Fibrosis and Stricturing Disease in Crohn's Disease

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Abstract

Crohn's disease (CD) has a protean presentation including inflammatory, stricturing, fistulizing, and perianal disease morphologies. The incidence of fibrostenosing CD and the need for surgery have largely remained unchanged despite the use of anti-inflammatory drugs including biologics. Fibrosis is a common occurrence in ulcerative colitis. Clinical, serologic, and imaging markers lack accuracy to predict, diagnose, and prognosticate fibrostenosing CD. There are no established clinical trial end points to measure efficacy of anti-fibrotic drugs. Management of fibrostenosing CD needs a multidisciplinary approach involving medical, endoscopic, and surgical management. Targeted anti-fibrotic therapies are necessary to treat fibrostenosing CD in the future.

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7.1 Introduction

CD has a protean presentation. The variability in disease phenotype over time leads to the need for classifying the disease into inflammatory, stricturing, fistulizing, and perianal disease per the Montreal Classification [1]. It is common for stricturing and fistulizing CD to coexist. One study on surgical specimens suggested that 64% of patients had fistulizing CD of which 41% of specimens had fistulae within a stricture and about 56% had fistulae proximal to the stricture speculating that mechanical factors may contribute to their formation [2]. The anatomic distribution of strictures follows the sites affected by inflammation and includes the ileum followed by ileocolic region, albeit strictures can occur in other locations including the upper gastrointestinal tract, colon, and rectum [3, 4]. Long-term studies continue to show a 20–40% prevalence of fibrostenosing Crohn's disease (CD) in populations across Asia, Europe, and North America with a follow-up over a timeframe of 4–10 years [5–9]. Pathophysiologically, intestinal fibrosis is associated with increased extracellular matrix (ECM) generation and mesenchymal cell proliferation leading to progressive narrowing of the intestinal lumen, which ultimately progresses to mechanical obstructive symptoms. Animal models of inflammation-induced fibrosis indicate the continuation of the fibrotic process despite abatement of the inflammatory process [10].

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Population-based studies demonstrate that 20% of patients develop fibrostenotic complications within 20 years of a CD diagnosis while >30% develop this complication within 10 years of diagnosis at tertiary referral centers [6, 11, 12].

Fibrostenosing CD continues to be a significant risk factor for surgery, and there has been no significant change in the need for surgery despite introduction of immunosuppressant therapy [6, 8]. A recent population-based study from Europe indicates that while the use of immune modulators and biologics has increased over the past decade, there has been no change in the progression of disease from an inflammatory to a complicated course [13]. Other studies show that the incidence of fibrostenosing CD and the need for surgery have either remained unchanged or have decreased in some parts of the world while it has increased in other parts and the exact etiological factors remain elusive [8, 9, 14]. Attempts to develop predictive models to determine occurrence or speed of disease progression and attempts to "personalize" IBD care continue to be made. This is critical to define patient populations at risk amendable to tailored anti-fibrotic therapies or to learn about the pathophysiology of fibrosis [15, 16]. Despite numerous projects to develop genetic, epigenetic, serologic, radiologic, or clinical predictors to direct physicians at personalizing IBD treatment, none have achieved clinical applicability due to variable penetrance of genetic and epigenetic factors and low accuracy of serologic, radiologic, and clinical predictors [15, 16].

7.2 Overview on the Mechanisms of Fibrogenesis

Common etiopathogenic mechanisms of fibrosis include an expansion of the mesenchymal cell pool, consisting of fibroblasts, myofibroblasts, and smooth muscle cells. Multiple sources of mesenchymal cells have been described, namely, endothelial to mesenchymal transformation, epithelial cell to mesenchymal transformation, stellate cells, or fibrocytes derived from the bone marrow [17]. Activation of myofibroblasts causes increased ECM production [18].

7.3 Risk Factors for the Development of Fibrostenotic CD

Animal models show that the predisposition for and degree of fibrosis in general may be variable in differing genotypes in fibrotic conditions including PSC and lung fibrosis [19, 20]. Also a phenomenon of rapid progression of fibrosis has been observed clinically in patients undergoing liver transplantation [21]. These concepts may be extrapolated to fibrostenosing CD.

Clinicians continue to rely on certain clinical factors to predict and prognosticate fibrostenosing CD. These factors include need for corticosteroids, early onset of disease, frequency of flares, smoking, perianal disease, and small bowel involvement [22–24]. However, using these factors for prediction may often be too late as they already represent a more complicated CD course and fibrosis may already be present at the time of prognostication. Also these clinical predictors lack validation in large prospective or ad hoc studies. Hence, there is an increased interest in the discovery of accurate and noninvasive biomarkers.

7.4 Biomarkers as a Diagnostic and Predictive Tool for Fibrostenosing CD

Several biomarkers have been purported for the prediction of complications, association, or diagnosis of fibrostenosing CD. Prognostic biomarkers that have been tested for the prediction of fibrostenosis include genetic markers and antimicrobial antibodies.

7.4.1 Predictive Biomarkers

In general, genetic markers include those that are predominantly associated with autophagy (e.g.,

ATG16L1), recognition of muramyl dipeptides (MDP) bacterial components (e.g., NOD2), interleukin and interleukin receptor-associated genes (e.g., IL-23 receptor), epithelial cell adhesion (e.g., discs large homologue 5 (DLG5)), or matrix regulation (e.g., metalloproteinase-3 (MMP-3)).

A meta-analysis of predictive genes included assessing the occurrence of high-risk NOD2 single nucleotide polymorphism (SNPs) among CD patients which predicted an increased risk of stenosing CD (OR = 1.94, (95% CI, 1.61–2.34)) with an OR for small bowel involvement at 2.53 (95% CI, 2.01–3.16) [25].

It is speculated that gut injury followed by exposure of microbial components to the intestinal immune system initiates an immune response and may be responsible for eliciting the formation of antibodies which are detectable in the serum. The first such antibody studied included anti-*Saccharomyces cerevisiae* (ASCA) [26]. This was followed by other antibodies, including the anti-glycan antibodies; anti-mannobioside carbohydrate antibody (AMCA), anti-laminaribioside carbohydrate antibody (ALCA), or anti-chitobioside carbohydrate antibody (ACCA) and non-glycan antibodies to bacterial components including anti-outer membrane protein C (OmpC), anti-I2, or anti-CBir1.

The odds ratio of predicting combined penetrating and stricturing CD showed an incremental rise as the degree of immune responses to a combination of glycan and non-glycan antibodies increased, i.e., by the number of positive antibodies (OR = 1.1, 2.3, 5.5, and 11 for 1, 2, 3, and 4 positive immune responses, respectively) using OmpC, anti-I2, anti-CBir1, and ASCA [27]. In another study, anti-I2, anti-CBIR1, or ASCA antibodies aided in predicting complicated CD but were unable to differentiate stricturing and nonstricturing CD [28]. Findings similar to this combination were seen when anti-glycan antibodies were used exclusively [26]. Overall, these predictors are not accurate enough to be used in clinical practice and show variable sensitivity and specificity based on the number of antibodies used to predict complications including strictures with sensitivities and specificities varying from 42% to 71% and 48% to 75%, respectively, and are elaborated in Table 7.1 [26, 29–31].

Table 7.1 Diagnostic and predictive biomarkers in fibrostenosing Crohn's disease

Biomarker (type)	Country of origin	Study characteristics	Sensitivity	Specificity	Accuracy (ROC)	Additional comments
ATG16L1 (genetic) [51]	Australia	Cohort study	–	–	–	Frequency of ATG16L1 T300A GG genotype associated FSCD with a frequency of 0.39, $p < 0.001$
NOD2 mutations (genetic) [52]	USA	Meta-analysis	36% (pooled)	73% (pooled)	0.56 (pooled)	RR for NOD2 mutant allele for complicated CD (stricturing or fistulizing) = 1.17 (95% CI) 1.10–1.24; $p < 0.001$). RR for P.G908R mutation for complicated CD (stricturing or fistulizing) = 1.33 (95% CI 1.11–1.60; $p = 0.002$)
CX3CR1 (genetic) [53]	Germany	Retrospective cohort	–	–	–	Prevalence in FSCD vs non-FSCD for V249i (55% vs 41%, $p = 0.035$) 3020insC (23% vs 6.7% $p = 0.001$)
MMP-3 (genetic) [54]	Denmark	Prospective	–	–	–	Significant differences were seen between MMP-1, MMP-2, MMP-3, and MMP-9 relative to TIMP-1, TIMP-2 which were increased in inflamed and non-inflamed IBD on surgical resection. No significant difference was noted between inflamed and fibrotic specimens

(continued)

Table 7.1 (continued)

Biomarker (type)	Country of origin	Study characteristics	Sensitivity	Specificity	Accuracy (ROC)	Additional comments
IL12B (genetic) [33]	Western Europe	Cohort	–	–	–	OR for homozygosity for the rs1363670 G-allele (IL12B gene) = 5.48 (95% CI 1.60–18.83; $p = 0.007$)
JAK2 (genetic) [34]	Europe	Cohort	–	–	–	HR for stenosis for combination of NOD2, JAK2, ATG16L1; =1.29, $p = 3.01 \times 10^{-02}$
MAGI1 (genetic) [55]	Europe	Cohort	–	–	–	Variants in *MAGI1*, *CLCA2*, *2q24.1*, and *LY75* loci were associated with FSCD ($p_{\text{combined}} = 2.01 \times 10^{-8}$)
miRNA-200a and miRNA-200b (epigenetic) [56]	China	Prospective	–	–	–	Mean serum miRNA-200b FSCD vs control, $P < 0.05$, FSCD vs non-FSCD $p > 0.05$
miRNA-29b (epigenetic) [39]	Italy	Cohort	–	–	–	Notes a reduction in the mean levels of *miR-29a* in FSCD relative to inflammatory CD ($p = 0.049$)
miRNA-19a/b (epigenetic) [40]	Italy	Cohort	–	–	0.67	Mean serum miR-19-3p (miR-19a-3p and miR-19b-3p) was reduced in FSCD vs non-FSCD subjects by >2-fold, $p = 0.007$ and 0.008
ASCA (AMA) [29]	Germany	Cohort	–	–	–	OR for complicated CD (stricturing/fistulizing) ASCA: 3.5 (95% CI, 1.9–6.4)
Anti-CBir1 (AMA) [27]	USA	Cohort	–	–	–	Prevalence of anti-CBir1+ vs anti-CBir1- in complicated CD (stricture/fistula) was 19% vs 12%, $p = 0.36$
Anti-I2 (AMA) [27]	USA	Cohort	–	–	–	Prevalence of anti-I2+ vs anti-I2 - in complicated CD (stricture/fistula) was 31% vs 12%, $p = 0.003$
Anti-OmpC (AMA) [27]	USA	Cohort	–	–	–	Prevalence of anti-OmpC+ vs anti-OmpC- in complicated CD was 36% vs 12%, $p = 0.006$
Anti-glycan antibodies (AMA) [29]	Germany	Cohort	–	–	–	OR for complicated CD (stricturing/fistulizing) were ASCA: 3.5 (95% CI, 1.9–6.4) AMCA: 2.4 (95% CI, 1.2–4.8) ALCA: 2.3 (95% CI, 1.1–4.8)
AMA [57]	Ireland	Cohort	–	–	–	% age of involvement distinguishing inflammatory CD vs complicated CD (stricturing and fistulizing CD) differed using anti-OmpC, ASCA IgA, and anti-CBir on univariate analysis ($p < 0.05$)
Anti-glycan antibodies [37]	Canada	Cohort	–	–	–	ASCA IgG positivity was predictive of complicated CD (stricturing/penetrating) (OR = 3.01; 95% CI, 1.28–7.09; $P = 0.01$)

Table 7.1 (continued)

Biomarker (type)	Country of origin	Study characteristics	Sensitivity	Specificity	Accuracy (ROC)	Additional comments
Anti-glycan antibodies (AMA) [26]	USA	Meta-analysis	–	–	–	Pooled diagnostic OR to detect complications (fistulizing and stricturing CD) for ASCA and ACCA were 2.8 (95% CI: 2.1, 3.8) and 2.5 (1.9, 3.2), respectively, when analyzed individually or a combination of >2 anti-glycan antibodies pooled diagnostic OR was 2.8 (2.2, 3.7)
YKL-40 (AMA) [48]	Turkey	Cohort	–	–	–	Mean YKL-40 levels in FSCD vs non-FSCD (167.50 ± 119.30 ng/mL vs 80.12 ± 56.38 ng/mL ($P = 0.003$))
N-terminal propeptide of type III collagen (ECM) [42]	Italy	Case series	–	–	–	Serum N-terminal propeptide of type III collagen before surgical resection vs after surgical resection, (5.0 ± 1.8 vs 2.7 ± 0.7 microg/l ($p = 0.0001$))
Basic-FGF (growth factor-cytokine) [46]	USA	Cohort	–	–	–	Mean FGF levels between non-FSCD, FSCD, and fistulizing CD were 13.18 ± 1.85, 11.94 ± 2.93, and 11.96 pg/ml ± 2.64, $p = 0.91$
Basic-FGF [47]	Italy	Cohort	–	–	–	Significant difference between serum b-FGF and bowel wall thickness FS-CD when compared to other phenotypes
Fibronectin (ECM) [43]	Denmark	Cohort	16%[a]	83%[a]	–	Significant drop of mean fibronectin after surgery
Peripheral fibrocytes [50]	Japan	Prospective	–	–	–	Surgical specimens showed increased fibrocyte/total leukocyte % age in inflammatory lesions (22.2%) vs non-affected areas of the intestine (2.5%) and fibrotic areas ($p < 0.001$). Percentage of circulating $CD45^+$ collagen I^+ fibrocytes/total leukocytes were higher in patients with Crohn's disease (3.5%) than in healthy controls (1.5%)

Abbreviations: *ALCA* anti-laminaribioside, *AMA* antimicrobial antibodies, *AMCA* anti-mannobioside, *ATG* autophagy protein, *ASCA* anti-*Saccharomyces cerevisiae* IgG, *CD* cluster of differentiation, *CLCA* calcium-activated chloride channel, *ECM* extracellular matrix, *FGF* fibroblast growth factor, *FSCD* fibrostenosing CD, *HR* hazard ratio, *JAK* Janus kinase, *MAGI* membrane-associated guanylate kinase, *MMP* matrix metalloproteinases, *NOD* nitric oxide dismutase, *miRNA* micro-RNA, *TIMP* tissue inhibitor of metalloproteinases, *RR* risk ratio, *USA* United States of America
[a]To detect FSCD prior to or after surgery (normal plasma fibronectin being 206–379 mg/L)

7.4.2 Association Biomarkers

Biomarkers used for association include genetic markers and antimicrobial antibodies. Genetic biomarkers associated with fibrostenosing CD include variations in matrix metalloproteinase-3 (MMP-3) genes, i.e., 5T5T genotype at MMP-3 SNP-1613 5 T/6 T, which significantly increases the risk of stenotic complications in CD during follow-up (91.2% vs 71.8%) [32]. In another study, the presence of at least one of three NOD 2 SNPs was significantly associated with development of stricturing disease (40% vs 33%) [33]. Other SNPs significantly associated with development of stricturing disease include rs1363670 G-allele (69% vs 35%) [33]. Genetic markers

such as NOD2 mutations, JAK2, or ATG16L1 polymorphisms were associated with stenotic CD as derived from a large European GWAS study called the IBD chip study showing a hazard ratio of 1.42 [34]. In this study, the association between stenosis and genetic scores created using significant single nucleotide polymorphisms (SNPs) in a univariate analysis demonstrated a HR for stenosis of 1.29 using a combination of NOD2, JAK2, and ATG16L1 among patients with low and high score [34].

The IBD-5, disks large homologue 5 (DLG5), autophagy-related protein (ATG16L1), and IL-23 receptor (IL23R) were associated with CD and UC and their complications in a large Dutch-Belgian cohort; however, no clear association with fibrostenosing CD was identified [35]. In a meta-analysis of two studies, the pooled diagnostic odds ratio (DOR) to assess association with complications (fistulizing and stricturing CD) was calculated to be highest with ACCA and ASCA at 2.8 (95% CI: 2.1, 3.8) and 2.5 (1.9, 3.2), respectively, when analyzed for individual antibodies or 2.8 (2.2, 3.7) when using a combination of >2 anti-glycan antibodies [26]. More recent studies since the publication of this meta-analysis continue to suggest association with complicated disease phenotype with the highest association using AMCA and ASCA antibodies [36, 37].

7.4.3 Diagnostic Biomarkers

Biomarkers include a combination of genetic biomarkers, micro-RNAs, ECM molecules, fibroblast growth factors, and circulating fibroblasts.

miRNAs are RNA molecules that inhibit posttranscriptional expression of genes. Serum miR-200b was noted to be elevated, and serum miR-29a was noted to be decreased in ten fibrostenotic CD subjects compared to inflammatory CD [38]. Mucosal biopsy samples also demonstrate decreased expression of miR-29 in strictured versus nonstrictured segments of the bowel which mirrored decreased serum expression of miR-29 [39]. Similarly serum miRNA-19 was diminished in stricturing CD yielding a AUC = 0.67 to detect stricturing CD phenotype [40].

ECM biomarkers include inhibitors of metalloproteinases (TIMPs) in intestinal resection samples, propeptides of collagen in serum, and serum fibronectin. These markers are noted to be elevated in the serum of patients in stricturing CD; however, these studies failed to establish any measure of sensitivity, specificity, or accuracy due to lack of reliable cutoff values [41–43]. Contradictory findings were noted for the marker serum propeptide of collagen III which was noted to be elevated in fibrostenosing CD prior to intestinal resection followed by a drop after surgery when compared to controls, while another study showed no correlation to disease phenotype or activity [42, 44]. Other ECM markers that were analyzed include MMP-induced changes in vimentin (VICM), MMP-induced changes of biglycan molecules (BGM) that cross-link collagen, neutrophil elastase (ELNE), MMP-mediated type V collagen degradation (C5M), and type V collagen propeptide (Pro-C5) [45]. Although this study showed high AUC (>0.8) using such biomarkers to differentiate IBD from IBS and UC from CD, this study failed to diagnose fibrostenosing CD as a disease phenotype [45].

Growth factors promoting fibroblast expansion and activation, including basic fibroblast growth factor (b-FGF), have been demonstrated to be elevated in serum and biopsy specimens of surgically resected bowels of subjects with stricturing CD when compared to healthy controls. The Pearson correlation between b-FGF and disease activity was statistically significant at 0.53 [46]. These findings were also correlated in vivo showing an association between serum b-FGF levels and bowel wall thickness as measured on doppler studies [47]. Another growth factor of endothelial cells and fibroblasts called YKL-40 has been demonstrated to be elevated in the serum of fibrostenosing CD subjects compared to controls in one study which was contradicted in another study [48, 49]. Although sensitivity and specificity could not be established, there was significant correlation between YKL-40 levels and clinical disease activity

($r = 0.681$) and the presence of intestinal strictures ($r = 0.457$) [48].

Circulating fibrocytes have been tested as biomarkers in other fibrotic diseases, and examination of this phenomenon in CD yielded significantly higher ratios of the percentage of $CD45^+Col^+$/leukocytes, $ICAM^+$ fibrocyte/leukocyte, and $CXCR^+$ fibrocyte/leukocyte ratios in CD, and these fibrocytes were shown to produce higher amounts of collagen I after stimulation by lipopolysaccharides in vitro [50].

The lack of predictive and diagnostic accuracy and consistency between studies precludes the use of these biomarkers for predicting or diagnosing fibrostenotic CD [28]. This has also limited the use of these biomarkers as end points to assess outcomes in fibrostenosing CD in clinical trials [28].

These biomarkers are elaborated further in Table 7.1.

7.5 Diagnostic Evaluation

Histopathologic analysis of surgical resection specimens indicates stenotic CD is associated with inflammation and fibrosis and rarely are they exclusive of each other [58]. Identifying and distinguishing inflammation and fibrosis has implications for management [35]. Endoscopy with biopsies is limited in detecting deeper intramural inflammation or fibrosis and cannot assist in their differentiation. Cross-sectional imaging allows for the detection and characterization of mural and extramural complications and is encouraged at first presentation of intestinal stenosis [35, 59].

7.5.1 Imaging

Common imaging techniques used include CT enterography (CTe), MR enterography (MRe), and ultrasound (US). Stenosis is usually defined as a thickening of the bowel wall with a narrowing of the small bowel lumen with pre-stenotic dilation [60]. The pooled sensitivity and specificity of US for detecting small and large bowel stenosis ranged from 75% to 100% and 90% to 93%, respectively [61–63]. The sensitivity for ileal stenosis was 86% and was 58% for colonic stenosis in one study, indicating that certain locations of strictures may represent a limitation of this method [62]. High-resolution US showed a sensitivity and specificity for detecting stenotic CD of 86% and 90% when correlated to clinical symptoms and surgical findings [64]. US imaging is radiation-free and is useful to visualize the terminal ileum and colon as well as for therapeutic interventions including abscess drainage [59]. Some limitations include inadequate visualization due to gas-filled bowel loops and large body habitus. High-frequency (5–17 MHz) linear array probes help with better visualization of wall thickness and wall layer discrimination [65]. Delineation between fibrosis and inflammation in stenotic lesions remains a challenge although contrast-enhanced US (CE-US) may offer some advantages wherein microbubble contrast agents are injected intravenously prior to US imaging [66]. However, these techniques have not achieved clinical applicability in the delineation of fibrosis and inflammation in IBD strictures.

CTe enables the detection of stenotic lesions, pre-stenotic dilation, fistulae, and abscesses with high accuracy. CTe is able to detect small bowel stenosis with a sensitivity and specificity of 85% and 100%, respectively [67]. Data on colonic stenosis is limited. However, CTe may lead to significant cumulative exposure to radiation more so in young patients with childbearing potential and the risk of occurrence of radiation-induced cancers [68]. Enteroclysis which entails fluoroscopic or endoscopic placement of an enteroclysis tube into the duodenum distal to the ligament of Treitz with infusion of contrast media may be used to image jejunal anatomy better due to limited distension proximal to mid-ileum on CTe [69].

Sensitivity and specificity of MRI in detecting stenotic lesions ranged from 82% to 100%, respectively [63]. The inherent advantages of MRe include lack of radiation exposure and multi-planar and cine imaging with high contrast enhancement, while increased costs are a major limitation. In addition, MRI may help grade inflammation based on certain characteristics

including hyperintensity on T2, mucosal enhancement, ulcerations, and blurring of margins [70]. In this same study, fibrosis correlated with the percentage of enhancement gain (enabling the discrimination between mild-moderate and severe fibrosis), the pattern of enhancement at 7 minutes, and the presence of stenosis [70]. Although not available yet for clinical use in humans, magnetic transfer (MT) may be used for distinguishing stiffer tissue including muscle and fibrotic tissue from inflammation as shown in some animal studies [71].

Taken together the accuracy of cross-sectional imaging for the detection of stenosis is high, but none of the currently available techniques has been validated to distinguish inflammation from fibrosis.

7.6 Management: Monitoring and Therapeutics

We describe the clinical management of fibrostenosing CD as recommended by the European Crohn's and Colitis Organisation [ECCO] [72]. A multidisciplinary approach is suggested in the management of fibrostenotic CD including a collaborative effort from gastroenterologists, colorectal surgeons, radiologists, and pathologists. A brief overview is illustrated in Fig. 7.1. Management of fibrostenosing CD can be broadly categorized into medical management (anti-inflammatories), endoscopic management, surgical management, and often an overlap between medical and surgical co-management.

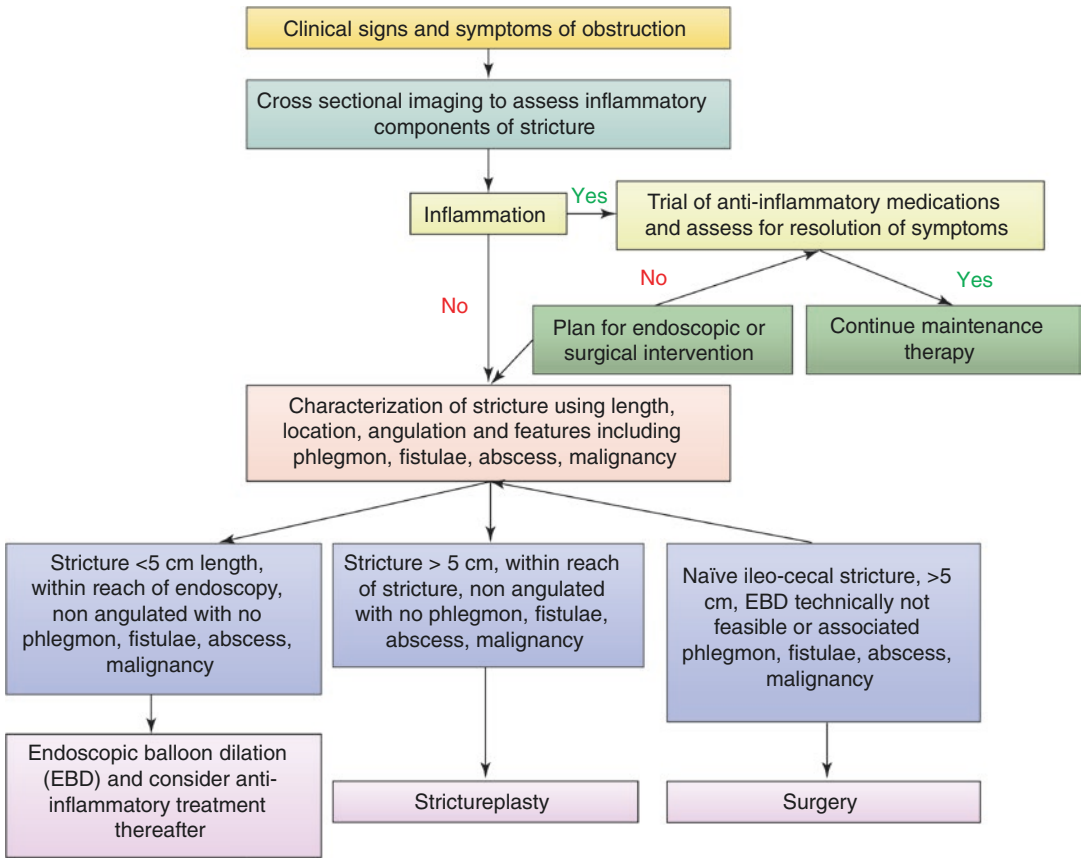

Fig. 7.1 Management of fibrostenosing Crohn's disease

7.7 Medical Management

An acute intestinal obstruction should be managed with appropriate cross-sectional imaging, bowel rest, nasogastric decompression, intravenous hydration, and electrolyte replenishment guided by laboratory data. Signs of peritonitis should warrant a surgical evaluation [35].

Since most strictures have fibrotic and inflammatory components, steroids and biologics help relieve obstruction by decreasing inflammation in an acute and subacute setting after bowel rest [73]. However, current therapies lack efficacy in reversing fibrosis, making endoscopic balloon dilation (EBD) with through the scope (TTS) balloons, and surgical management necessary.

7.8 Endoscopic Balloon Dilation (EBD)

EBD may be feasible for short segment strictures (<5 cm) within reach of a traditional colonoscopy or upper GI endoscopy, including terminal ileal and anastomotic strictures, upper GI strictures, and small intestinal strictures, respectively. Successful dilation with a technical efficacy of 89% and clinical efficacy of 81% has been quoted in a pooled analysis with a complication rate of 2.8% [74]. EBD and strictureplasty are contraindicated in the presence of an abscess, phlegmon, fistula, high-grade dysplasia, or malignancy [72]. Serial EBD of recurrent strictures is an efficacious approach, and a decision about surgical approach versus serial dilation may be made on technical feasibility, symptom-free interval, and patient preferences [35]. Other approaches including intralesional steroids, anti-TNFs, and stents are not currently recommended by the ECCO consensus [35].

7.9 Surgery

Surgical intervention including surgical resection and/or strictureplasty should be the preferred option for longer strictures (>5 cm). Fibrostenosing jejunal and ileal disease can be managed by "conventional" or side-to-side [Heineke-Mikulicz and Finney] and "nonconventional" strictureplasties. Nonconventional methods are used in patients who have multiple strictures in close proximity with the short gut from prior surgeries [75].

Short strictures defined as <10 cm are best treated with the Heineke-Mikulicz technique, and longer strictures (10–25 cm) are treated with Finney's strictureplasty. A meta-analysis comparing conventional and nonconventional strictureplasties showed no difference in the rates of complications between the two techniques [76]. Laparoscopic surgery for fibrostenotic CD is increasingly common in experienced centers to enable superior recovery, better cosmesis, less adhesions and incisional hernias, and similar surgical recurrence rates [77].

7.10 Future Therapies

While no specific anti-fibrotic therapy is available for fibrostenosing CD, this approach would be highly desirable given the potential to prevent or treat strictures without the need for endoscopic or surgical intervention. Potential targets include the blockade or administration of cytokines including TGF-β, TNF-α, IL-13, and IFN-ϒ and/or effector pathways to these cytokines as derived from other fibrotic diseases [78–81].

TGF-β plays a central role in fibrogenesis through its TGF-β effector pathways which are often classified as canonical pathways (SMAD pathways) and noncanonical pathways (phosphoinositide 3-kinase (PI3K), PAK22-abl, the mechanistic target of rapamycin (Akt-mTOR), cellular Abelson non-receptor kinase (c-Abl-protein kinase C-δ/c-Abl-PKC-δ), and c-Jun N-terminal kinase (JNK)) [81]. In addition, TGF-β increases inhibitors of MMPs and decreases matric metalloproteinases.

Targets used for anti-TGF-β therapy include using neutralizing antibodies to TGF-β receptors (metelimumab, CAT-152, LY238770), peptide inhibitors to TGF-β1, 3 (P144), ligand traps to TGF-β (sTβRII), or blocking the production of TGF-β (pirfenidone). These therapies have been

used predominantly in systemic sclerosis, prevention of fibrosis after trabeculectomy, diabetic nephropathy, and idiopathic pulmonary fibrosis and are in phase 2 and 3 clinical trials as described in Table 7.2. Other therapeutic interventions include blocking canonical pathways that are expressed downstream of TGF-β receptors (Wnt pathway, ALK5/SMAD pathway, SMAD3) and noncanonical pathways (c-Abl, sarcoma tyrosine kinase inhibitor, rho-associated kinases (ROCK), protein kinase (PKC-δ)) [80, 81]. Of these, c-Abl inhibitors (imatinib) or ROCK inhibitors (fasudil) are in clinical trials for treatment of bone marrow fibrosis in CML and diabetic retinopathy (Table 7.2).

Table 7.2 Anti-fibrotic therapies in phase 2 and phase 3 clinical trials for fibrotic conditions

Potential drug	Mechanism of drug action	Clinical trial	Disease applicability Ref
Drugs targeting TGF-β and its effector pathways			
CAT-192 (metelimumab)	Monoclonal antibody to TGF-β1	Phase 1, 2	Systemic sclerosis [85]
CAT-152	Antibody to TGF-β2	Phase 3	Fibrosis after trabeculectomy [86]
LY238770	Antibody to TGF-β1	Phase 2	Diabetic nephropathy, CKD (NCT01113801: trail terminated due to lack of efficacy)
Avotermin	Recombinant hTGF-β3	Phase 2	Surgical scars (NCT00432211/NCT00656227: trials unfinished)
P144	Peptide inhibitor to TGF-β1, 3	Phase 2	Systemic sclerosis (NCT00574613: results pending)
Pirfenidone	Blocks production of TGF-β	Phase 3	IPF [87]
IFN-gamma	Inhibition of TGF-β through SMAD3 pathway	Phase 3	SSc-IPF [88]
Imatinib	c-Abl (noncanonical pathway)	Phase 2, 3 Phase 3	Bone marrow fibrosis in CML [89] Sclerotic skin GVH reaction
Losartan	Anti-inflammatory (anti TGF-β activity?)	Phase 2, 4	IPF (NCT00879879: results available, publication pending) Liver fibrosis (NCT01051219: results pending) [90] HIV fibrosis (NCT01529749: results pending)
Fasudil	Inhibition of ROCK (noncanonical TGF-β pathway)	Phase 3	CAD [91], vascular modulation in diabetic macular degeneration (NCT01823081: results available, publication pending), Raynaud's (NCT00498615: results available, publication pending)
CC-930	JNK inhibitor (noncanonical TGF-β pathway)		IPF, DLE (NCT01203943, NCT01466725: both studies terminated due to risk profile)
Other cytokine targets			
Tocilizumab	(anti-IL-6)	Phase 2	Systemic sclerosis [92]
Humanized IL-13 antibody (lebrikizumab)	Monoclonal antibody to IL-13 which inhibits activation of fibroblasts	Phase 2	IPF (NCT01629667: terminated due to lack of efficacy) Asthma [84]
Miscellaneous mechanisms			
D-penicillamine	Prevention of collagen cross-linking by copper containing lysyl oxidase enzyme leading to decreased ECM stiffness	Phase 3	Scleroderma [93]

Abbreviations: *Abl* Abelsen, *IL* interleukin, *JNK* c-Jun N-terminal kinase, *JAK* Janus kinase, *PKC* protein kinase C, *ROCK* rho-associated kinases, *TGF* transforming growth factor, *TNF* tumor necrosis factor
NCT numbers are obtained from clinicaltrials.gov

IL-13 promotes TGF-β activity and decreases MMPs [82, 83]. However, monoclonal antibody trials were terminated due to lack of efficacy in lung fibrosis, but show good efficacy in moderate to chronic asthma [84].

TNF-α has pleiotropic effect and is considered both anti- and profibrotic [78]. Other relevant mechanisms of drugs in phase 2 and 3 clinical trials are explained in Table 7.2.

7.11 Future Directions

Significant advances have been made in the management of fibrostenosing IBD, but key questions remain. At the pathogenesis stage, these include the discovery of mechanisms that cause a switch from inflammatory to fibrosing disease and determination of factors that auto-propagate fibrosis despite reduction in mucosal inflammation. Major challenges include the need for more representative experimental animal models for fibrostenosing CD as current approaches may not be ideal [94]. Mouse models of intestinal fibrosis have been reviewed recently [94–96]. At the clinical level, major challenges that have been identified include the lack of diagnostic and prognostic biomarkers that enable the definition of suitable patient populations or depict their response to therapy. Future directions should include a concerted effort to develop standardized imaging scores. These biomarkers and imaging scores may lead to measurable outcomes in clinical trials with new drug therapies. In the therapeutic realm, limiting systemic toxicity from anti-fibrotic treatment in CD will remain an essential milestone, considering the localized and patchy distribution of fibrostenotic CD and its association with internal penetrating disease. Several initiatives are currently ongoing making the testing of specific anti-fibrotics in IBD in the near future a realistic prediction.

Summary Points

- The incidence of fibrostenotic Crohn's disease and need for surgery have not changed significantly despite increased use and availability of anti-inflammatory agents.
- Accurate and reproducible biomarkers to diagnose, predict, and prognosticate fibrostenotic CD are lacking, which is true for clinical practice and clinical trials.
- Management of fibrostenotic CD involves a multidisciplinary approach and includes medical, surgical, and endoscopic management.
- There are multiple candidate pathways to block the fibrogenic process.
- Anti-fibrotic treatments for other organs are currently in preclinical or early clinical trial phases bringing an anti-fibrotic therapy in IBD within reach.

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