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# Prevention and treatment of stricturing Crohn's disease – perspectives and challenges

**Joseph Sleiman**[1,#], **Sara El Ouali**[1,2,#], **Taha Qazi**[1], **Benjamin Cohen**[1], **Scott R. Steele**[3], **Mark E. Baker**[4], **Florian Rieder**[1,5,*]

[1]Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

[2]Digestive Diseases Institute, Cleveland Clinic Abu Dhabi, United Arab Emirates

[3]Department of Colorectal Surgery, Digestive Diseases and Surgery Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

[4]Section Abdominal Imaging, Imaging Institute, Digestive Diseases and Surgery Institute, Cleveland, Ohio, USA

[5]Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

## Abstract

**Introduction:** Fibrostenosis is a hallmark of Crohn's disease (CD), remains a challenge in today's clinical management of inflammatory bowel disease patients and represents a key event in the disease course necessitating improved preventative strategies and a multidisciplinary approach to diagnosis and management. With the advent of anti-fibrotic therapies and well-defined clinical endpoints for stricturing CD, there is promise to impact the natural history of disease.

**Areas covered:** This review summarizes current evidence in the natural history of stricturing Crohn's disease, discusses management approaches as well as future perspectives on intestinal fibrosis.

**Expert opinion:** Currently, there are no specific therapies to prevent progression to fibrosis or to treat it after it becomes clinically apparent. In addition to the international effort by the Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium to standardize definitions and propose endpoints in the management of stricturing CD, further research to improve our understanding of mechanisms of intestinal fibrosis will help pave the way for the development of future anti-fibrotic therapies.

[*]**Corresponding author:** Florian Rieder, Address: Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, 9500 Euclid Avenue – NC22, Cleveland, OH, 44195, riederf@ccf.org.
[#]co-first authors

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## 1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gut, characterized by transmural inflammation and variable asymmetric, segmental involvement along the entire gastrointestinal tract. Stricturing disease is a known complication of CD and is likely a result of chronic relapsing and remitting inflammation[1]. Up to approximately 20% of patients present with stricturing complications at diagnosis and more than half of patients develop clinically apparent strictures in their lifetime[2,3]. Strictures are a main cause of hospitalization and surgery in patients with Crohn's disease[4]. Although several treatment options are currently used in the management of strictures, there are currently no anti-fibrotic therapies to address fibrosis directly and potentially alter the CD natural history[5].

In this review, we summarize the current pathophysiology of stricturing CD, describe the natural history of stricture formation and its complications, and detail the methods for detection, as well as the treatment strategies. Finally, we review the concept of prevention of stricturing CD, and end with an outlook into the future of therapies and advances in the realm of fibrostenotic CD.

## 2. Epidemiology and natural history

Stricture formation in Crohn's disease with the associated bowel obstruction and/or penetrating disease leads to substantial morbidity in patients and is a common occurrence. Approximately 20% of patients present with complicated CD at diagnosis, including 10.8% with a stricturing phenotype[6]. In a population-based cohort study in Olmsted County, the cumulative incidence of stricturing or penetrating disease, as defined by the Montreal classification, was 22% (95% CI, 17.2–26.5) within 1 year of diagnosis[7]. Approximately 15% and 21% of patients with CD were found to progress to a stricturing phenotype by 10 and 20 years, respectively[7]. In a more recent European population-based inception cohort (the Epi-IBD cohort), 29% of patients presented with complicated CD at diagnosis, including 21% with a stricturing phenotype. Among patients with non-stricturing non-penetrating disease at diagnosis, rates of progression to complicated disease were found to be similar to previous cohorts, with ~ 10% of patients progressing to stricturing disease at the end of the 5-year follow-up[8].

Further, it is highly likely that studies using the hierarchical Montreal or Vienna classification underestimate the incidence of stenosis in CD. In these classification paradigms, internal penetrating disease is recorded separately, irrespective of an underlying stricture. In the vast majority of cases, internal penetrating disease is associated with a stricture[9]. A retrospective study found patients with internal fistulas were 5.7 times more likely to have an underlying stricture than patients without fistulas[10]. In a study examining the histopathology of surgical resection specimens, 96.3% of fistulas were associated with a

stricture[11]. Although fistulizing disease is commonly thought to occur due to progression of stricturing disease, there are no prospective studies to support this notion. These data lead to the estimate that over the lifetime of patients with CD, more than half develop a clinically apparent stricturing phenotype[12].

The most common site of strictures along the gastrointestinal tract is the small bowel. However, strictures can occur anywhere along the intestinal tract and generally follow the segmental location of inflammation[13]. Colonic strictures deserve special consideration given the increased risk of dysplasia compared with small bowel strictures[14]. A colonic stricture in a patient with CD carries a colorectal cancer risk of 3.6% at 5 years and 4.9% at 10 years[15]. Even with negative endoscopic biopsies and brush findings, 3.5% of colonic strictures in patients with inflammatory bowel disease (IBD) may harbor dysplasia or malignancy on histopathologic evaluation after surgical resection[14]. Given the increased risk of malignancy as well as the paucity of data evaluating outcomes of medical therapy in patients with colonic strictures, earlier referral to surgery should be considered, especially in the setting of ongoing medically refractory inflammation or lack of response to endoscopic approaches such as endoscopic balloon dilation[16].

Unfortunately, the rate of progression of CD to a stricturing phenotype has only been minimally altered by the therapies currently available to treat the disease[17–19]. Most theorize that this is partly due to the existence of damaged tissue by the time of CD diagnosis, but also due to possible non-inflammatory pathways that may not be reversible with medical therapy[9].

Strictures are an important indication for surgery. Together with fistulas and abscesses, stricturing complications may account for 40–70% of surgeries across the first 10 years of CD diagnosis[20]. Unfortunately, postoperative recurrence of strictures is common, especially at the ileocolonic anastomotic site[21]. The 10-year risk of re-operative management after initial resection for CD is estimated to be around 35%[22].

## 3. Pathophysiology

Although not yet fully understood, the pathogenesis of stricturing CD involves an intricate interplay of both inflammatory and non-inflammatory pathways in the development of fibrostenosis[1,7]. Over the past 15 years, there has been a paradigm shift in the understanding of the extent of stricture reversibility, as well as the existence of fibrotic pathways outside of inflammatory pathways[1,23]. Chronic inflammation, nevertheless, remains a key contributor to intestinal fibrosis, as shown by both its impact on fibrosis expression patterns, and on the evidence of fibrosis reduction through anti-inflammatory molecules, at least *in vitro* and in experimental animal models[24–26].

Fibrosis in the digestive tract, similar to other organs, involves the aberrant deposition of collagen-rich extracellular matrix (ECM), which is largely driven by activated mesenchymal cells. It also involves smooth muscle hyperplasia and hypertrophy[27], which together with an increase in the number of myofibroblasts[28], contribute to the luminal narrowing that ultimately culminates in intestinal obstruction[3]. Different pathways may drive

fibrogenesis, including pro-fibrotic molecules and signaling pathways, such as transforming growth factor beta (TGF-β), tyrosine kinases, interleukin (IL)-11[29], IL-17[30], IL-34[31], reactive oxygen species (ROS) and peroxisome proliferator activator receptors[23], among other factors. These so called “profibrotic” molecules can directly activate a vast array of fibroblasts, myofibroblasts and smooth muscle cells, and lead to transient or permanent expansion of these mesenchymal cells in damaged tissue[20]. Interestingly, animal models of inflammation-induced fibrogenesis suggest that levels of fibrotic mediators may remain elevated despite the resolution of inflammation, offering one explanation for inflammation-independent pathways to fibrosis[32,33]. Other proposed mechanisms include an increased ECM stiffness and changes in ECM turnover. The first is a property held by a pathologically altered ECM, as can be found in CD, where physical tissue properties alone can be a strong mesenchymal cell activator[34]. The latter relates to an imbalance of down-regulated matrix degrading enzymes, such as matrix metalloproteinases (MMP), and up-regulated inhibitors of matrix metalloproteinases, such as tissue inhibitors of MMPs (TIMPs). This is believed to lead to a net positive ECM deposition[1,35,36]. Unique to the intestine, the gut microbiota likely has an impact on fibrogenesis. The bacterial protein flagellin was found to be a critical driver of the fibrogenic response of intestinal mesenchymal cells[37]. Supporting this concept, it was also shown that intestinal fibrosis cannot develop in animals lacking a microflora[1].

## 4. Clinical features and diagnosis

Although symptoms of obstruction, such as nausea, vomiting, post-prandial abdominal pain, distention and dietary restrictions may suggest the presence of a stricture, they are not highly correlated with strictures on imaging or endoscopy[38]. In addition, there is no correlation between the presence of obstructive symptoms and the severity of small bowel strictures[38]. This suggests that symptoms alone are not accurate enough to diagnose strictures and further testing is therefore required to diagnose stricturing CD[38].

The CrOhN’s disease anti-fibrotic STRICTure therapies (CONSTRICT) group, an international group of IBD experts, has proposed endoscopic and radiologic definitions of strictures in order to standardize diagnostic criteria[38]. According to the CONSTRICT criteria, stricturing on endoscopy refers to the “inability to pass an adult colonoscope through the narrowed area without prior endoscopic dilation with a reasonable amount of pressure applied”[38]. The presence of stenosis is also included in both validated CD endoscopic scores, the Simple Endoscopic Score for Crohn’s Disease (SES-CD) and the Crohn’s Disease Endoscopic Index of Severity (CDEIS)[39,40]. This item, however, comprises the least reliable one within each score[41] and therefore is not the optimal approach to stricture diagnosis. In addition, endoscopy is not able to assess inflammation and/or fibrosis in a transmural fashion.

Cross-sectional imaging is important as it helps better define the characteristics of a stricture and allows full thickness evaluation of the bowel wall. It also assesses the extramural components of the stricture including the mesentery and concomitant penetrating disease[42]. Imaging modalities used for the diagnosis of strictures include abdominal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)[42–46].

Several studies have assessed their accuracy in identifying a stricture[42]. While the sensitivity and specificity are high for all imaging modalities (sensitivity/specificity for stricture diagnosis in each of ultrasound elastography, CT enterography/enteroclysis, MR enterography, hybrid positron emission tomography with CT/MR were 88–100/0–100%, 92.3–100/38–100%, 75–100/91–96%, 85%/not reported, respectively), MR enterography remains the preferred diagnostic method because the stricture and its components can be more fully characterized using multiple, different sequences without and with contrast enhancement and without ionizing radiation[42].

Despite high reliability of detecting a stricture with imaging, a recent systematic review found significant heterogeneity in definitions of strictures[42]. The CONSTRICT group therefore proposed a consensus-based definition of stenosis on imaging in an effort to standardize diagnostic criteria[38]. For clinical purposes outside of clinical trials, a combination of at least 2 of the following features for a diagnosis is required: localized luminal narrowing (> 50% luminal narrowing), bowel wall thickening and pre-stenotic dilation (in most cases > 3 cm). For clinical trials, all 3 features should be present[38].

Imaging may also assist in assessing the extent of inflammation and fibrosis within strictures, which could guide management. Anti-inflammatory therapy can be considered in the setting of an inflammatory component, whereas a purely fibrotic stricture is unlikely to respond to anti-inflammatory therapy and would be better managed with EBD or surgery[1,47]. However, these features often coexist, making it difficult to accurately distinguish inflammatory from fibrotic stricture[1,42,47,48]. In fact, a recent study found that despite a pre-operative diagnosis of purely fibrotic strictures, histologic assessment of surgical specimens revealed a predominant component of chronic inflammation in all strictures[49]. Equally, other resection studies found a strong correlation between inflammation and fibrosis with purely fibrotic strictures being exceedingly rare or non-existent[50,51]. This led to the conclusion of the CONSTRICT consensus group that current imaging approaches are able to detect inflammation with high accuracy, but are not able to distinguish inflammation from fibrosis[38].

In one investigation, delayed contrast enhancement on MR differentiated between mild to moderate and severe fibrosis deposition with good sensitivity and specificity, independently of the degree of inflammation[52]. However, delayed enhancement did not allow the distinction of mild from moderate or moderate from severe fibrosis, all of which are important for clinical decision making and for a clinical trial endpoint. New imaging techniques such as diffusion-weighted imaging, magnetization transfer MRI, MR with dynamic contrast enhancement, shear-wave and strain-wave ultrasound elastography or artificial intelligence may help better quantify the degree of fibrosis but are still under evaluation and not yet used in routine clinical practice[9,48]. Ideally, imaging would be able to identify even pre-fibrotic characteristics. Many groups are now employing radiomics and artificial intelligence to imaging in an effort to determine if any pre- or early fibrotic characteristics are present. It may be that those findings are present in the mesenteric fat rather than the bowel wall itself.

Given the poor estimation of the extent of fibrosis by imaging, histopathology of intestinal resection specimens should be the standard for fibrosis quantification and is critical to develop novel imaging approaches, as it serves as the gold-standard for these studies. A recent systematic review performed by the STAR consortium detected a large heterogeneity across proposed histopathologic scoring systems and none of them was tested for reliability or validated based on modern index methodology[53]. The development of a reproducible and validated histopathologic scoring system is greatly needed and for this reason the STAR consortium is currently developing a novel histopathologic score for stricturing CD.

Importantly, strictures are not diagnostic of inflammatory bowel disease and occur in other conditions, some of which can coexist with CD. These include diverticular disease, malignancy, radiation enteritis, nonsteroidal anti-inflammatory drugs (NSAID) enteropathy and cryptogenic multifocal ulcerous stenosing enteritis[54]. A detailed clinical assessment, in addition to imaging and histopathology, can help exclude other conditions. Biopsies have a limited role in diagnosing fibrosis but may be helpful in ruling out an underlying malignancy. However, dysplasia may still be missed[9].

## 5. Treatment

The management of stricturing CD, similar to its diagnosis, may be complex and requires the collaborative efforts of gastroenterologists, radiologists and colorectal surgeons. Several modalities are used in the management of stricturing CD and are described below (Figure 1).

### 5.1 Acute small bowel obstruction

In most cases, acute small bowel obstruction requires hospitalization. Complications (free perforation, abscess, fistulizing disease or malignancy) should be excluded by rapid evaluation with a physical examination and especially cross-sectional imaging (in the acute setting this is most often a CT enterography)[16]. GI decompression with a naso-gastric tube, hydration and electrolyte replacement are the mainstay of initial management, followed by close monitoring of the clinical status, as well as C-reactive protein and abdominal X-rays[9,16]. Although corticosteroid therapy is generally used in this setting, evidence is limited. In a small case series of 26 patients with CD, a majority of patients developed recurrence of obstructive symptoms within 2 years[55]. Adjustment of anti-inflammatory therapy, endoscopic interventions, surgery or a combination thereof are often required. In a recent retrospective cohort of patients with CD presenting with acute small bowel obstruction, 22.5% required surgery within 6 months. Factors associated with surgery within 6 months included female gender, BMI <25, the presence of penetrating disease, length of affected segment and bowel wall enhancement on CT scan[56].

### 5.2 Medical Approach

**5.2.1 Immunomodulators—**Azathioprine and mesalamine have been compared in a randomized controlled study of 72 patients with sub-occlusive ileal CD. Patients received either azathioprine or mesalamine after initially responding to 3 days of intravenous hydrocortisone therapy. Azathioprine was associated with significantly lower rates of hospitalization (61% vs 83.3%; $P = 0.03$) and surgery (25% vs 56%, respectively; $P = 0.01$)

during follow-up[57]. In addition, azathioprine was associated with significantly lower rates of recurrent sub-occlusion and longer occlusion-free time intervals in a post-hoc analysis[58]. Although methotrexate is used in the treatment of Crohn's disease[59,60], this therapy has not been evaluated in the setting of stricturing CD.

### 5.2.2 Biologic agents

**5.2.2.1 Anti-TNFs:** Anti-tumor necrosis factor (anti-TNF) agents in the treatment of stricturing CD in both prospective and retrospective cohorts are effective and safe[61–65]. However, these observational studies had no controls.[66] Contrary to prior belief[67,68], these agents do not appear to cause further stricturing as a response to rapid healing[61–65,69].

Adalimumab was evaluated in a single arm, multicenter prospective observational cohort study of 97 patients with small bowel stricturing CD (the CREOLE study)[61]. At 24 weeks, 64% were still on therapy without having received steroids or undergone endoscopic balloon dilation or surgery. Continued adalimumab treatment was successfully maintained in 29% of patients at 4 years, with about half of all patients requiring surgery during this time frame. This study also developed a predictive risk score for adalimumab efficacy, in which a score of at least 4 points was associated with 88% probability of treatment success at 24 weeks[61]. Factors independently associated with treatment success were obstructive symptoms for less than 5 weeks, the use of immunosuppressants at the time of adalimumab initiation, a CD obstructive score >4, stricture length less than 12cm, marked enhancement on delayed phase, pre-stenotic bowel diameter of 18 to 29mm, and the absence of fistulizing disease[61].

A recent multicenter retrospective study evaluated the efficacy of early anti-TNFs in 262 biologic-naïve patients with a newly diagnosed CD-associated stricture. At 1 year, 73% had steroid-free drug persistence, with no hospitalization, endoscopic therapy, surgery or any change in therapy. However, after a median follow-up of 40 months, drug persistence had decreased to 26%, and 32% had undergone surgery[70]. Interestingly, starting anti-TNF within 18 months after the diagnosis of stricturing disease was associated with higher effectiveness[70]. Although this study demonstrates that a proportion of patients respond to anti-TNFs and that early treatment may be beneficial, it does highlight the need for other therapeutic alternatives for stricturing disease.

**7.2.2.2 Vedolizumab and ustekinumab:** Although other biologics such as vedolizumab and ustekinumab are safe and effective in Crohn's disease[71,72], there are no data on their effect on strictures. Interestingly, deep remission in a patient with stricturing CD receiving combination vedolizumab, ustekinumab and azathioprine has been described[73]. Strictures or fistulas were present in 118/212 (55.7%) of patients receiving vedolizumab for moderate to severe CD in the US VICTORY consortium[74]. In this cohort, two out of the 212 patients underwent resection for small bowel strictures at 12 months of therapy. Unfortunately, in this series, the effect of vedolizumab on stricture formation was not separated analyzed.

Overall, in a recent systematic review evaluating treatment outcomes in stricturing CD, a pooled rate of 28.3% (95% CI: 18.2%−41.3%) for surgical resection was observed over a median follow-up of 23 months in patients receiving any systemic medical therapy[66].

## 5.3 Endoscopic Approach

### 5.3.1 Endoscopic balloon dilation

**5.3.1.1 Patient selection:** Endoscopic balloon dilation (EBD) can be performed in the setting of an endoscopically accessible, non-angulated and short stricture (<5 cm long)[75]. There should be no contraindications including complications such as penetrating disease, abscess or malignancy[16]. The endoscopist should also evaluate for contraindications for an endoscopic procedure[1]. EBD can be used in both naïve and anastomotic strictures and can be performed in the upper, mid and lower gastrointestinal tract[75,76]. Although all endoscopically reachable strictures may be theoretically dilated, certain locations are associated with worse outcomes[75]. For example, duodenal strictures are associated with a 5-times increased hazard for shorter time to surgery compared with strictures in the jejunum, ileum or colon[77]. Colonic strictures can be dilated, but surgery should be strongly considered given the increased risk of dysplasia or malignancy[14].

**5.3.1.2 Technique:** EBD is typically done using a through-the-scope balloon and can be accomplished either through an antegrade or retrograde approach[16]. Although a higher maximal caliber of dilation was associated with an increased likelihood of technical success in a pooled analysis, this did not translate into increased clinical efficacy[75]. Before dilation, biopsies of the stricture should be performed to exclude the rare malignancy[47].

**5.3.1.3 Outcomes:** A pooled analysis of 33 retrospective studies, including 1463 patients with a total of 3212 EBDs found a technical success rate of 89.1%, and an immediate clinical efficacy rate of 80.8%. Technical success was defined as the ability to pass a colonoscope through the non-traversable stricture after dilation or correct stent placement[75]. The rate of re-dilation and surgery at 24 months was 73.5% and 42.9%, respectively. Factors associated with better short-term outcomes are EBD technical success, stricture length <5 cm, and the absence of ulcers[47].

**5.3.1.4 Complications:** In the above-mentioned pooled analysis, the rate of complications was 3–4% and included bleeding, hospitalization, infection or perforation[75,78]. Repeat dilations, naïve vs anastomotic strictures, and presence of active inflammation at the site of the stricture were not associated with increased risk of complications[47,75,79].

### 5.3.2 Other endoscopic therapies

**5.3.2.1 Intralesional therapy:** Other endoscopic modalities include intralesional corticosteroids or infliximab injection. The only randomized controlled trial evaluating intralesional therapy was terminated early due to a trend toward re-dilation in the intralesional steroid injection group[80]. A recent systematic review of this technique showed no impact on outcomes[66]. Thus, this modality is not currently recommended[81].

**5.3.2.2 Stents:** Based on limited data, stent placement in strictures in CD has some efficacy[82,83]. Unfortunately, this technique is associated with a high rate of complications, including stent migration, fistula formation or perforation[81,83]. This technique is therefore not currently recommended[81], but novel approaches such as removable, biodegradable or custom-made stents may change this recommendation.

**5.3.2.3 Stricturotomy:** Needle-knife therapy, including stricturotomy and radial incision and cutting, has been evaluated in the setting of CD-associated strictures in non-controlled settings and case series. Although available data show promise[84–86], further data are needed to understand its potential benefit, its long-term efficacy and in particular its potential risks compared with conventional methods.

## 5.4 Surgical Approach

**5.4.1 Indications—**Surgical management is indicated for symptomatic stricturing disease that is refractory to or not amenable to medical or endoscopic therapy, as well as in cases associated with suspected or confirmed malignancy or penetrating disease, especially with complex fistulae[87]. Stricture length ≥ 5 cm was also found to be associated with an increased need for surgery in a pooled data analysis of EBD outcomes[75]. In this study, every 1 cm increase in stricture length led to an increased hazard for surgery by 8% [75]. Additionally, surgical resection at time of diagnosis or early during the disease course may lead to longer clinical remission periods, decreased long-term surgery rates and decreased need for steroids and biologic therapies during follow-up[88–90]. Ultimately, surgical intervention depends upon the disease and stricture pattern, patient preference, whether there are associated complications, such as abscess, phlegmon or internal penetrating disease and an interdisciplinary team discussion[9].

**5.4.2 Surgical techniques—**If feasible, a laparoscopic approach is favored over laparotomy due to faster recovery, fewer adhesions and comparable rates of surgical recurrence[47,91]. Using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database, a recent study evaluating surgical outcomes in stricturing disease found laparoscopy to be associated with fewer complications and a shorter hospital stay[92].

Segmental resection and strictureplasty are the mainstays of surgical treatment of stricturing disease[93]. Bypass surgery is another consideration for select upper gastrointestinal strictures, though in general, is not the preferred approach.[94] Segmental resection involves the resection of the affected segment typically followed by the construction of an end-to-end, end-to-side or side-to-side anastomosis[87]. The optimal type of anastomosis has long been debated in the surgical literature and is generally guided by surgeon preference[87]. A recent meta-analysis found the Kono-S (antimesenteric functional end-to-end handsewn) anastomosis sparing the mesentery to be associated with a lower incidence of both endoscopic and surgical recurrence, as well as a decreased anastomotic leak rate[95].

Strictureplasty, on the other hand, may be preferred in the setting of diffuse small bowel stricturing disease, rapidly recurring disease or if there are concerns with short bowel syndrome[87]. This intervention should also be considered in the case of multiple well-

spaced out strictures that would necessitate an extensive bowel resection[81]. This technique should not be performed in cases where penetrating or malignant disease is suspected, or in those cases where multiple strictures are adjacent to one another and would be better off addressed by resection [87]. Prior to stricturoplasty, stricture biopsy should be performed in order to rule out malignancy [87].

Strictureplasty is a safe and effective technique.[96] In a meta-analysis of 1,112 patients who underwent 3,259 strictureplasties, the recurrence rate at 5 years was found to be 28%[96]. Interestingly, 90% of patients experienced recurrence at a non-strictureplasty site. This observation has been seen in other studies using radiologic follow-up of patients after strictureplasty, showing regression of the disease in the strictureplasty sites even in patients were not exposed to medical therapy[97–99]. The reason for the disease improvement at strictureplasty sites remains unclear. Resolution of fecal stasis has been proposed as a possible contributing factor[97]. Strictureplasty methods vary largely based on stricture length and their unique technical challenges; initial methods were adapted from techniques for pyloroplasty[100]. The 2 most common methods include the Heineke–Mikulicz and the Finney technique, for short (<10 cm) and intermediate-length strictures (10–20 cm), respectively[87]. Other less frequently used methods include the “non-conventional” isoperistaltic Michelassi, d’Hoore or Michelassi II techniques for long strictures (>25 cm) or repeated juxtaposed areas of continuous disease [87]. Although strictures located in the ileocecal region are traditionally referred for surgical resection, ileocolonic strictureplasties are emerging as a possible alternative for extensive disease[97]. The latter technique may in fact serve as a novel human model to study stricture regression, as it is amendable to endoscopic evaluation and sampling.

Strictureplasty is typically not recommended with CD colonic strictures, as they carry a higher risk of underlying or future malignancy, and these are more commonly managed with segmental resection [87].

## 6. Prevention and reversibility of fibrosis

Patient risk stratification close to diagnosis in naïve, non-complicated CD would be ideal to determine which patients may or may not progress to stricturing CD. This would guide clinical decision making (e.g. combination therapy, how often to monitor, and additionally the design of future clinical trials). The TREAT registry and the ACCENT I trial found that disease duration, disease severity, ileal location and new corticosteroid use were associated with an increased risk of progression to stenotic CD[69]. The pediatric RISK inception cohort of 913 patients were followed close to diagnosis and later analysed for clinical factors, genotype, serology, and ileal gene expression signatures. 9% developed complications during follow up. A validated risk model was able to predict complicated CD at diagnosis with an area under the receiver operator curve (ROC) of 0.72[18]. Interestingly, certain fecal bacterial strains identified at diagnosis were linked to the later development of fibrostenosis. Although other predictors have been evaluated, including clinical, serological, genetic and epigenetic biomarkers, these have not been shown to be specific for the development of stricturing disease. None of the available markers has been validated or can be recommended for clinical practice at this time [1].

### 6.1 Potential targets for anti-fibrotics

Given the current inability to predict strictures, reversing fibrosis in already existing strictures would therefore be an important goal in CD management. Reversibility of fibrosis has in fact been documented in other organs, such as the lung, heart, skin or kidney[3]. In CD, as discussed above, studies have shown disease regression at strictureplasty sites[97,98], suggesting possible fibrogenesis reversal in this setting[1].

Some of the mechanisms involved in the process of fibrosis reversal in other organs are being investigated in the intestine[5]. Tranilast inhibits transforming growth factor-β (TGF-β), which is involved in fibrogenesis through activation of mesenchymal cells[1]. This molecule has shown anti-fibrotic properties in skin, cardiac and pulmonary tissue[101]. In CD, it was evaluated in a small prospective study of patients with asymptomatic strictures and was found to be associated with lower rates of developing symptoms over a median follow-up of 2 years compared with controls[102]. Pirfenidone, one of only two anti-fibrotic agents approved for the treatment of idiopathic pulmonary fibrosis (IPF), has been found to inhibit fibroblast proliferation and MMP-3 production in patients with CD[103]. Pirfenidone is thought to act in part through reduction of TGF-b1-mediated fibrosis signaling[3,103]. Nintedanib is the other molecule approved for IPF treatment which may represent a potential antifibrotic target for intestinal fibrosis [3]. Interleukin-36 (IL-36) is thought to induce the expression of genes that mediate fibrogenesis[104]. Antibodies to interleukin-36 (IL-36) receptors were recently found to reduce fibrosis and inflammation in mice with chronic intestinal inflammation, suggesting a possible role for the treatment of intestinal fibrosis in IBD[104]. In addition, AMA0825, a Rho kinase inhibitor, was found to reverse and prevent intestinal fibrosis in animal models of chronic intestinal inflammation and fibrosis[105,106]. Interestingly, when combined with anti-TNF, AMA0825 prevented histopathologically documented fibrosis as well, suggesting a role for combination therapy with anti-inflammatory agents[106]. Several additional molecules have also been evaluated with promising results. A summary of potential anti-fibrotic targets can be found in table 1.

## 7. Expert Opinion

Stricturing complications are common in patients with CD. Despite advances in medical and endoscopic therapies, most CD patients eventually undergo surgery for complicated CD. Unfortunately, postoperative recurrence is common. The ultimate goal would therefore be to *prevent* the development of aberrant tissue repair, manifesting as intestinal fibrosis. Despite the availability of an increasing number of biologic therapies, the progression to stricturing complications has to date largely remained unchanged. Therefore, an important current objective would be to attempt to *reverse* already established fibrosis.

Increased knowledge of fibrosis pathophysiology will likely lead to the identification of novel anti-fibrotic targets. Alongside targeted molecular therapies, research is evolving in the space of regenerative medicine. This encompasses cell-based therapies, either using regulatory T cells, mesenchymal cells or amniotic epithelial cells, as well exosome-based approaches for the treatment of intestinal fibrosis. Although promising, implementation of these therapies would likely be challenging given issues surrounding the cost, logistics, delivery and possible risks that are yet to be clarified[124]. Another potential target may be

the gut microbiota, which has been found to have an impact on fibrogenesis in CD[1,37]. A microbiome-based therapy could be topically delivered and may be gut selective.

Given the inability of our presently available therapies to prevent or reverse CD-associated strictures, there is an urgent need for the development of anti-fibrotic agents in CD. However, this requires a better understanding of intestinal fibrosis and faces several important challenges as outlined below.

The pathophysiology of CD-associated strictures needs to be further elucidated. It will be crucial to better understand predictors of stricturing disease among patients with CD, in order to allow risk-stratification and early identification of patients at risk for progression to specifically stricturing complications[77]. Another research priority will be the identification of biomarkers associated with CD fibrosis, which would ideally allow monitoring of response while on therapy [77]. Although a number of animal models are used in research, none of them fully recapitulates the pathogenesis leading to fibrosis in IBD. Linking pro-fibrotic pathways in the murine system to pathways in human disease will better utilize their translatability[1]. This will support mechanistically validating pathways of fibrogenesis and screen therapeutic agents prior to human trials. Recently, murine precision-cut intestinal slices were successfully used and allowed the assessment of several anti-fibrotic compounds[125]. Intestinal organoids are another promising model for representing *in vivo* physiology. Spironolactone was examined in this setting and was found to block the fibrogenic response of human intestinal organoids to TGF-β[126]. Both approaches could emerge as alternate preclinical screening models for anti-fibrotic therapies.

As anti-fibrotic therapies are being developed, attention should be paid to developing gut-selective drugs, in an attempt to minimize systemic side-effects and potential detrimental effects on wound healing elsewhere in the body. However, this may be challenging to achieve as there is currently no specific intestinal anti-fibrotic target and existing gut selective delivery systems may not achieve transmural penetration [77].

Ultimately, the development of anti-fibrotic molecules requires standardization of diagnostic criteria and outcomes prior to proceeding with clinical trials. The STAR consortium, an international group of experts, is leading a global initiative to define important endpoints in CD fibrosis, paving the way for future clinical trials. Such endpoints include patient-reported outcome measures (PROs), radiologic and histopathologic indices, some of which are currently being validated in prospective studies[9]. The first clinical trial with an anti-fibrotic stricture therapy is set to start in 2021, which will further accelerate interest in this field of large unmet clinical need and ultimately benefit patient care.

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Declaration of Interests

F Rieder is on the advisory board or consultant for Agomab, Allergan, AbbVie, Boehringer-Ingelheim, Celgene, CDISC, Cowen, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Index Pharma, Janssen, Koutif, Metacrine, Morphic, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Takeda, Techlab, Theravance, Thetis, UCB. B L Cohen receives the following financial support: advisory boards and consultant for Abbvie, Celgene-Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, TARGET RWE; CME Companies: Cornerstones, Vindico; speaking: Abbvie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Abbreviations

| | |
|---|---|
| **Anti-TNF** | anti-tumor necrosis factor |
| **CDEIS** | Crohn’s Disease Endoscopic Index of Severity |
| **CONSTRICT** | CrOhN’s disease anti-fibrotic STRICTure therapies |
| **CD** | Crohn’s Disease |
| **CT** | computed tomography |
| **EBD** | Endoscopic balloon dilation |
| **ECM** | extracellular matrix |
| **IBD** | inflammatory bowel disease |
| **IPF** | idiopathic pulmonary fibrosis |
| **IL** | interleukin |
| **MAPK** | mitogen-activated protein kinase |
| **MMP** | matrix metalloproteinases |
| **MRI** | Magnetic resonance imaging |
| **NF-κB** | Nuclear factor kappa B |
| **NSAIDs** | nonsteroidal anti-inflammatory drugs |
| **NSQIP** | National Surgical Quality Improvement Program |
| **PPARγ** | Peroxisome Proliferator Activated Receptor Gamma |
| **PROs** | patient-reported outcome measures |
| **ROC** | receiver operator curve |
| **ROS** | reactive oxygen species |
| **SES-CD** | Simple Endoscopic Score for Crohn’s Disease |
| **STAR consortium** | The Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium |
| **TGF-B** | Transforming growth factor beta |

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## Article Highlights

- More than half of patients with Crohn's disease (CD) develop clinically apparent strictures with subsequent intestinal obstruction or penetrating disease. This has remained largely unchanged despite advances in medical therapy
- Both inflammation-dependent and inflammation-independent mechanisms may drive fibrogenesis in CD
- A stricture is defined radiologically by the presence of at least 2 out of the 3 following criteria: localized luminal narrowing (>50% luminal narrowing), bowel wall thickening and pre-stenotic dilation (generally > 3 cm in diameter).
- Endoscopic balloon dilation is an option for short, non-angulated strictures which are accessible endoscopically and not associated with penetrating disease or malignancy
- Bowel resection and strictureplasty are the mainstays of surgical treatment of stricturing disease
- Colon strictures deserve special attention given an increased risk of dysplasia compared with small bowel strictures. Earlier referral to surgery should be considered

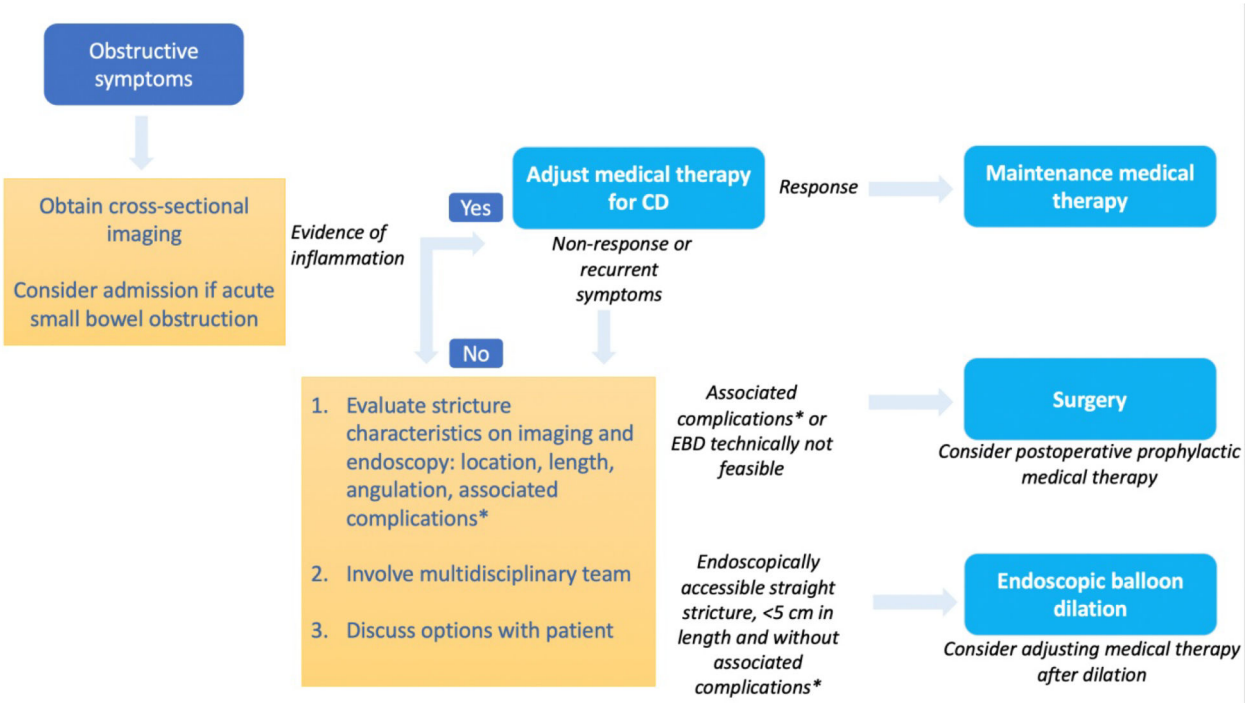


**Figure 1.**

Algorithm for the management of symptomatic small bowel strictures in Crohn's disease.

CD: Crohn's disease. EBD: endoscopic balloon dilation. *abscess, fistula, malignancy

**Table 1.**

List of potential anti-fibrotic agents that have been tested in murine or human intestinal models.

| Molecules | Mechanism of action | Model system | Outcome relevant to the gastrointestinal tract | References |
|---|---|---|---|---|
| AMA0825 | Rho-associated protein kinase inhibitor | Murine intestinal fibrosis | Prevention and reversal of intestinal fibrosis | [106] |
| Tranilast | Reduction of TGF- β activity | Pilot study in human CD patients | Reduced rate of symptom occurrence in asymptomatic strictures | [102] |
| GED-0507–34 Levo | PPARγ Receptor agonist | Murine intestinal fibrosis | Prevention of intestinal fibrosis | [107] |
| Il-36R antibody | Interleukin 36 receptor inhibition | Primary human cells and murine intestinal fibrosis | Prevention and reversal of intestinal fibrosis and reduction in profibrotic gene signatures in human fibroblasts | [104] |
| Thalidomide | Regulates multiple inflammatory and fibrosis pathways | Murine intestinal fibrosis | Regulation and reversal of intestinal fibrosis | [108] |
| Andrographolide sulfonate | Inhibits activation of macrophages, suppresses Th1/Th17 response, and down-regulates MAPKs and NF-κB pathways | Murine intestinal fibrosis | Prevention of intestinal fibrosis | [109,110] |
| EW-7197 | Transforming growth factor-β type I receptor kinase inhibitor | Murine intestinal fibrosis | Prevention of intestinal fibrosis | [111] |
| TM5275 | PAI-1 inhibition | Murine intestinal fibrosis | Reversal of intestinal fibrosis | [112] |
| Pirfenidone | Inhibits cell proliferation and collagen I production | *In vitro* primary human intestinal fibroblasts. | Inhibition of fibroblast growth and suppression of collagen production | [113] |
| Mouse p40 peptide-based vaccines | Sustained Blockage of IL-12 and IL-23 | Murine intestinal fibrosis | Prevention and reduction of intestinal fibrosis | [114–116] |
| Wu-Mei-Wan, a classic traditional Chinese herb medicine | Inhibition of colon fibroblast activation | Murine intestinal fibrosis | Prevent intestinal fibrosis | [117] |
| ICG-001 | TGF-β/ WNT signaling inhibition | Intestinal fibroblasts | Inhibition of β-catenin and collagen I production | [118] |
| Melanin-concentrating hormone antibody | Melanin-concentrating hormone blockage | Murine intestinal fibrosis | Reduction of collagen production and reduction of fibrosis | [119] |
| Daikenchuto (Da-Jian-Zhong-Tang) | Activating myofibroblast transient receptor potential ankyrin 1 channel | Murine intestinal fibrosis | Prevention of intestinal fibrosis | [120] |
| Losartan | Downregulation of TGF-β1 expression | Murine intestinal fibrosis | Prevention of intestinal fibrosis | [121] |
| Triptolide (PG490) | Anti-inflammatory and immunomodulatory activities | Murine intestinal fibrosis | Prevention and reversal of intestinal fibrosis | [122] |
| BGB324 | AXL Receptor tyrosine kinase inhibitor | Human colonic fibroblasts, murine intestinal fibrosis, Human intestinal organoid culture, colon resections of patients with CD | Prevention and reversal of intestinal fibrosis | [123] |

CD: Crohn's disease; TGF- β: Transforming growth factor beta; PPARγ: Peroxisome Proliferator Activated Receptor Gamma; MAPK: mitogen-activated protein kinase; NF-κB: Nuclear factor kappa B.