**Mechanisms, Management, and Treatment of Fibrosis in Patients with
Inflammatory Bowel Diseases**

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Abbreviations

CD	Crohn's disease
CT	Computed tomography
ECM	Extracellular matrix
EMA	European Medicine Agency
EMT	Epithelial-to-mesenchymal transformation
IBD	Inflammatory Bowel Disease
IL	Interleukin
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging

TIMP	Tissue inhibitors of matrix metalloproteinases
TGFB	Transforming growth factor beta
TNF	Tumor necrosis factor
UC	Ulcerative colitis

Abstract

In the last 10 years, we have learned much about the pathogenesis, diagnosis, and management of intestinal fibrosis in patients with inflammatory bowel diseases (IBD). Just a decade ago, intestinal strictures were considered to be an inevitable consequence of long-term inflammation in patients who did not respond to anti-inflammatory therapies. IBD-associated fibrosis was seen as an irreversible process that frequently led to intestinal obstructions requiring surgical intervention. This paradigm has changed rapidly, due to the anti-fibrotic approaches that may become available. We review the mechanisms and diagnosis of this serious complication of IBD, as well as factors that predict its progression and management strategies.

Keywords: Crohn's disease, ulcerative colitis, dilation, treatment

One decade ago, intestinal strictures were considered to be an inevitable consequence of long-term inflammation in patients with inflammatory bowel diseases (IBD) who did not respond to anti-inflammatory therapies. Correctly regarded as the result of an excessive production of extracellular matrix (ECM) by activated mesenchymal cells, IBD-associated fibrosis was seen as an irreversible process that frequently led to intestinal obstructions requiring surgery. However, specific anti-fibrotic approaches may become available. What are the mechanisms of stricture formation in patients with IBD, and how can these be most effectively predicted, detected, followed, and treated?

Mechanisms of Fibrogenesis

Despite our increasing ability to control inflammation with new drugs, such as biologics, there has been little progress in preventing intestinal inflammation from progressing to fibrosis^{1,2}—many patients with Crohn’s disease (CD) still undergo surgery for strictures³. This raises the question of whether inflammation is the only factor that promotes fibrosis, or whether inflammation-independent mechanisms mediate a self-perpetuating fibrostenotic process.

The mechanisms that induce fibrosis and excessive ECM deposition in the gut are believed to be comparable to those that induce fibrogenesis in other organs (**Figure 1**). Tissue repair mechanisms, which restore integrity to tissues with inflammatory damage, involve a controlled response mediated by mesenchymal cells and the ECM⁴⁻⁶. In contrast, fibrosis is an exaggerated response characterized by accumulation of collagen-rich ECM, produced by a permanent or transient numerical expansion of mesenchymal cells, including fibroblasts, myofibroblasts and smooth muscle cells⁷.

Mesenchymal cells can be activated through multiple pathways, such as autocrine factors, paracrine signals, microbe-associated molecular patterns, damage-associated molecular patterns, or ligation of other pattern recognition receptors^{8,9}. Inflammation per se is a strong activator of mesenchymal cells; CD-associated chronic inflammation alters DNA methylation and gene expression patterns to mediate development of intestinal fibrosis¹⁰. Inflammation also contributes to development of lung fibrosis; anti-tumor necrosis factor

agents and thalidomide have been tested in randomized controlled trials ^{11, 12} (see [Supplemental Table 1](#)).

Multiple soluble factors commonly produced during an inflammatory response also promote fibrogenesis. Transforming growth factor beta (TGFB) is an important mediator of fibrogenesis that activates mesenchymal cells. Although blocking TGFB signaling appears to be a logical way to control fibrogenesis, this approach may have undesirable effects because TGFB has immune-regulatory functions, including the induction of regulatory T cells ¹³⁻¹⁵. So, its suppression could aggravate inflammation. Other fibrogenic molecules include activins, connective tissue growth factor, platelet-derived growth factor, insulin-like growth factors 1 and 2, epidermal growth factor, endothelins, interleukin-13 (IL13), and others ^{8, 9, 16-18}. Agents that inhibit growth factors, such as pirfenidone, specific antibodies to TGFB, substitution of serum amyloid protein, recombinant antibodies against IL13, have been investigated in randomized controlled trials of patients with kidney, skin, or lung fibrosis ¹⁹⁻²³ (see [Supplemental Table 1](#)). Inhibitors of tyrosine kinases, which activate many different proteins in fibrogenic signaling pathways, might also be developed. These compounds can inhibit multiple growth factor signaling pathways at the same time. BIBF1120 and imatinib have been investigated in patients with lung fibrosis ^{24, 25}; (see [Supplemental Table 1](#)).

Endothelin (initially known as a vasoconstrictor) and the renin-angiotensin system (initially known as a regulator of arterial blood pressure) also have important roles in the initiation or progression of fibrosis. They might also promote fibrogenesis mediated by other growth factors and cytokines ^{26, 27}. Randomized controlled trials of antagonists to both systems have been completed ²⁸⁻³³ ([Supplemental Table 1](#)).

A number of animal models have been developed for studies of fibrogenesis (reviewed in ³⁴). In the most frequently used models, fibrosis is chemically induced, with agents such as trinitrobenzenesulfonic acid ^{35, 36} or dextran sodium sulfate ^{37, 38}. Although these models are convenient, colonic inflammation and subsequent fibrosis are induced by substances that are toxic to epithelial cells, which may not mimic the natural insult that leads to

development of fibrosis³⁴. Mice infected with *Salmonella typhi* and then given streptomycin develop transmural inflammation and fibrosis³⁹, but this bacterial species has not been implicated in the pathogenesis of IBD or development of intestinal strictures in humans. Injection of the bacterial component peptidoglycan-polysaccharide into the intestinal wall of mice also induces inflammation and fibrosis, increasing production of TGFB1⁴⁰. This model allows the study of the influence of microbial products on fibrogenesis. However, it is not clear if this model relates to pathogenesis of IBD.

SAMPI/YitFcsJ mice, develop a spontaneous ileitis that has many features of Crohn's disease, with fibrosis, and similar mechanisms of development^{41, 42}. However, it is a challenge to breed these mice, making maintenance of large colonies necessary, which is expensive. Radiation-induced intestinal fibrosis also has been studied. The factors that induce fibrosis in this model are certainly different from those of IBD, but this model might be used to study anti-fibrotic agents⁴³⁻⁴⁶. In a recently developed model, heterotopic transplantation of small bowel tissues^{47, 48} leads to rapid fibrosis within 2 weeks, associated with increased intestinal expression of mediators of fibrosis such as $\alpha\text{v}\beta 6$ integrin, IL13, and TGFB. This model is artificial, but it has been used to test anti-fibrotic agents^{47, 49}. None of these models perfectly recapitulate IBD, but they provide an opportunity to define mechanisms and pathways of fibrogenesis and screen therapeutic agents³⁴ (see [Supplemental Table 2](#)).

Animal models of inflammation-induced fibrogenesis have shed light on the kinetics of the expression of inflammatory and fibrotic factors⁵⁰ ([Figure 2](#)). Levels of inflammatory and fibrotic factors increase during active inflammation. When animals are given anti-inflammatory agents however, the levels of only the inflammatory factors decrease, whereas levels of fibrotic mediators remain increased⁵⁰—this could be one mechanism that promotes fibrosis in the absence of inflammation. The composition and stiffness of the ECM are also likely to be involved. Fibroblasts from patients with CD produce increased levels of cell migration-inducing hyaluronan-binding protein through an autocrine pathway regulated by IL6⁵¹. Hyaluronan degradation generates damage-associated molecular pattern fragments, which sustain inflammation and fibrosis to contribute to the cycle of

inflammation and fibrosis. The ECM is a storage site for cytokines and fibrotic growth factors, including TGF β ^{52, 53}. These can be released and promote deposition and crosslinking of ECM components that change its local mechanical properties, making it stiffer⁵⁴. This stiffness can perpetuate fibrogenesis by activating mesenchymal cells, even in the absence of additional activating factors ⁵⁴⁻⁵⁶. Contraction of mesenchymal cells can further increase stiffness and regulation of contraction, independent of inflammation ⁵⁷.

Various lines of evidence indicate an involvement of the gut microbiota in fibrogenesis. Genetic variants encoding bacterial sensing receptors as well as serum antibodies against microbial components have been associated with the risk of intestinal fibrosis ^{58, 59}. Animal models do not develop intestinal fibrosis in the absence of a microflora ³⁴ and in vitro data indicate a specific action of the bacterial protein flagellin in the fibrogenic response of intestinal mesenchymal cells ⁶⁰⁻⁹. Microflora-derived signals could therefore be another inflammation-independent mechanism that promotes fibrogenesis, with the potential advantage of being modifiable.

Another level of control for tissue repair and fibrosis is through regulation of ECM turnover. In the normal gut, the fine balance between ECM production and degradation is maintained by matrix metalloproteinases (MMPs) that break down ECM and tissue inhibitors of matrix metalloproteinases (TIMPs) that counteract this degrading activity. Only when ECM production is increased and surpasses degradation or when degradation is reduced fibrosis will occur. The balance between MMPs and TIMPs seems to be altered in IBD ^{61, 62}. This is, however, difficult to interpret because MMPs have pleiotropic functions and can also proteolytically activate or degrade non-matrix substrates and therefore only affect not only the ECM but inflammation itself^{61, 62}. This complexity might account for findings in mice that inhibition of MMP9 prevents fibrosis ⁴⁹. It should be noted that matrix turnover is a continuous process and can be observed in areas of already established organ fibrosis ⁶³. Turnover might even accelerate with increased ECM deposition ⁶⁴, so therapeutic interventions might be feasible even in late stages of stricture formation or in already-established strictures.

In patients with CD, these factors and mechanisms ultimately lead to the pathologic thickening of all layers of the intestinal wall from the mucosa and muscularis mucosa to the muscularis propria. The submucosa is filled with dense collagen bands and islands of smooth muscle cells, and an expansion of the muscularis mucosa occurs ^{65, 66}. It is noteworthy that the amount of fibroblast islands within CD strictures correlates with the expression of fibrotic cytokines and ECM molecules ⁶⁷⁻⁶⁹. The total collagen is increased with a relative increase of collagen III and V ^{70,71} accompanied by an increase in fibronectin and tenascin C ⁷².

Another feature of long-term CD is the so-called fibromuscular obliteration of the submucosa associated with a thickening of the muscularis propria ⁷³. Obliteration of the submucosa is associated with stricturing disease, especially in the small bowel ⁷⁴. These abnormalities are not unique to CD, because increases in collagen I and III and fibronectin have also been observed in intestinal tissues from patients with UC ⁷⁵. In this form of IBD the muscularis mucosa can be greatly thickened ⁷⁶, but fibrosis extends to the submucosa, at a maximum, with the thickness of the submucosa remaining unchanged ^{4, 77, 78}.

All these observations will not only increase our understanding of the mechanisms of intestinal fibrogenesis, but also indicate possible targets for anti-fibrotic therapies, through modulation of soluble inflammatory or fibrotic factors, ECM turnover, or the microbiota. Relatively little attention has been paid to the origin of mesenchymal cells in intestinal fibrogenesis. Despite the common belief that intestinal mesenchymal cells arise from locally proliferating precursors ⁷⁹, it has become increasingly evident that cells that mediate fibrogenesis derive from a multiple sources. These include epithelial cells via epithelial to mesenchymal transition (EMT) ⁸⁰⁻⁸², endothelial cells via endothelial to mesenchymal transition ⁸³, intestinal stellate cells differentiating into myofibroblasts ⁸⁴, circulating precursors (so called fibrocytes) ⁸⁵ and the bone marrow ⁸⁶. Controlling the accumulation of mesenchymal cells in IBD appears now to be a feasible proposition as inhibiting the influx of mesenchymal cells should lead to reduced deposition of ECM and either prevent, reduce, or eliminate fibrosis (**Figure 1**).

Prevalence of Fibrosis and Factors Associated with Development

How many patients are affected by intestinal fibrosis and how can we predict its development or presence? CD has a fibrostenosis phenotype at diagnosis in at least 10% of patients, but most patients initially present with a purely inflammatory phenotype, without complications (strictures or fistulae) ^{87, 88}. Population-based studies have found that approximately 20% of patients develop fibrostenosis within 20 years of a CD diagnosis ⁸⁹; more than 30% develop this complication within 10 years of diagnosis at tertiary referral centers ^{87, 88}. However, most of these studies used the Vienna or Montreal classification systems, based only on information about patients' symptoms, and therefore likely underestimate the true incidence of the fibrostenotic phenotype (**Figure 3**).

In patients with CD the presence of internal penetrating disease often accompanies strictures, and fistulae have a high positive-predictive value (86.2%) for the existence of concomitant strictures ^{90, 91}. Due to this strong association, many experts believe that strictures precede the development of internal penetrating disease and fistula formation, which would make fistulae a later step in the progression of CD. No longitudinal or prospective studies have been performed, however, to support this model of disease progression. Surgical resection can relieve the acute obstruction by removing an affected segment, but CD almost invariably recurs leading to repetitive stricture formation and obstruction ⁹². The location of strictures seems to be determined by the segmental location of inflammation, the most common site being the terminal ileum or the ileocecal region. Strictures, however, can occur in any segment of the intestine, including the upper gastrointestinal tract ⁹³⁻⁹⁶.

Although the location of CD is usually considered to be stable, the speed of progression varies—CD can progress at any time in a patient's lifetime ⁸⁷⁻⁸⁹. For this reason it would be more prudent to stratify patients into at-risk subgroups based on progression of the mechanisms of fibrogenesis. Preventive approaches or treatments could then be selected for each patient.

To date there are no specific or reliable markers for predicting which patients will develop stricturing CD. Multiple markers have been tested, including clinical, serologic, genetic, and epigenetic ^{97, 98}. Although some may predict complicated CD per se (including stricturing, fistulizing disease and need for surgery), none of these markers is specific for fibrostenosis and currently none can be recommended for clinical practice (**Table 1**). In the case of clinical markers, symptoms alone may already indicate the existence of complicated CD and may only serve as descriptors of a fibrostenotic phenotype, rather than factors that predict its development.

Ulcerative colitis has been long considered as a non-fibrotic disease, but recent evidence indicates otherwise. The prevalence of fibrosis-associated colonic strictures in patients with UC has been reported to range from 2% to 11.2%, ^{99, 100} compared to about 8% in patients with colonic CD ⁹⁶. Even in the absence of a stricture, some degree of fibrosis is found in 100% of colectomy specimens from patients with UC ^{78, 101}, and the degree of fibrosis is proportional to the degree of inflammation ¹⁰¹. Given the colonic location, there is always the concern that a stricture may be a sign of malignancy, but most (71%–100%) UC-associated strictures are benign ^{77, 102, 103}. Clinical factors linked to strictures in UC are disease duration and mucosal ulcer size, but no controlled data are available.

Diagnosis

Patients are usually diagnosed with strictures when they cause symptoms, such as those of IBD, or when patients present to the hospital with signs of intestinal obstruction (**Figure 3**). Patients often then undergo cross-sectional imaging analyses by ultrasound, computerized tomography (CT), or magnetic resonance (MRI), which all identify stenoses in the small intestine and colon with high levels of sensitivity and specificity¹⁰⁴ (79% sensitivity and 92% specificity for ultrasound, 89% sensitivity and 99% specificity for CT, and 89% sensitivity and 94% specificity for MRI). US detects stenosis with lower sensitivity due to the difficulty of visualizing the entire small bowel or colon ¹⁰⁴. Pure inflammation or pure fibrosis are rarely encountered in strictures—in most instances inflammation and fibrosis co-exist to varying degrees ^{105, 106}. In order to treat these patients, it is critical to understand the composition of their strictures, in terms of relative proportions

inflammation and fibrosis, to determine whether anti-inflammatory therapy is required. Separating inflammation from fibrosis is far more challenging—in surgical specimens, only a small fraction of strictures is graded as purely inflammatory or purely fibrotic, and most have varying degrees of inflammation and fibrosis^{107, 108}. This could account for the inability of conventional imaging techniques to grade the degree of fibrosis¹⁰⁹. The currently most advanced imaging technique is MR enterography, which assesses using the percentage of gain in gadolinium enhancement within the stricture, and is able to separate severe fibrosis from mild or moderate fibrosis, independently of the degree of inflammation¹¹⁰. New imaging techniques are being developed, including MR with dynamic contrast enhancement¹¹¹, magnetization transfer MRI,¹¹² and ultrasound elastography^{113, 114}. These technologies are promising, but not yet ready for routine clinical use.

The endoscopic definition of a stenosis in a patient with CD is based on commonly used classification system—the simple endoscopic score-CD and the CD-endoscopic index of severity. In these, stenosis is considered to be a narrowing of the lumen that cannot be passed with the endoscope^{115, 116}. These scoring systems are not particularly useful for diagnosis and clinical decision making, because only the mucosa is visualized by endoscopy—transmural evaluation and grading of inflammation vs fibrosis are not possible.

There is no endoscopic classification system for fibrosis or stenosis in patients with UC. Endoscopic biopsies carry the same limitations as routine endoscopy can only sample the superficial layer. No validated histopathology-based scoring system is available to grade the severity of fibrosis¹⁰⁹. In addition, no serologic, biochemical, genetic, or epigenetic biomarkers are available that correlate with the degree of intestinal fibrosis (the overall fibrotic burden of a patient) with high enough accuracy to allow their use in clinical practice¹⁰⁹.

Management of Fibrostenosing IBD

The management of patients with fibrostenosing CD may include medical, endoscopic, and surgical therapy. Depending on each specific situation, optimal care should be delivered

by an inter-disciplinary team comprising gastroenterologists, radiologists, and colorectal surgeons (**Figure 4**). Patients suspected of having an intestinal obstruction should first undergo cross-sectional imaging and, if stenosis is confirmed, be hospitalized.

Medical management

The first step is to assess the degree of inflammation in the stricture using the diagnostic approaches delineated in the preceding section, such as endoscopy, CT or MRI. Signs of inflammation on CT or MRI are the comb sign (engorgement of the vasa recta), intestinal wall thickening, and hyper-enhancement or lymphadenopathy ¹⁰⁴. If inflammation is confirmed, then health care providers should initially attempt anti-inflammatory therapy, which might decrease wall edema with a subsequent reduction of bowel wall thickness and relief of the obstructive symptoms ^{7, 117}. Although this is the first step at most IBD centers, the data to support this approach are limited. In one study, the use of corticosteroids in 26 patients with CD and acute small bowel obstruction relieved obstructive symptoms in all but 1 patient within a 3-day period. Eighteen patients had recurrence of their obstructive symptoms and were treated a second time with corticosteroids, and all patients responded. The main determining factor of whether or not patients would eventually need surgery was the symptom-free interval. In this study the need for surgical intervention was high (46% in this series) if the symptom-free interval was less than 8 months ¹¹⁷.

Patients who are steroid dependent or even steroid refractory can be treated with anti-tumor necrosis factor (TNF) agents. Initially there were concerns about this approach, due to the possible promotion of stricture formation caused by rapid healing of ulcers ^{118, 119}. However, data from ultrasound studies ¹²⁰, the CD Resource, Evaluation and Assessment Tool (TREAT) registry, ¹²¹ and randomized controlled clinical trials ¹²² do not support this contention. A prospective multicenter observational cohort study (CREOLE) testing the effects of induction and maintenance therapy with the anti-TNF agent adalimumab in patients with CD with symptomatic small bowel strictures found that 61% of patients met the primary endpoint, at week 24, of requiring no steroid or need for endoscopic dilation no surgery, no adverse events, and no need for an alternate anti-TNF ¹²³. More than half of the patients fulfilled these criteria after 2 years treatment with adalimumab. The

investigators also devised a scoring system to predict the efficacy of anti-TNF therapy, assigning 1 point each for the use of immunosuppressants, short duration of obstructive symptoms, high degree of symptom severity, severe delayed T1 enhancement on MR enterography, and the absence of fistulizing disease; 2 points were assigned for the presence of pre-stenotic dilation between 18 and 29 mm. For subjects with at least 4 points, the odds of adalimumab efficacy were 88% ¹²³. There are no data on the use of immunomodulators, vedolizumab, or other biologics for these patients.

If anti-inflammatory therapy is not successful in relieving obstructive symptoms or if symptoms recur within a short interval, then endoscopic therapy, strictureplasty, or intestinal resection should be considered. The decision among these choices should be made based on stricture location, stricture length, stricture angulation, accompanying complications (such as phlegmon, abscess, dysplasia or malignancy), length of symptom-free interval, and patient preference ¹⁰⁹.

Endoscopic management

Various procedures are available for endoscopic management of fibrostenosing IBD, including endoscopic balloon dilatation (EBD), intra-lesion injection of corticosteroids or anti-TNF agents, and metallic biodegradable or removable stents.

EBD is indicated when strictures are within reach of the instrument (for colonoscopy, upper endoscopy or balloon assisted enteroscopy), less than 5 cm in length, non-angulated, and are not accompanied by complications. This indication is based on a large body of observational data that have recently been summarized ¹²⁴. In a pooled descriptive analysis of 33 retrospective studies (**Supplemental Table 3**), comprising 1463 CD patients, endoscopic dilation was successful in 90%. Clinical response, meaning a short-term relief of symptoms, was achieved in 80.3% of patients. The complication rate, defined as bleeding, perforation or hospitalization was 2.7%, and 69.2% of subjects had not undergone surgery after a median follow-up of 40.1 months ¹²⁴. The only characteristic able to predict a reduced need for surgery prior to EBD was a stricture length of 5 cm or more in a multivariate analysis ¹²⁴. Interestingly, the presence of active inflammation at the

site of the stricture, the presence of a naïve vs an anastomotic stricture, or any technical features, such as balloon diameter or dilation time, did not affect short-term or long-term outcomes or rates of complications¹²⁴. Upper gastrointestinal strictures are also amenable to EBD. Technical, clinical success and complication rate appear to be comparable with those of ileo-colonic strictures, but time to re-dilation or surgery appears to be shorter compared to ileo-colonic strictures^{95, 124}. Findings from larger observational case series have supported the feasibility of EBD in balloon-assisted enteroscopy^{125, 126}.

The post-dilation injection of corticosteroids (triamcinolone) into the stricture has been evaluated in a systematic review of observational studies, and no outcome differences were noted, regardless of steroids injection¹²⁴. Two prospective randomized controlled trials have been performed. These were a single-center study of 29 pediatric patients with CD, in which steroid injection prolonged the time to re-dilation or surgery,¹²⁷ and a multi-center study of adults that was terminated due to a shorter time to re-dilation in the steroid group compared to placebo¹²⁸. At this time, at least in adults, there is no evidence for the benefit of steroid injection after EBD. A few case studies of injection of anti-TNF agents into patients with CD-associated strictures have reported success^{129, 130}, but recent findings from the CREOLE trial, along with unclear anti-inflammatory effects, make this intra-lesion approach questionable.

Endoscopic metallic stents have been successfully used for strictures of some other conditions, such as esophageal or colonic malignancies^{131, 132}. Observational data are available for CD-associated strictures. The technical and clinical success rate is as high as 100%, but initial enthusiasm has been dampened because two thirds of the patients had major complications, such as stent migration and fistula formation leading to perforations¹³³. One alternate solution to these complications is the use of biodegradable stents, but there have been only a small number of reports on this approach¹³⁴. Stent integrity and radial force are maintained for 6–8 weeks and disintegration occurs around 12 weeks after implantation. Overall the short-term success rate appears to be high with a lower complication rate compared to metal stents, but more data are needed before reaching a definitive conclusion. Another emerging alternative are removable metal stents^{135, 136}.

Using a spincterotome or needle knife procedure to carve the stricture together with EBD has the theoretical advantage of reducing the rate of re-stricturing at the possible cost of a higher rate of complications. Using a spincterotome after EBD appears not to increase complication rate ¹³⁷. The first case series using needle knife procedure in lower gastrointestinal strictures has been published ¹³⁸, but no head to head comparison with conventional interventions was performed, and this procedure cannot currently be recommended for routine clinical care. Future controlled studies need to clarify whether the possibly higher complication rate justifies a possible increase in long-term efficacy.

Should systemic medical therapy be escalated after dilation? In a retrospective chart review cohort study with 54 CD patients that underwent EBD for anastomotic ileo-colonic strictures the median length of stricture was 20 mm with a median Rutgeerts score ⁹² of i2 at time of EBD. Patients were followed until repeat dilation or need for surgical intervention ¹³⁹. A change to medical combination therapy with anti-TNF and an immunomodulator was associated with a decreased need for repeat dilations (hazard ratio 0.23). Severe inflammation at the site of the stricture (Rutgeerts i4) was linked to an increased need for early anastomotic resections (hazard ratio 4.33) ¹³⁹, suggesting that control of inflammation after dilation in anastomotic CD strictures may delay the time to re-dilation or surgical recurrence.

Serial dilations of the same stricture are feasible and frequently employed in clinical practice and this approach is supported by observations that short-term, long-term outcome as well as complication rates remains unchanged compared to the first dilation ¹⁴⁰.

Surgical management

If the stricture is >5 cm, endoscopic dilation is technically not feasible, and the stricture is located in the ileocecal region (localized long ileocecal stricture) surgical resection should be considered. The rationale is the possible prevention of subsequent complications, such as obstruction or fistulization. In these type of strictures surgery is considered superior to medical therapy (even though no comparative data exist) ^{7, 109, 124, 141-143}. Two retrospective studies indicate that early surgery (from the time of diagnosis) prolongs clinical remission

and reduces the risk of re-operation compared to medical therapy alone ^{144, 145}. Comparable findings have been reported in a pediatric population ^{146, 147}. In the case of accompanying complications, features, such as abscess, fistula, phlegmon, dysplasia, or malignancy surgical resection is clearly indicated ¹⁰⁹.

Strictures outside of endoscopic reach that are >5 cm and have no accompanying complications can be considered for a bowel preserving operation, the so called strictureplasty. This approach preserves bowel length and reduces the risk of an anastomotic leak. Short strictures are amendable to the Heineke-Mikulicz procedure (<10 cm), for intermediate strictures (10–25 cm) the Finney procedure can be used, and non-conventional strictureplasties (e.g. isoperistaltic Michelassi technique) are indicated for long (>25 cm) segment strictures or multiple strictures that are in close proximity to each other ¹⁴⁸⁻¹⁵¹. When comparing complications and recurrences between conventional (Henieke–Mikulicz and Finney) and non-conventional strictureplasties (Michelassi) no significant differences were found ¹⁵². Recently ileocolonic strictureplasties in patients with terminal ileal strictures have been described ¹⁵³.

Colonic strictures present a special situation that should be managed with caution, due to the potential presence of a malignancy. The incidence of malignancy in patients with CD and colitis is comparable to that of patients with UC ^{154, 155}. Among patients with a colonic stricture and endoscopic biopsies and brush findings negative for dysplasia or cancer, 3.5% of those who underwent surgical resection were found to have dysplasia or malignancy in a histopathologic evaluation ¹⁵⁶. If a patient with CD has a colonic stricture at diagnosis or during follow up, the risks for colorectal cancer at 5 and 10 years are 3.6% and 4.9%, respectively ¹⁵⁷. These data should be discussed with the patient to decide about resection versus continued surveillance. Strictureplasty is not recommended for IBD-associated colonic strictures ¹⁴¹.

Prior to surgical intervention, nutritional status should be optimized. A laparoscopic approach over laparotomy is preferred, due to faster recovery and less pain with comparable rates of surgical recurrence ¹⁵⁸⁻¹⁶¹. Novel techniques include single port

laparoscopic surgery, which could further reduce pain compared to conventional laparoscopy ¹⁶².

Reversibility of Stricturing IBD

The paradigm that inflammation leads to intestinal fibrosis, intestinal obstruction, and the need for surgery is changing, due to findings from studies of other organs, including skin, kidney, and liver, in which fibrosis has been shown to be reversible ^{21, 29, 163, 164}. Clinical observations in intestinal fibrosis suggest that fibrogenesis is not a 1-way street, but is also reversible. In a large combined analysis of 1112 patients with CD after strictureplasty, the overall symptomatic recurrence rate of jejunoileal strictures was 39% and for ileocolonic strictures was 36%. Interestingly this symptomatic recurrence was caused by only 3% of previously treated jejunoileal and 20% of previously treated ileocolonic ¹⁶⁵. When patients underwent small bowel series 6 months or longer after strictureplasty, narrowing of the site of the original strictureplasty was found in only 11% after a median of 2 years ¹⁶⁶. In other words, once a strictureplasty has been performed the treated stricture is rarely the cause of symptomatic recurrence of IBD.

These observations have been confirmed in serial ultrasound examinations after strictureplasty, in which a progressively reduced thickness of the intestinal wall was noted ¹⁶⁷. This suggests that surgical intervention can halt or even reduce fibrogenesis. Multiple mechanisms that could be responsible for reversing fibrosis on a molecular level have been suggested ¹⁶⁸. The novel surgery technique of strictureplasty over the ileocecal valve allows colonoscopic surveillance and serial sampling, which might be a promising model to study reversibility in the human intestine ¹⁵³.

In addition to the compelling observations of reversibility of intestinal fibrosis, a large pipeline of specific anti-fibrotic drugs is becoming available for organ fibrosis, such as for the liver, kidney, lung, heart, and skin ^{169, 170}. A detailed discussion of the possible mechanisms of involved the therapeutic effect is outside the scope of this review, but reviews are available ^{169, 170}. Agents are being developed to target growth factors, inflammation, and oxidative stress, the ECM, and intracellular enzymes and receptors and

might be tested in patients with IBD. The small molecules prifenidone and nintedanib have been recently approved by the European Medicines Agency and the US Food and Drug Administration for treatment of idiopathic pulmonary fibrosis ¹⁶⁹, and could be options for treatment of fibrostenosing IBD.

Future Directions

Preventing intestinal fibrogenesis or reversing already established bowel strictures in patients with IBD should remain the ultimate goal. We need to close the large gap between our significant clinical need for anti-fibrotic IBD therapies and our wealth of knowledge on mechanisms of fibrosis, findings from animal models of fibrosis, and data on anti-fibrotic therapies from other organs. The complexity of mechanisms of intestinal fibrosis is comparable to that of intestinal inflammation. The system is highly intricate, dynamic, and multifactorial, so single-target approaches are not likely to be successful ¹⁶.

For testing preventive approaches in humans, early-stage IBD presents a unique window of opportunity for intervention, as fibrosis might become self-perpetuating once ECM deposition and increased ECM stiffness become established ¹⁷¹. In order for trials of this kind to be feasible, we need robust biomarkers to detect intestinal fibrosis and early response to therapy ¹⁶⁹.

As our understanding of intestinal fibrosis continues to evolve, new anti-fibrotic therapies will come within reach. Our comprehensive overview of mechanisms, diagnosis, and management of intestinal fibrosis will hopefully serve as a platform for future investigations and advances.

Figures

Figure 1. Pathophysiology of intestinal fibrosis: Soluble factors (red) and different origins of mesenchymal cells (blue). CTGF: connective tissue growth factor; EGF, epidermal growth factor; EndoMT: endothelial-to-mesenchymal transition; ET: endothelins; PDGF: platelet-derived growth factor

Figure 2. Model for kinetics of the expression of inflammatory, fibrotic factors, and matrix stiffness in active inflammatory bowel disease before and after treatment.

Figure 3. The true incidence of fibrostenosis is likely underestimated due to the subclinical accumulation of extracellular matrix over time.

Figure 4. Care algorithm for small bowel and ileocecal strictures in patients with CD. In patients with CD or ulcerative colitis, colonic strictures require special care.

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Table 1: Predictors of fibrostenosing Crohn's disease

Clinical, environmental, endoscopic	Reference
Diagnosis < 40 years of age	172, 173
Need for steroid therapy at diagnosis	172, 173
Perianal fistulizing disease	172, 173
Early use of azathioprine or anti-TNF	174
Small bowel disease location	174
Deep mucosal ulceration	175
Smoking	174, 176, 177

Genetic markers

NOD2	58
ATG16L1	179
IL-23R	224
CX3CR1	180, 181
MMP-3	178
IL12B	182
JAK2	183
MAG1	223

Epigenetic markers

miRNA-200a and 200b	184
miRNA-29b	185
miRNA-19a/b	186

Serology

ASCA	187, 188
Anti-CBir1	189, 190, 191
Anti-I2	189, 190, 191
Anti-OmpC	189, 190, 191
Anti-glycan antibodies	187, 192
YKL40	193

Anti-I2: Pseudomonas-associated sequence I2; ASCA: Anti-Saccharomyces cerevisiae antibodies; ATG16L1: autophagy-related protein 16-1; CBir1: bacterial flagellin cBir1; CX3CR: Chemokine fractalkine receptor; IL: Interleukin; JAK: Janus kinase; miRNA:

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Figure 1

Figure 2

Figure 3

Figure 4

*Fistula, abscess, phlegmon, dysplasia or malignancy

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