilation, occurred in 2.8% per procedure and 6.2% per patient. However, it remains unclear whether the efficacy and the complication rate may differ based on a different dilation strategy and technique (single-session versus multiple-session dilation, one-step versus graded dilation) and which stricture type may benefit from one method over the other, still a prerogative of the single operator expertise; the number of dilations, the interval between dilations, and the length of follow-up highly varied between, and in some cases within, the included studies; moreover, some patients may have been dilated in the absence of overt obstruction, limiting the results' reliability and stratification.

Overall, EBD is indicated in CD patients with symptoms of bowel obstruction and non-complicated, non-angulated strictures shorter than 5 cm [9]; graded dilation with balloons up to a maximum size of 18-20 mm is recommended [9]. Currently, there is no full agreement on whether or not to perform endoscopic dilation in asymptomatic patients; the patient's symptoms do not necessarily correlate with the functional impairment caused by the stenosis, whereas the endoscopic treatment could delay or prevent symptoms and complication risk. Notably, symptomatic patients who undergo EBD typically have a poorer response to treatment and are at a higher risk of subsequent surgery compared to asymptomatic patients [9]; similarly, in CD-related strictures, pre-stenotic dilatation is associated with increased risk of bowel obstruction and surgery [16], as well of poor response to EBD, despite representing the setting of the highest potential benefit of the endoscopic strategy when effective (10.1016/j.cgh.2016.10.030 [17]).

Beyond the many details to be clarified for proper standardization, recent comparative studies (Table 1) and ongoing trials promise to give new insights into the therapeutic role of EBD in CD; for instance, a prospective multicenter observational study is underway to evaluate the role of EBD in ameliorating mucosal and transmural inflammation of the prestenotic intestinal tract, as a better fecal flow and a clearance of inflammatory mediators and microbiota could improve the local gut microenvironment and reduce upstream inflammation (NCT04803916).

Table 1. Comparative studies currently available on the management of CD-associated strictures.

	Study Design	Strictures location	Treatment and No of pts	Technical Success Rate	Long-term Outcomes (years fu)	Adverse events, %
Lian et al. [17] 2017	Retrospective	Ileocolic anastomosis	176 EBD 131 surgery	-	average time to surgery/re-surgery delayed by 6.45 years in EBD group	1.1 (perforation) 8.8 (~ infection)
Chen et al. [18] 2024	Retrospective	Duodenal	30 EBD 18 surgery	-	2.96 years recurrence-free 6.31 years recurrence-free, p=.01	0,74 16.67
Lan et al. [19] 2018	Retrospective	Anastomosis (85.7% ileocolic)	21 ES 164 EBD	100% 89.5%	9.5% surgery (0.8) 33.5% re-surgery (4)	8.8 (bleeding) 1.1 (perforation)
Lan et al. [20] 2019	Retrospective	Ileocolic anastomosis	35 ES 147 ICR	-	11.3% surgery (0.8) 10.2% re-surgery (2.2), p .83	10.2 (~ bleeding) 31.9 (~ ileus)
Lan et al. [21] 2020	Retrospective	Distal ileum, ileocecal valve	13 ES 32 ICR	100% 100%	15.4% surgery (1.8) 18.8% re-surgery (1.5), p .79	6,9 (perforation) 25 (~ infection)
Loras et al. [22] 2022	Randomized trial	-	41 EBD 39 FCSEMS	-	80% no re-intervention (1) 51% no re-intervention (1), p .0061	2 (perforation) 3 (perforation)

ES, endoscopic electroincision; EBD, endoscopic balloon dilation; FCSEMS, fully-covered self-expandable metallic stents; fu, follow-up ICR, ileocolic resection; p, p-value; pts, patients; ~, most frequent.

2.2. Intralesional Corticosteroid Injection

The role of intralesional corticosteroid injection following EBD is unclear, due to two outdated prospective, randomized, clinical trials providing conflicting results. East et al. compared local quadrantic injection of 40 mg of triamcinolone after EBD of ileocolic anastomotic CD short strictures (<5 cm) to saline placebo [23]; 1 of 6 patients in the placebo group compared to 5 of 7 patients in the steroid group required redilation, with a statistical trend to a difference in time to repeat dilation, which was worse in the steroid group (p 0.06, HR 6.1). In a similar setting, Di Nardo et al. enrolled 29 pediatric CD patients with both de novo (17) and anastomotic (12) short strictures to receive or not intralesional quadrantic injection of 40 mg triamcinolone after EBD. In the placebo arm, 5 and 4 patients out of 14 required redilation and surgery at 12-month follow-up, respectively; only 1 out of 15 patients in the experimental arm required redilation, and none required surgery. The groups differed significantly in time without re-dilation (P=0.04) and surgery (P=0.02) [24]. The results of these two trials are quite contrasting, despite a similar injection technique; however, a proper comparison between the two studies is limited by small sample sizes, different populations, and different stricture locations. In 2022, Feleshtynsky et al. explored the efficacy of intralesional prednisolone injection after EBD compared to EBD alone in 64 CD patients [25]. The stricture recurrence risk in the combination arm was 4.5 times lower than in the EBD-alone arm at 12-month follow-up, with persistency of clinical remission in 90.7% versus 65.7% of the patients and a lower redilation rate in the combination arm (1.1 ± 0.3 versus 1.44 ± 0.66). Notably, the combination arm observed a better epithelial structure and decreased cellular infiltration and fibrotic deposition at the histological level. No significant difference was reported in terms of perforation and bleeding risk; however, no data concerning stricture location was shown. As a result, the true benefits or harms of intralesional steroid injections after EBD are not known and this technique is not recommended in clinical practice, still representing a missed chance in stricturing CD management.

2.3. Endoscopic Balloon Dilation in the Upper Gastrointestinal Tract

Available data on endoscopic management of strictures of the upper gastrointestinal tract is still low, at least partially because of the lower prevalence of upper gastrointestinal localization and the more frequent complex disease when the upper gastrointestinal tract is involved, often requiring surgical intervention. Most studies do not provide a separate analysis on the use of EBD for CD-associated strictures of the upper gastrointestinal tract; conversely, Betterworth et al. analyzed data from multicenter cohort studies, with a total of 94 CD patients who underwent EBD for strictures of the upper gastrointestinal tract (107 duodenum, 30 stomach, 4 both); technical and clinical success rate was 100% and 87% respectively, major complications occurred in 2.9% per procedure, and

patients with small-bowel disease location had a higher hazard for symptom recurrence and need for redilation. The long-term outcomes were not significantly different compared to the strictures of the ileocecal tract during a follow-up period of 24 months (70.5% vs 75.9% symptom recurrence, 59.6% vs 73.5% need for redilation, and 30.8% vs 42.9% surgery) [16]. In a recent cohort study, 86 patients with benign duodenal stenosis including 19 CD patients who underwent EBD in 16 years of a single-center experience (2002-2018) had a high rate of technical and clinical success, which was higher for repeated EBD in CD patients (91.7%), compared to the clinical success rate of repeated EBD for all other aetiologies (74.3%), with 2 cases of bleeding (2.3% and no perforations [26]. Furthermore, patients who underwent aggressive initial dilation were less likely to repeat dilation compared to non-aggressive initial dilation (mean 5.39 versus 4.07 mm more than the estimated caliber of the stricture, p 0.07). However, among the 19 patients with CD, 6 required surgical intervention anyway.

Despite limited evidence available, EBD appears to be gaining traction for duodenal disease as well [18], demonstrating its potential use also in upper gastrointestinal tract disease. Overall, EBD is considered comparably effective in the short term in the upper and lower gastrointestinal tracts, although there is still a need to evaluate its impact on late outcomes.

2.4. Focus on Dilation during Enteroscopy, a Stand-alone Situation?

CD-related deep small bowel strictures require access through device-assisted enteroscopy, including balloon-assisted enteroscopy (BAE), with similar outcomes as for strictures reachable by ileocolonoscopy [5,27–29]. In a recent meta-analysis with 463 CD patients who underwent EBD for deep small bowel strictures, the overall technical success reported was 94.9%, with a short-term clinical efficacy of 82.3%. During follow-up (median time 25.5 months, IQR 6-53 months), 48.3% of patients reported a recurrence of symptoms, 38.8% were re-dilated, and 27.4% underwent surgery [13]. A nationwide, multicenter, retrospective Japanese study reported surgical conversion rates of 26.0%, 45.6%, and 55.7% at 1, 5, and 10 years post-EBD, respectively [30]; however, this study is based on a large population of patients undergoing dilation with enteroscopy over dilation of the low gastrointestinal tract (181 over 305), with no differential analysis on deep small bowel strictures. Another prospective, multicenter, Japanese study analyzed EBD through BAE in 95 CD patients, reporting clinical success in 69.5% of the patients, associated with a larger balloon diameter (15.20 ± 1.70 vs 13.65 ± 2.59 mm, $p=0.03$) and with a good safety profile (5%, all conservatively managed complications) [27]. Furthermore, a systematic review concluded that dilation of 15 mm or more is a risk factor for perforation [31]; consequently, the final target diameter generally recommended is 12-15 mm in this setting, despite heterogeneous data [32]. Focusing on complications, in a systematic review, the incidence rates of severe bleeding, and complications requiring surgery were between 1.82% and 3.21%, whereas the incidence rate of perforation was found to be 0-10% in several observational studies [13,27,33]. Possibly due to the increased difficulty and invasiveness associated with the procedure, higher complication rates were observed after enteroscopic EBD compared to EBD for ileocecal and gastroduodenal stenosis [15,16].

Overall, lacking specific and comparative evidence on EBD efficacy stratified on the localization of strictures, these data allow us to affirm at least that EBD during BAE is comparable to the EBD performed in the localizations achievable by colonoscopy in terms of short-term safety and efficacy, and favor of a similar efficacy of EBD regardless of stricture location; of course, lacking location-specific data, it is still not possible to speculate further, especially on long-term effectiveness and surgery rate.

3. Endoscopic Electroincision: Strictureotomy and Strictureplasty

In recent years, there has been increasing interest in stricturotomy (ESt) and strictureplasty (ESTx) as an alternative to EBD in the endoscopic management of stricturing CD; similarly to EBD, these procedures lack standardization in technique and outcome terminology, possibly delaying their exact placement in the IBD landscape. In 2020, the Global Interventional Inflammatory Bowel Disease Group provided detailed guidance and suggested the use of 'endoscopic electroincision (ES)' as a unique term for techniques utilizing electrocautery to cut strictured tissue. Electroincision to widen

the stenotic lumen (ES_t) can be performed using different needle-knives in radial, horizontal, or circumferential orientations, with the possibility of endoscopic clipping after the incision to consolidate the cut with a secondary closure, keeping the lumen wider (ES_x) [9]. Endoscopic electroincision is commonly used for papillotomy in endoscopic retrograde cholangiopancreatography, with recent data on esophageal and, more recently, biliopancreatic strictures [34–36].

In 2011, Nal et al. published the first case series describing 10 IBD patients with long, fibrotic ileal-pouch strictures refractory to EBD who were treated with ES [37]; the same group from the Cleveland Clinic lately retrospectively evaluated the efficacy and safety of ES in treating primary and secondary strictures in IBD patients, comparing it with EBD and ileocolic resection [19–21,38]. The retrospective study included 50 UC patients with ileal-pouch anastomosis stricture and 35 CD patients (mostly ileocolic anastomosis), with a total of 127 strictures treated with ES, demonstrating a 100% technical success of the procedure [38]. In a median follow-up of 0.9 years, 60.6% of strictures required multiple treatments after the first ES, mostly a subsequent ES (44.9%), an EBD (22.8%), or both combined (11.0%). The cumulative 3-year surgery-free survival rate was 62.0%. Only one patient (0.4% per procedure) experienced perforation, and 9 patients (3.3% per procedure) had postprocedural bleeding. The study comparing ES with EBD included CD patients with anastomotic strictures (85.7% ileocolic), showing technical success of 100% in the 21 patients treated with ES and 89.5% in the 164 patients treated with EBD ($P=0.25$) [19]. No significant difference in the need for additional endoscopic treatment was found between the two groups ($P=0.85$). Only 2 patients (9.5%) in the ES group required subsequent surgery, compared to 55 (33.5%) in the EBD group ($P=0.03$). However, it has to be noted that the follow-up duration varied between the two groups, with a median of 0.8 years (IQR: 0.1–1.6) for the ES group and 4.0 years (IQR: 0.8–6.9) for the EBD group ($P < 0.0001$). ES showed a lower risk of perforation than EBD (0% vs 1.1%), though there were major concerns about bleeding (8.8% vs 0%). When compared with ileocolic resection (ICR), ES showed comparable surgery-free survival in two different retrospective studies; in the first study on ileocolic anastomosis strictures, 4 out of 35 patients (11.3%) in the ES group and 15 out of 147 patients (10.2%) in the ICR group required subsequent surgery ($p=0.83$), where the median follow-up duration was 0.8 years for the ES group and 2.2 years for the ICR group ($p<0.001$) [20]; in the second study on primary distal ileal and ileocecal valve strictures, 2 out of 13 patients (15.4%) in the ES group and 6 out of 32 patients (18.8%) in the ICR group required subsequent surgery ($p=0.79$) [21]. In this case, the median follow-up duration was comparable: 1.8 years for the ES group and 1.5 years for the ICR group ($p=0.84$). In both studies, ES showed a lower incidence of major adverse events compared to ICR; nevertheless, the two groups differed significantly in stricture complexity, with the ICR group having statistically longer and more symptomatic strictures. Even if the majority of the strictures treated with ES in the published studies were located in the ileocolic anastomosis, ES was found to be feasible and safe also for the refractory rectal anastomotic stricture [39].

In the IBD setting, low data on ES efficacy is available. Recently, 24 patients with endoscopic non-traversable anorectal/anopouch strictures (18 CD and 4 UC patients) were treated with ES, with a technical success of 100%, yet a mean time to endoscopic reintervention with subsequent ES of 5.3 months; over a 12.8-month follow-up, two patients (8%) required surgical intervention for refractory stricture disease. No 30-day post-procedure adverse events were reported [40]. ES has been used for deep small bowel strictures in CD (including both the ileum and the jejunum). A multicenter cohort study evaluated the efficacy and safety of BAE-assisted ES for treating these strictures in 28 CD patients with 58 non-passable deep small bowel strictures, resulting in a technical success of 96% and a 1-year cumulative surgery-free rate of 74.8% [41]. Finally, ES is a feasible option for CD-associated anorectal strictures, although evidence is still low [9].

Overall, ES is a promising procedure for the endoscopic management of stricturing CD, though a slow learning curve could hinder the widespread use of these techniques. Two randomized clinical trials (BEST-CD and DESTRESS) are currently underway to compare EBD and ES in terms of clinical success, need for surgery, and safety with 1-year follow-up in patients with short CD-associated strictures (NCT05521867, NCT05009212).

4. The Graveyard of Endoscopic Techniques: Is There Room for a Second Chance?

The history of the endoscopic treatment of stricturing CD has seen the development of several techniques, eventually failing to emerge from the overgrowth to clinical practice due to several reasons, including inconsistent clinical trial results, technical difficulties, invasiveness for the patient, poor reproducibility, limited large-scale applicability, and cost. Among the most explored, local injection therapy with anti-tumor necrosis factor (anti-TNF) and endoscopic stents have shown promising results, as well as ongoing novel attempts of improvement to access the IBD treatment landscape.

4.1. Anti-TNF Intralesional Injection

Anti-TNF injection has shown promise, although this approach has been nearly abandoned also in the trial setting. In 2008, a pilot study involving 3 CD patients investigated infliximab (IFX) local injections (90–120 mg) into colonic strictures, resulting in clinical efficacy at 5-8 months in all patients; one patient unresponsive to IFX therapy saw the complete resolution of the stricture after the first local injection and remained symptom-free for 5 months after a second injection, one patient required additional stricture dilation, the third one needed five injections every four months [42]. Similarly, another exploratory study from 2014 assessed the efficacy of intralesional injections of 40 mg of infliximab combined with EBD in EBD-refractory small bowel strictures (either primary or anastomotic) in 6 CD patients; five out of 6 patients underwent serial EBD at 0, 2, and 6 weeks, receiving intralesional infliximab injections after each session. All patients showed a decrease of modified Simple Endoscopic Score for Crohn's Disease (mSES-CD) by an average of 3 points (reduction in ulcer size, ulcerated surface area, and disease-affected surface area of the distal visible part of the narrowed tract) and improved symptoms, with no adverse effects observed at 6-month follow-up [43]. However, although the authors specify that all enrolled patients had not been previously exposed to infliximab, they do not provide information on any concomitant medical therapies the patients might have been receiving.

A larger, multicenter, randomized, controlled trial on the efficacy of injecting adalimumab into intestinal CD strictures is displayed on [trialgov](https://clinicaltrials.gov), but it was eventually not published (NCT01986127). While local anti-TNF therapy seems well tolerated, more extended follow-up and larger randomized controlled clinical trials would be necessary to establish its potential benefits; however, effectiveness could be possibly significant moving from a one-time therapy to repeated injection, with anticipated issues concerning quality of life, invasiveness, and health care costs [42,44].

4.2. Self-Expanding Metal Stents

Self-expandable metallic stents (SEMS) constitute an effective, non-surgical treatment for neoplastic intestinal obstruction, both as a palliative measure and as a bridge to surgery [45]; SEMS must be fully or partially covered with a plastic film, which prevents colonization by the intestinal mucosa and allows a smooth delayed extraction. Loras C. et al. conducted an extensive review of the literature, describing 19 studies, for a total of 65 patients, describing SEMS as a safe and effective alternative to EBD and surgery for the treatment of short stenosis in CD patients, with possible advantages for complex or longer (>5 cm) strictures [45]. A retrospective study by the same group, involving 17 CD patients treated with SEMS for symptomatic refractory colonic and ileocolic anastomosis strictures, reported a clinical efficacy rate of 64.7%, with patients remaining free of symptoms for an average follow-up period of 67 weeks [46]; migration occurred in 52% of patients, and there were 4 cases of impaction, with one patient requiring surgery due to proximal stent migration. Another retrospective cohort involving 5 patients with anastomotic strictures, with uncovered SEMS placed for an average of 9.7 months, reported an 80% clinical efficacy rate at a mean follow-up of 28 months [47]; the complication rate was 20% (n=1), and the 4 patients who did not require re-intervention showed an average long-term luminal patency of 34.8 months [47]. A prospective cohort study involving 11 patients who received SEMS showed a 60% clinical success rate, with an adverse event rate of 73% (8/11), of which two patients required surgery related to the

procedure, 6 patients experienced stent migration after an average time of 3 days. As a result, it was concluded that the risk of complications was too high to recommend the routine use of endoscopic metal stents for CD strictures [48]. In a recent study with 21 CD patients, SEMS placement and following removal at day 7 resulted in clinical remission in 88% (14 of 16) of patients during follow-up (3-50 months) [49], with an adverse event rate of 21%, including abdominal pain and asymptomatic stent migration. In a comparative study, 80 CD patients with symptomatic strictures (60% shorter than 4 cm) were randomized to fully-covered SEMS (39) or EBD (41); despite a similar safety profile, the stent group had a significantly higher proportion of patients requiring new therapeutic intervention at one-year follow-up due to symptoms recurrence (49% vs 20%) [22]; notably, the difference in efficacy between EBD and fully-covered SEMS was not significant for strictures over 3 cm (both treatments achieving nearly 65% success) and primary stenosis (respectively 60% and 70%), with a high migration rate representing a potential limiting factor. Given the high rate of stent migration, Branche et al. investigated the Hanarostent stent, a partly covered SEMS with an antimigratory design and an early removal protocol; following promising results of an exploratory study in 7 CD patients [50] they conducted a larger national study with the same device in 46 CD patients (73.9% with anastomotic stricture, median length of 3.1 ± 1.7 cm) observing clinical efficacy in 58.7% of the patients at 26 months follow-up, with no perforations and only 3 stent migrations reported (6.5%) [51]. Comparative research is ongoing with a randomized clinical trial comparing EBD followed by SEMS placement versus surgical intervention in CD patients with de novo and primary symptomatic stenosis less than 10 cm long [52].

4.3. Lumen-Apposing Metal Stents

Lumen-apposing metal stents (LAMS) are short, fully covered metal stents with large flanges at each end to anchor the stent and minimize migration risk [53,54]. Initially designed for draining pancreatic fluid collections, LAMS has been used off-label to manage short-segment luminal strictures [55,56], with several studies showing promising outcomes. Regarding CD patients, evidence is low; in the light of two case reports on anastomotic strictures showing short-term clinical efficacy and no post-procedural complications [57,58], Hedjoudje et al. evaluated LAMS for lower gastrointestinal anastomotic strictures in 28 patients, including 18 with CD-associated anastomotic strictures. Technical success was achieved in all patients, with clinical efficacy at the last follow-up visit in 85.7% (24/28) of patients; among the 3 patients experiencing adverse events, one patient missing his three-month CT scan experienced failed stent extraction seven months post-placement and subsequently required surgical resection. Spontaneous asymptomatic stent migration occurred in 47% (13/28) of patients, without recurrent symptoms or significant complications [59]. Unfortunately, the authors did not provide a separate analysis for the subgroup of patients with IBD.

4.4. Biodegradable Stents

Considering the high migration rates and the need for follow-up endoscopy for the removal of SEMS, biodegradable stents (BDS) have been developed and primarily evaluated for esophageal strictures, yielding promising outcomes [60–62], though they are not approved for bowel strictures. BDS exert a constant radial force for approximately 4-5 weeks to treat the underlying esophageal disease, while progressive hydrolysis-mediated self-degradation prevents tissue overgrowth and leads to dissolving within 12 weeks [63]. A prospective study evaluated polydioxanone monofilament stents, which provide 6-8 weeks of radial force before degradation, in a cohort of 11 patients with benign small and large intestinal stenosis naïve to EBD [64], showing a technical success rate of 91%, with no adverse events other than early stent migration in three patients. However, few studies, mainly case reports and series, have investigated BDS in stricturing CD. Rejchrt et al. reported successful BDS insertion for small and large bowel stenosis in 10 out of 11 CD patients, with early stent migration (2 days to 8 weeks) observed in three patients [64]. Karstensen et al. documented the case of a 52-year-old man with CD, successfully treated with a custom-made biodegradable polydioxanone monofilament stent (15 cm) for a 12 cm small bowel stricture, remaining symptom-free at 3-month follow-up [65]. However, a subsequent study by the same group involving 6 CD

patients with intestinal stenosis at various locations (duodenal bulb, ileocolic anastomosis, afferent limb of a J-pouch, and sigmoid colon) refractory to EBD and treated with biodegradable stents, reported clinical success in only one patient. Failures were attributed to mucosal overgrowth in two patients, stent migration in one patient, and stent collapse in another [66].

5. New Techniques and Future Scenarios for Stenosis and Fibrosis Treatment in IBD Involving Pathogenesis and Molecular Pathways

Future scenarios for stenosis treatment in IBD are likely to involve a combination of minimally invasive procedures and targeted therapies. As we improve our knowledge of fibrosis pathogenesis and stenosis development in IBD, novel therapeutic opportunities are emerging. The advent of single-cell transcriptomics has better defined the transcriptional profile of fibroblasts in CD and ulcerative colitis (UC) [67,68]; targeting fibroblasts at a cellular and molecular level has been a promising subject of investigation: for instance, when adding pirfenidone, an agent approved for treating idiopathic pulmonary fibrosis, to fibroblasts isolated from patients with stricturing CD, their function and proliferation is inhibited via transforming growth factor beta 1 (TGF β 1) pathway downregulation [69]. Parallely, several small experimental molecules have been tested as potential inhibitors of the main molecular pattern of fibrosis, with still inconclusive and inconsistent results [70,71]. Moreover, stem cell manipulation and administration offer a promising scenario, with a constantly increasing body of evidence; human adipose-derived mesenchymal stem cells, pretreated in vivo with interferon (IFN) γ and kynurenic acid, ameliorate intestinal injury in a fibrosis rat model [72]. Both prophylactic and therapeutic treatment with bone marrow-derived mesenchymal stem cells improves fibrosis and reduces collagen deposition, via interleukin(IL)-1beta, IL-6, and IL-13 downregulation, and IL-10 upregulation [73]. In experimental colitis mice, mesenchymal stem cells can reduce the thickness of submucosa/muscularis propria, as well as collagen deposition; furthermore, in human primary intestinal myofibroblasts mesenchymal stem cells reduce the TGF- β 1-induced fibrogenic activation [74]. Antibodies targeting proteins involved in collagen remodeling have been identified as a possible therapeutic strategy as well; the inhibition of matrix metalloproteinase-9 (MMP-9), a type IV collagenase overexpressed in fistulizing and structuring CD, led to reduced collagen deposition in heterotopic xenograft models of intestinal fibrosis [75]. Among other unexplored therapeutic targets is teduglutide, already approved for the treatment of short bowel syndrome, showing a reduction of fibrogenesis and improved fibrolysis since the first week after surgery in a murine model of ileal resection and anastomosis [76,77]. More recently, the anti-fibrogenic effects of glucagon-like peptide 2 (GLP2) have been demonstrated even in the liver of a murine model of cholangitis [78].

Novel biomarkers and pharmacological agents will play a crucial role in enhancing treatment outcomes, possibly involving novel local delivery systems to allow tissue-targeted therapy and minimize side effects. Over the past two decades, there was a slow but consistent understory of research and development of a large number of nanoparticles (NPs) in IBDs; NPs are polymeric fine units with at least one dimension up to 100 nm, which can be built to reach an intended target, be detected with a molecular imaging technique and further engineered to locally deploy a certain agent, with several mechanisms of activation including charge-mediated targeting, micro-environment triggered release targeting, and ligand-mediated targeting [79,80]. Nanomedicine combined with endoscopy has built up a solid background in ex vivo and in vivo preclinical settings, with minimal preliminary clinical data concerning esophageal and biliary cancers [79,81,82]; however, there is still no impact on clinical practice, in part due to safety concerns and heterogeneity of NPs, practical application, and study designs. The dual potential of NPs as drug-eluting and detectable nanovehicles represents an exciting perspective in IBD, potentially leading to dose-controlled and selective insite bioavailability of a drug or a therapeutic intervention targeting inflamed mucosa [83]. Among intestinal delivery systems, another remarkable product recently developed is a biocompatible hydrogel amenable to the endoscopic application (CoverGel), showing intriguing preclinical data; in experimental colitis mice, when comparing CoverGel + IFX versus subcutaneous

IFX alone, it was observed similar efficacy on inflammation, with significantly lower levels of ATI in the CoverGel group [84].

5. Conclusions

In the last decades, endoscopy has been engaging stricturing CD as a minimally invasive approach aiming to delay and prevent surgery and promote a superior quality of life. Although EBD is indeed the standard of care for short strictures, the extensive data available is burdened by wide variability in dilation technique and study settings, leaving several unsolved issues mostly concerning long-term outcomes; moreover, there is no real-life data on the adherence to the evidence for EBD in CD, which further prevents consistency of the evidence to come. In this scenario, novel endoscopic techniques are emerging, to improve and extend endoscopic management indications, with still preliminary conflicting results and active research ongoing. Moreover, the new insight into the molecular patterns of fibrosis paves the way for future developments, possibly aided by new endoscopic local drug-eluting systems.

More long-term, head-to-head prospective studies are essential to eventually move endoscopic management out of the gray area between a bridge to surgery and an organ-sparing technique.

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