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ECCO Topical Review

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European Crohn's and Colitis Organisation Topical Review on Prediction, Diagnosis and Management of Fibrostenosing Crohn's Disease

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Abstract

This ECCO topical review of the European Crohn's and Colitis Organisation [ECCO] focused on prediction, diagnosis, and management of fibrostenosing Crohn's disease [CD]. The objective was to achieve evidence-supported, expert consensus that provides guidance for clinical practice.

Key Words: Stricture; management; consensus

1. Introduction

The Crohn's disease [CD] course is frequently complicated by intestinal strictures, which can be fibrotic, inflammatory, or mixed, leading to stenosis and ultimately symptomatic obstruction.[1,2] Fibrosis is a consequence of local chronic inflammation and is characterised by excessive extracellular matrix [ECM] protein deposition produced by activated myofibroblasts.[3,4] Despite recent advances in the pathophysiological understanding of CD and a significant improvement in anti-inflammatory therapies, mechanisms driving the development of complications of the disease, including the formation of fibrotic strictures, are less well understood. No specific anti-fibrotic therapy exists.[5] Despite the therapeutic advances in the treatment of inflammatory bowel disease [IBD] in the past two decades, the incidence of intestinal strictures in CD has not significantly changed.[6,7,8,9,10] There is paucity of data in this area and currently no standard exists that can guide clinicians dealing with this condition.

This led the European Crohn's and Colitis Organisation [ECCO] to generate a topical review consensus group on stricturing CD. Given the paucity of prospective controlled data in this area, a

topical review is distinct from the ECCO consensus guidelines and is intended to provide guidance in clinical areas which lack evidence. To organise the work, subgroups were classified into three major topics—prediction, diagnosis, and management. The working parties performed a systematic literature search of their topic with the appropriate keywords, using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level [EL] was graded according to the 2011 Oxford Centre for Evidence-Based Medicine [http://www.cebm.net/index.aspx?o=5653]. Provisional statements were then posted on a weblog. Discussions and exchange of the literature evidence among the working party members was then performed on the weblog. Two preliminary voting rounds followed by revision of the statements were performed. The working parties met in Barcelona on February 18, 2015 to agree on the statements. A statement was accepted after agreement by at least 80% of participants, termed a *Current Practice Position*, and numbered for convenience in the document.

This paper reflects a joint effort by gastroenterologists, radiologists, colorectal surgeons, and basic scientists. It provides guidance on the prediction, detection, and management of strictures in patients with CD. The group leaders and their working parties wrote the final section of each subgroup. Statements are intended to be read in context with qualifying comments, and not read in isolation. The final text was edited for consistency of style by the steering committee [FR and AD] before being circulated and approved by the participants. In several areas the level of evidence is generally low, which reflects the paucity of randomised controlled trials. Consequently expert opinion is included where appropriate.

2. Prediction of fibrostenosing Crohn's disease

2.1. Definitions

Current Practice Position on Fibrosis 1:

Fibrostenosing Crohn's disease is defined by persistent luminal narrowing and can include obstructive symptoms [EL 5]

The natural history and behaviour of CD are highly heterogeneous. Even though the most common initial presentation of CD is purely uncomplicated inflammatory disease, within 10 years of diagnosis more than 70% of CD patients develop a stricturing or perforating complication.[11,12,13,14] More than one-third of CD patients develop a distinct fibrostenosing phenotype manifested by progressive narrowing of the bowel lumen and clinical signs of intestinal obstruction.[11,15,16] Stricturing and perforating disease, which may coexist in the same patient, represent the main indication for surgery in CD patients.[17,18] Disease recurrence at the site of anastomosis, however, is common, and recurrent stricture formation may also occur.[19]

Current Practice Position on Fibrosis 2:

Intestinal fibrosis is a common and serious complication of Crohn's disease, which can occur at any time during the disease course [EL3]. Intestinal fibrosis, which affects all layers of the bowel wall, is characterised by extracellular matrix [ECM] protein accumulation and mesenchymal cell expansion [EL3]

CD is a dynamic disorder whose phenotype may evolve with time.[15] Whereas the location of inflammation is a relatively stable clinical feature, changes in disease behaviour can occur throughout the disease course.[11,12,14,16] Approximately 30–50% of the patients already have stricturing or penetrating disease at the time of diagnosis, and of those with uncomplicated disease at the time of diagnosis about half will then develop either stricturing or penetrating complications during follow-up.[14] Intestinal fibrosis and strictures, given the transmural nature of CD, affect all layers of the bowel wall with histomorphological thickening.

Current Practice Position on Fibrosis 3:

Intestinal fibrosis can result in stricturing Crohn's disease. Stricturing and penetrating disease can commonly coexist in the same patient [EL4]

An overlap may exist between stricturing and penetrating disease, since internal fistulae may complicate long-standing intestinal stenosis, and many patients undergoing surgery for intestinal obstruction will be found to have entero-enteric fistulae.[20,21,22] Fistulae are thought to develop in regions of full-thickness bowel wall inflammation in a high-pressure region upstream from a stricture,[17,23] but prospective data supporting this are missing. In one study, the positive predictive value of fistulae in predicting strictures was 86.2%.[24] It is also widely believed that strictures, once present, are gradually progressive over time, but longitudinal data to confirm this are lacking.

The most common locations of clinically apparent strictures are the ileum and the ileocolonic region, presumably due to the smaller diameter of the ileum relative to the colon.[25,26] However, strictures can appear at any site affected by CD, including the upper gastrointestinal tract, the colon, and the rectum. The frequency and location of strictures probably follow the distribution of inflammation: 40–55% terminal ileum and colon, 15–25% colon alone, 25–40% exclusively ileum, and up to 10% in the upper gastrointestinal tract; but data supporting this hypothesis are lacking.[27,28] There is no relationship between symptoms and progression of the intestinal lesions, since strictures and fistulae may develop for several years with only mild symptoms or, in some cases, without any symptoms at all.[16]

Current Practice Position on Fibrosis 4:

No accurate and specific predictor for intestinal fibrosis exists [EL5]. Clinical features and biomarkers are not strictly specific for fibrostenosis, but rather predict a complicated or disabling Crohn's disease course [EL3]

2.2. Clinical predictors

It is currently unknown which CD patients will develop a fibrostenotic disease phenotype and in what time frame these changes may occur. This knowledge is crucial for understanding the pathophysiology of the disease.[5,12,29,30] The ability to stratify CD patients into at-risk populations can allow for determination of the follow-up schedule and the intensity of observation required in patients with a higher versus lower likelihood of fibrostenotic changes.

No specific and accurate clinical predictors or clinical diagnostic tools for intestinal fibrosis exist, and to date no genetic or serological marker of fibrosis is in routine clinical use. Clinical features and biomarkers have not been shown to be strictly specific for fibrostenosis, but rather represent a complicated or disabling CD course.[16,18,30]

Several clinical factors, including CD diagnosis made under the age of 40 years, need for steroid therapy at diagnosis, perianal fistulising disease, weight loss > 5 kg, early use of azathioprine or anti-tumour necrosis factor [TNF] therapy, smoking, terminal ileal disease, and deep mucosal ulceration, have been identified as

predictive of a more aggressive and complicated disease, rather than an underlying predisposition for intestinal fibrosis, strictures, and obstruction.[2,18,30,31,32,33,34,35,36,37,38] CD classifications, such as the Vienna and Montreal Classifications, merely identify fibrosis after it has become clinically significant, so that these clinical categories are frequently not predictors of disease phenotype but simply descriptions of disease behaviour well after the complication has occurred.[26,39]

2.3. Imaging predictors

Current Practice Position on Fibrosis 5:

Cross-sectional imaging, endoscopy, or histology cannot predict the development of fibrostenosing Crohn's disease [EL5]

Currently, no imaging modality specifically predicts the CD phenotype.[18,30] Barium small bowel follow-through can only determine the extent and severity of luminal narrowing. Cross-sectional imaging techniques, such as computed tomography enterography [CTE] and magnetic resonance enterography [MRE], are insufficient as they only depict one specific point in time. They are diagnostic of a stricture [see below], but not predictive. Endoscopy [colonoscopy, double-balloon endoscopy] can detect mucosal lesions and luminal narrowing—ie a stricture after it is already established[32]—and to date no histological feature predicting specifically fibrostenosing CD has been described. To assess the disease progression in CD, a longitudinal tool, the Lémann score, has been proposed to measure the progressive and cumulative structural bowel damage, including fibrosis.[40,41] This score could be an effective tool to assess fibrostenosing CD as it combines different techniques [MRE, endoscopy], depending on the location of the disease.

2.4. Genetic and epigenetic predictors

Current Practice Position on Fibrosis 6:

The presence of several genetic variants [alone or in combination] is primarily associated with small bowel Crohn's disease and a fibrostenotic phenotype [EL1 4]

The hypothesis of a genetic background responsible for the stricturing behaviour in CD is supported by the re-occurrence of intestinal strictures in some CD patients undergoing intestinal resection compared with CD patients who never develop a stricture in a lifespan.[18,29,30] Fibrosis is a dynamic and multifactorial process and develops by interactions between genetic and environmental factors, with different genetic polymorphisms influencing fibrosis in animal models and human case–control studies. Studies suggest that variants of genes encoding immunoregulatory proteins, pro- and anti-inflammatory cytokines, and fibrogenic factors may impact on CD intestinal fibrosis.[30,42,43,44]

Variants in the nucleotide-binding oligomerisation domain containing 2 [NOD2] gene in CD with/without variants of Toll-like receptors [eg TLR4] or autophagy-related-16L1 [ATG16L1] have an increased risk of small bowel fibrostenosis.[45,46,47,48] Fibrostenotic CD appears also to be linked to other genetic variants such as those in the interleukin 23 receptor [IL23R] gene, chemokine fractalkine receptor CX3CR1 gene, matrix metalloproteinase [MMP]-3 gene, or rs1363670 locus near the interleukin [IL]12B gene.[48,49,50,51,52] Gene variants are promising markers, but their population frequency is low and they exhibit incomplete penetrance. Carrying at least one NOD2/CARD15 variant increased the risk of stenosing CD (odds ratio [OR]: 1.94; 95% confidence interval [CI]: 1.61–2.34) and, more prominently, the risk of small bowel involvement [OR: 2.53; 95% CI: 2.01–3.16].[45,47] Furthermore, CD patients carrying NOD2 gene variants have an increased need for surgery due to stricturing disease, and a higher rate of postoperative recurrence.[46] Toll-like receptor variants, especially TLR4, are associated with small bowel fibrostenotic disease.[30] Two polymorphisms of the chemokine fractalkine receptor CX3CR1 are associated with fibrostenotic CD, independently of NOD2.[50,52] Variants in the IL23R gene are associated with CD fibrosis, merely ileal disease.[49] Matrix metalloproteinases [MMPs] are endopeptidases involved in extracellular matrix [ECM] degradation, and tissue inhibitors of metalloproteinases [TIMPs] preserve ECM. Single nucleotide polymorphisms [SNPs] in MMP-3 increase the risk of stenotic complications in CD.[51] Currently the routine use of genetic testing for the prediction of fibrostenosing CD is not recommended.

Epigenetics may be defined as mitotically heritable changes in gene function, not explained by changes in DNA sequence.[53] The main epigenetic mechanisms include DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes. Micro RNAs [miRNA] are small, noncoding RNAs of 18–25 nucleotides that regulate gene and protein expression by repressing specific target genes post-transcriptionally; miRNA-200a and miRNA-200b are over-expressed in the serum of fibrostenosing CD subjects.[54] It has been demonstrated that levels of miR-29b are reduced in the mucosa overlying strictured gut in CD patients, and that collagen up-regulation induced in vitro by transforming growth factor β [TGF-β] in CD myofibroblasts can be prevented by miR-29b transfection. Moreover, serum levels of miR-29 were found to be lower in patients with stricturing CD compared with those without strictures, thus highlighting the potential usefulness of miR-29 as a future biomarker of fibrostenosing disease.[55] Recently, it has been shown that serum levels of miR-19a/b are reduced in CD patients with a fibrostenosing phenotype.[56]

Of note, in a multivariate analysis the association between miR-29b and a stricturing phenotype was found to be independent of confounding clinical variables such as disease duration and the presence of ileal disease.[55] Currently the routine use of epigenetic testing for the prediction of fibrostenosing CD is not recommended.

2.5. Serological predictors

Current Practice Position on Fibrosis 7:

Crohn's disease patients with a stronger humoral immune response towards microbial components are more likely to develop earlier complicated Crohn's disease, including fibrostenosing disease [EL1-3]

A number of circulating antibodies directed against microbial peptides have been detected in CD patients, such as anti-*Escherichia coli* outer membrane protein C antibodies [anti-OmpC], anti-*Pseudomonas* associated sequence I2 antibodies [anti-I2], anti-bacterial flaggelin CBir1 antibodies [anti-CBir1], and anti-glycan antibodies which include anti-*Saccharomyces cerevisiae* antibodies [ASCA], anti-chitobioside carbohydrate IgA antibodies [ACCA], anti-mannobioside carbohydrate IgG antibodies [AMCA], anti-laminarin carbohydrate antibodies [anti-L], and anti-chitin carbohydrate antibodies [anti-C].[57,58,59,60] These antibodies are supposed to originate from an abnormal immune response

against the luminal microbiota.[61] It has been demonstrated that in both adult and paediatric CD patients, serum antimicrobial antibodies are qualitatively and quantitatively associated with disease progression to fibrostenosing/fistulising complications and increased need for surgery.[30,62,63,64,65,66,67,68] A recent meta-analysis, based on 11 studies, focused on four antibodies [ASCA, anti-OmpC, anti-I2, and antiCBir1]. ASCA showed the highest sensitivity, whereas anti-OmpC showed the highest specificity for complications and surgery. Moreover, the analysis of at least two antimicrobial antibodies was more effective than any single antibody in predicting disease progression towards complications.[69] However, none of the above-mentioned antibodies has been shown to be able to discriminate fibrostenotic from penetrating behaviour [or specifically predict fibrostenosing CD], nor thus to predict stricture development in CD patients.[70,71]

A prospective paediatric study showed that the risk of developing a stricturing/penetrating phenotype was 11-fold increased in CD patients with serological positivity for anti-CBir1, anti-OmpC, anti-I2, and ASCA in comparison with seronegative children.[63] These findings were confirmed in a subsequent larger study conducted through the detection of serum anti-CBir1, anti-OmpC, and ASCA.[66] In a small cohort study using adult patients, the presence of anti-glycan antibodies was predictive of a more complicated CD course without predicting fibrostenosis specifically.[59] Further prospective studies are required to clarify whether circulating antibodies, alone or in conjunction with other biomarkers, can be used to predict the disease course and the development of strictures in CD.

A number of ECM molecules and growth factors have been investigated in the serum of CD patients as possible biomarkers of intestinal fibrosis in CD patients, including fibronectin, collagen subtypes or propeptides, laminin, MMPs or TIMPs, basic fibroblast growth factor [bFGF], and human chitinase 3-like 1 [also known as YKL-40].[71,72] None of these markers to date has been shown to be predictive of fibrostenosing CD. Serum YKL-40 levels, a growth factor secreted by activated macrophages and neutrophils, which stimulates myofibroblasts to produce collagen,[73] is higher in CD patients with a fibrostenosing phenotype, although these results derive from studies conducted on a relatively small numbers of patients.[72,74,75] Further prospective studies are required to clarify whether ECM molecules and growth factors can be used to predict the disease course and the development of strictures in CD.[76,77]

3. Diagnosis of fibrostenosing Crohn's disease

Current Practice Position on Fibrosis 8:

Cross-sectional imaging has high sensitivity and specificity for the diagnosis of stenosis affecting the small bowel or the colon [EL 2]. Optimal distension by luminal oral contrast and anti-peristaltic agents is recommended to avoid misdiagnosis of strictures on CTE or MRE [EL 3]

Current Practice Position on Fibrosis 9:

Both inflammation and fibrosis are often present to varying degrees in symptomatic strictures, and cross-sectional imaging using ultrasonography, CT or MR may assist in identifying inflammation in stenotic segments [EL 3]. However, currently no cross-sectional imaging modality is able to determine the clinical significance of the fibrotic component of the stricture [EL 3]

Ultrasonography [US], CTE, and MRE have high sensitivity and specificity for the diagnosis of stenosis affecting the large or small bowel, and the respective accuracies are similar between US, CTE, and MRE.[78] Whereas the diagnostic accuracy of MRE and CTE requires the use of luminal contrast and anti-peristaltic agents to avoid misdiagnosis, their use is not necessary in US for detecting stenosis, although their detection increases when oral contrast is administered.[79]

Inflammation and fibrosis in CD are transmural, and thus cannot be accurately assessed by endoscopy. In contrast, cross-sectional imaging can detect transmural abnormalities. Classically, CD-associated strictures have been divided into inflammatory and fibrotic in the hope of being able to stratify patients for anti-inflammatory therapies. This differentiation seems unrealistic as, in different published series correlating imaging findings with histopathology, most strictures have a mixed pattern, with both inflammatory and fibrotic components. It is noteworthy that only few strictures were classified as 'purely inflammatory' or 'purely fibrotic' at histopathology. Most of them had an important overlap of different degrees of fibrosis and inflammation,[18,80,81,82,83,84,85,86,87] and this overlap represents an important challenge for detecting and quantifying fibrosis deposition in the bowel wall. An additional difficulty is the fact that absence of radiological findings of inflammation in a stricture does not predict the presence of tissue fibrosis.[80]

Only few studies have focused on the identification of independent predictors of fibrosis of the bowel wall by cross-sectional imaging. The US stratified echo pattern [different echogenicities in different bowel wall layers] at the site of strictures has been associated with collagen deposition, but these data have not been further validated.[88] Chiorean *et al.* found that the presence of fibrosis was associated with stenotic lesions detected by CTE, but did not provide any information regarding the degree of inflammation and fibrosis in stenotic lesions.[81] MR has superior soft tissue contrast for bowel wall tissue characterisation. Two studies using MRE with T1 and T2 conventional sequences produced conflicting results for fibrosis characterisation using T2 signal, wall thickness, and pattern of gadolinium enhancement.[82,87] A more recent publication revealed that the percentage of gain using gadolinium enhancement between 70 s and 7 min on MRE parallels the degree of fibrosis regardless of the degree of inflammation, thus being a reliable method for detecting the presence of severe fibrosis for both stenotic and non-stenotic segments. This last study proposed a novel classification of stenosis combining different degrees of fibrosis and inflammation, based on gain of enhancement and presence of ulcers, respectively.[84] In spite of the efforts to detect and quantify fibrosis in the bowel wall and its association to bowel irreversible damage,[89] the clinical significance of fibrosis and, in particular, its prediction for need of surgery have not been established.

Novel imaging modalities are not routinely used in clinical practice and may be subject to limitations in standardisation of techniques or in post-processing. MR with dynamic contrast enhanced [DCE] technique identified in humans a correlation between fibrosis, and maximum enhancement and initial slope of increase.[86] Magnetisation transfer MR [MT-MR] potentially is more sensitive than conventional MR to changes in collagen content. MT-MR imaging has good correlation with the degree of collagen deposition on the colonic wall in a rat model regardless the degree of inflammation.[90,91] Lastly, US elastography [USE] offered promising results for differentiating different degrees of fibrosis deposition using animal models.[92,93] USE detected in ex vivo human bowel specimens an increase in shear wave speed measurements when transmural

intestinal fibrosis was present. However, the same results suggested that USE might be less capable in differentiating non-transmural mild-to-moderate fibrosis from early, predominantly inflammatory disease.[94]

Current Practice Position on Fibrosis 10:

The presence and degree of fibrosis cannot be evaluated by biomarkers, endoscopy, or histology [EL5]

A biomarker defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'[95] would be desirable to specifically assess the presence and degree of intestinal fibrosis. Given their stability, genetic makers appear to be promising candidates in fibrostenotic CD.[71] NOD2 gene variants were evaluated as prognostic markers for stricturing CD [see above].[45] Specificity, however, is low, given that alleles were reported to be associated with an ileal disease manifestation and fistulising complications.[45] Serum antibodies directed against microbial peptides are associated with a more complicated CD course, but not specifically with a fibrostenotic phenotype. Available studies were not performed to differentiate between stricturing and penetrating disease complications or did not reach high specificity rates.[70,71,96,97]

Current Practice Position on Fibrosis 11:

No validated histopathological scoring system is available to grade the severity of intestinal fibrosis [EL5]

Intestinal strictures characteristically display thickening of all layers of the intestinal wall. Histological specimens demonstrate islands of smooth muscle cells in the submucosa with dense collagen deposition as well as disruption and expansion of the muscularis mucosa.[4,98,99,100] Collagen septa extend through a disorganised and thickened muscularis propria. Collagen is the major ECM component and a number of subtypes, each with different functions, have been identified. Strictured intestine is characterised by an increase in total collagen, and also in the relative amount of types III and V. Type III collagen has a greater propensity for contraction. During normal wound healing, when collagen deposition is rapid, the ratio of type III collagen to type I collagen is increased. This may be defined as the early stage of fibrosis, characterised by an increase in the accumulation of collagen type III in relation to collagen type I. In contrast, during the late stage of fibrosis when active collagen deposition diminishes, the ratio of type III collagen to type I collagen decreases.[101] Moreover, in CD a significant increase in submucosal type III collagen fibre content has been reported in stenosed intestine, with a particular increase in the outer aspect of the submucosa.[102] This suggests that type III collagen, present in the thickened small bowel, may contribute to the functional significance of stenosis by reducing the compliance of the submucosa. Fibronectin, a structural glycoprotein, is also over-expressed at sites of CD strictures. Tenascin, a component of the ECM synthesised by fibroblasts, smooth muscle cells, and myofibroblasts, is highly increased in inactive CD.[103] In the normal colonic mucosa, immunoreactivity for tenascin is confined to the basement membrane of the intercryptal surface epithelium and the muscularis mucosa. It is not normally present around the crypts.[99]

Accumulation of myofibroblasts and alterations of the nerves induce fibromuscular obliteration of the submucosa, associated with thickening of the muscularis propria, which results in motility disorders.[104,105] Muscularisation of the submucosa is a common feature of long-term 'burnt-out' CD.[106] Obliterative muscularisation of the submucosa [OMUS] has been observed in about one-third of small intestinal resection specimens of CD, usually in stricturing disease.[104] OMUS is especially associated with small bowel strictures, which are themselves closely associated with submucosal fibrosis.[106] Hypertrophy of intestinal muscle secondary to intestinal obstruction is associated with increase in collagen content, particularly in the muscular layer.

Excessive ECM deposition and its abnormal contraction lead to scar formation, tissue distortion, and ultimately intestinal obstruction. Furthermore, histological studies indicate that the amount of fibroblast islands within CD-associated strictures correlates with the expression of profibrotic cytokines and extracellular matrix proteins.[107,108,109] To date, no validated histopathological scoring system is available to grade the severity of intestinal fibrosis.[18] Clinical scoring systems correlate to some degree with intestinal inflammation, but not with fibrosis. In fact, the occurrence of strictures can confound the CD activity index. This lack of any standardised scoring system for histological or clinical fibrosis makes comparisons between existing studies impossible.

4. Management of fibrostenosing Crohn's disease

4.1. Medical management of fibrostenosing Crohn's disease

Current Practice Position on Fibrosis 12:

Patients with confirmed intestinal obstruction should be hospitalised and treated by a multidisciplinary team [EL5]

Current Practice Position on Fibrosis 13:

Management of stricturing Crohn's disease depends on location/length, the degree of concomitant inflammation, and accompanying features, such as abscess, phlegmon, or dysplasia [EL3]

CD patients with suspicion for intestinal obstruction should be managed by a multidisciplinary team consisting of a gastroenterologist, colorectal surgeon, radiologist, and if needed a pathologist. These patients should be hospitalised and treated with gastrointestinal nasogastric decompression, bowel rest, intravenous fluids [0.9% saline or lactated Ringer's solution for intravascular volume repletion], and electrolyte replacement guided by test results. Patients with signs of peritonitis should be seen by a surgeon immediately. The patients should undergo evaluation with cross-sectional imaging to assess a possible stricture for location, length, the degree of concomitant inflammation, and accompanying features, such as abscess, phlegmon, or signs of malignancy since this affects the management approach [see below].

Current Practice Position on Fibrosis 14:

Patients should undergo evaluation to assess the presence of inflammation in the stricture. Anti-inflammatory therapy should only be considered if the stenosis has an inflammatory component [EL4]

In addition to the above mentioned conservative management, traditionally intestinal strictures in CD have been treated by oral and intravenous corticosteroids and, in the case of intractable symptoms, bowel resection. With the emergence of immunosuppressants, such as azathioprine [AZA]/6-mercaptopurine [6-MP] and biologicals [eg anti-TNF], additional medical therapy options are available.[110]

At the current time, a variety of modalities are used to try to discriminate medically responsive strictures with an inflammatory component from those without, such as the above mentioned imaging [CTE, MRE] and laboratory [CRP, ESR] and stool [faecal calprotectin] biomarkers. Despite widespread use of corticosteroids, the data supporting their utility are limited. Yaffe and colleagues reported their experience with non-operative management of acute small bowel obstruction in 26 CD patients. In all but one patient, the obstruction was relieved within 72 h using a regimen that included clear liquid diet, small bowel tube, total parenteral nutrition, prednisone, intravenous fluids, and intravenous crystalline adrenocorticotropic hormone [ACTH]. Of the 26 patients, 75% experienced at least a second episode during a mean follow-up of 52 months, all of which again responded to medical management; 46% of patients eventually underwent elective surgery. If the patients remained free of obstruction after the initial episode for at least 8 months, the risk of surgery thereafter was only 17%, indicating that medical therapy can ultimately prevent surgery in a clinically meaningful proportion of patients.[111]

There was initially some concern regarding the use of the anti-TNF treatment infliximab [IFX] in patients with established strictures, based on two retrospective reports.[112,113] Subsequently this was challenged by a study of 15 CD patients with obstructive symptoms, treated with IFX. Small intestinal contrast ultrasound did not show any progression of strictures and, in 80% of the patients responding to IFX, the stenosis completely regressed.[114] Most importantly, data in large numbers of patients from the TREAT registry and the ACCENT I infliximab maintenance trial did not show an increased risk for the clinical occurrence of strictures.[115] A recent review on this topic reached the same conclusion.[116] Most recently, the GETAID reported the use of adalimumab [ADA] in symptomatic small bowel strictures in CD in a multicentre, prospective observational cohort study. At Week 24, 61% of the patients were free of steroids, did not require dilation or surgery, and did not report any adverse events. More than half of the responders were free of dilation or surgery even at year 2.[117] Hence, anti-TNF appears to be a valuable treatment option in steroid-dependent patients who present with intestinal obstruction. This is supported by an observational cohort of 11 CD patients, of whom 9 clinically responded to anti-TNF.[118] Data on efficacy of azathioprine or 6-mercaptopurine in stricturing CD are lacking.

Current Practice Position on Fibrosis 15:

No drug with proven specific intestinal anti-fibrotic effect is available [EL5]

Current treatment options [steroids, immunosuppressive drugs, biological therapies] may relieve inflammatory lesions and related symptoms, but none of them has a direct anti-fibrotic effect and they can neither prevent nor reverse established intestinal fibrosis and strictures, which may present years after remission of active inflammation.[6,7,8,9,119,120,121,122,123] Currently, no specific medical therapy exists to treat fibrotic intestinal strictures.[124]

Current Practice Position on Fibrosis 16:

Endoscopic balloon dilation, strictureplasty, and intestinal resection are reasonable treatment options for short strictures [EL4]

4.2. Endoscopic management of fibrostenosing Crohn's disease

If medical therapy fails to improve obstructive symptoms, endoscopic balloon dilation [EBD], strictureplasty, and resection are all equal alternatives in different clinical situations. The clinical situations are discussed below.

Current Practice Position on Fibrosis 17:

Appropriate, shorter strictures can be treated with endoscopic balloon dilation [EL 2]. Endoscopic balloon dilation has a high technical success rate and a favourable short- and long-term clinical efficacy with an acceptable complication rate [EL3].
Inflammation or ulceration at the site of the stenosis is not a contraindication to endoscopic balloon dilation [EL 3]

EBD has become an accepted modality for treatment of selected CD strictures. Main applications are short and isolated strictures within reach of a standard colonoscope, with many amenable strictures localised to the site of the ileocaecal anastomosis after ileocaecal resection.[125] EBD is also feasible in the upper gastrointestinal tract within reach of an upper endosocope[126] or in the mid small bowel via balloon-assisted enteroscopy.[25]

Most commonly, through the scope balloons [TTS] are used to reach and pneumatically dilate strictures. In general the available reports are highly heterogeneous with respect to techniques used, follow-up times, and endpoints applied. In a systematic review and descriptive pooled data analysis of 33 retrospective studies, including 1463 CD patients, the median stricture length was 2 cm. This analysis mainly included post-surgical strictures and all were dilated with TTS. Endoscopic dilation [EBD] was technically successful in 90% of cases. Long-term clinical efficacy [median follow-up was 40.1 months], defined as being free of surgery, was achieved in 69.2% of the patients. A stricture length of ≤ 5 cm was associated with a surgery-free outcome in a multivariate analysis [hazard ratio [HR]: 2.5; 95% confidence interval [CI]: 1.4–4.4].

Factors influencing outcome after endoscopic balloon dilation in fibrostenotic CD are largely unknown. Technically successful dilation,[128,129] stricture length ≤ 5 cm,[127] and absence of ulcers in the stricture[130] were positively associated with successful dilation. In contrast, neither CRP, endoscopic disease activity, or medical treatment after dilation influenced the subsequent disease course in a different study.[131] This was confirmed in a descriptive pooled data analysis with 1463 patients, in whom the presence of inflammation did not influence the short- or long-term outcome and also did not have an effect on the complication rate.[127] The majority of the observations were made with anastomotic strictures. No difference was noted when comparing the long-term dilation efficacy or probability of surgery-free survival of naive versus post-surgical strictures.[127]

Current Practice Position on Fibrosis 18:

The presence of an abscess, phlegmon, fistula, high-grade dysplasia, or malignancy associated with the stenosis is a contraindication to endoscopic dilation and strictureplasty [EL 3]

When mechanically dilating the intestine, perforation is a valid concern. In the above mentioned systematic review, a major complication rate [defined as bleeding, perforation, or hospitalisation] of 2.7% was observed.[127] None of the tested factors, including stricture location, type, length, disease activity, balloon calibre, length, and pressure, were associated with complications. In a randomised controlled trial [RCT] with 29 paediatric patients with ED and intralesional steroid injection, no complications were reported.[132] To our knowledge, no death directly related to the procedure has ever been reported.

Small bowel adenocarcinoma is rare, but if overlooked can be fatal.[133] The endoscopist should therefore have a low threshold for taking a biopsy before EBD. There is no convincing evidence that such mucosal biopsies increase the risk of perforation with subsequent balloon dilation.[134]

Current Practice Position on Fibrosis 19:

The concomitant injection of corticosteroids, anti-TNF agents or the use of stents or cutting techniques can currently not be recommended [EL3]

Intra-lesional injection of steroids has been successfully used in other stricturing gastrointestinal conditions, such as peptic, corrosive, or anastomotic strictures or fibrosis post radiotherapy.[135,136,137,138] Triamcinolone is considered an appropriate agent given its prolonged local effect, believed to last for 3–4 weeks.[139]

In CD-associated strictures, most available evidence is retrospective and uncontrolled. In a systematic review, the use of steroid injection did not make a difference to outcome.[127] In a single-centre prospective RCT with 29 paediatric CD subjects, intra-lesional triamcinolone injections after EBD led to a longer time to re-dilation and to surgery in the steroid group compared with placebo. However, sample size was small and follow-up time short.[132] Conversely, a prospective study in 13 adult CD patients was terminated early after reporting that triamcinolone injection led to an earlier need for re-dilation compared with placebo.[140] However, in this series only anastomotic strictures were examined, the strictures were possibly long-standing [8–30 years after surgery], and the multicentre design could have influenced different endoscopic procedures among different centres. Small, non-controlled, case reports and series assessed the use of intralesional TNF-inhibitor therapy with encouraging results.[141,142]

Endoscopic metallic stent insertion has been tried in few patients. The initial success rate was reported to be 100%, but major complications, such as migration, perforation, or fistulisation were frequent [67% of patients].[143] In a prospective cohort study with 11 patients, the authors concluded that the complication rate is too high to make this a routine treatment option, even when extractable stents are used.[144,145] Biodegradable stents might be an emerging alternative.[146,147] Finally, carving the stricture with a sphincterotome supplementing EBD has been reported in one study with no increase in complications,[148] and this technique has been successfully combined with steroid injections.[149] A preliminary report indicates that patients receiving budesonide after dilation as opposed to dilation alone have a better outcome.[150]

Current Practice Position on Fibrosis 20:

Serial dilation of recurrent strictures is efficacious and feasible, and the choice between surgery versus repeated dilation should be made based on technical feasibility, the symptom-free interval, and patient preferences [EL3]

If clinical symptoms recur after an initial endoscopic dilation of a CD-associated stricture, re-dilation is an option. In subsequent dilations of the same stricture, clinical efficacy as well as long-term outcome appear to remain unchanged.[131] There is no indication that the rate of complication changes depending on the number of times a stricture is dilated.

4.3. Surgical management of fibrostenosing CD

Current Practice Position on Fibrosis 21:

Early surgery should be the preferred option for longer Crohn's disease strictures in symptomatic patients [EL3]

Agreement exists that localised ileocaecal, fibrostenosing CD is best treated with early surgical resection in symptomatic patients unsuitable for endoscopic dilation [technically not feasible or > 5 cm].[18,127,151,152,153,154] Early resection could prevent subsequent complications [eg fistulisation and obstruction] in high-risk patients with isolated ileocaecal CD, more effectively than prolonged medical treatment. Surgical recurrence after ileocolic resection is to be expected in 10% after 5 years and 15–20% after 10 years.[155,158] Baudry *et al.*[159] retrospectively reviewed the charts of 132 patients having ileocolic resection. Those who received scheduled ileocolonoscopy with tailored treatment had significantly lower clinical recurrence rates at 5-year follow-up.

Surgical timing for localised ileocaecal fibrostenotic CD is relevant. Aratari *et al.*[160] compared 83 patients who had surgery at time of the diagnosis with 124 patients who were treated medically first, and showed that the early surgery group had a longer clinical remission with less need of drugs, irrespective of disease pattern, at repeated surgery [penetrating versus non-penetrating, $p = 0.37$]. Latella *et al.* also reported that surgery performed at diagnosis, in 115 patients with CD, was associated with a lower risk of repeat surgery and a longer time to surgery after diagnosis, compared with 375 patients managed medically.[161] These findings were confirmed in the population-based study by Golovics *et al.*[162] and by Kulungowski *et al.*[163] in a paediatric population. Some studies suggest that ileocolonic strictureplasty in selected patients with CD of the terminal ileum is a viable alternative, possibly at the expense of a higher recurrence rate.[164]

Current Practice Position on Fibrosis 22:

Short small bowel strictures are best treated with the Heineke Mikulicz technique, and longer strictures with Finney-like procedures or isoperistaltic strictureplasty [EL4]

In attempting to preserve bowel length and to reduce the risk of leak, patients with fibrostenosing jejuno-ileal involvement can be managed by means of strictureplasty. Campbell *et al.*[165] classified these into 'conventional' [Heineke–Mikulicz and Finney] and 'non-conventional' strictureplasties.[166,167,168,169] Agreement exists that short [< 10 cm] strictures are best treated with the Heineke-Mikulicz technique, and that Finney-like procedures are suitable for strictures ranging between 10 and 25 cm.[18,170] A meta-analysis including 32 studies and 1616 patients with more than 5000 strictureplasties showed no differences in terms of complications and recurrences between conventional and non-conventional techniques.[165] The estimated risk of surgical recurrence of strictureplasty is 35% at 4–8 years after surgery.[165,171] Indications for non-conventional strictureplasties are multiple, close strictures, and patients with risks of

short bowel due to previous bowel resections.[151,152,153,168,172,173] It has been demonstrated in a 3D geometric model that an isoperistaltic type of strictureplasty induces less luminal narrowing than two Heinecke-Mickulicz strictureplasties in a row.[174] Contraindications are poor nutritional status and suspicion of or confirmed adenocarcinoma.[165,173,175,176] Some advocate the routine use of tissue biopsies.[175] In patients with a long involved segment of terminal ileum, a modified isoperistaltic strictureplasty over the ileocaecal valve could be a valid alternative to resection.

Current Practice Position on Fibrosis 23:

Any strictures of the colon should be carefully surveyed because of risk of overlooked carcinoma [EL4]

A recently published population-based study suggested that colonic strictures at diagnosis or during follow-up are associated with 3.6% and 4.9% probability of colorectal cancer at 5 and 10 years, respectively.[177] According to the ECCO evidence-based consensus for endoscopy in IBD, patients with strictures detected within 5 years should be considered at 'high risk', and receive surveillance colonoscopy yearly.[178] In the CD-affected colon, malignancy is more frequent and the incidence is comparable to ulcerative colitis.[179,180] In a GETAID study, dysplasia or cancer was detected in 3.5% of patients with IBD who underwent surgery for colonic strictures.[181] Strictureplasty is therefore not recommended in colonic strictures, by the ECCO guidelines for the management of CD.[151]

Current Practice Position on Fibrosis 24:

The laparoscopic approach in fibrostenotic disease is preferable because of superior recovery, better cosmesis, less adhesions and incisional hernias, and similar surgical recurrence rates [EL1]

Patients with localised, fibrostenosing ileocaecal CD are the ideal candidates for laparoscopic resection.[182,183,184,185] Systematic reviews indicate that laparoscopic surgery is associated with less pain, lower morbidity, and faster recovery to work and everyday life.[182,184,185,186,187,188] Patel *et al.*[189] showed in their meta-analysis that long-term results with regard to surgical recurrence were similar between open and laparoscopic surgery. Incisional hernia was reduced in the laparoscopically treated patients.[189] The rates of conversion vary between 6% and 10% [186]. Alves *et al.*[190] suggested that the risk is increased in patients with recurrent disease [OR 2] and intra-abdominal abscess or fistula [OR 15]. Single-port laparoscopic surgery is a valid alternative for multiport laparoscopic resection. Gardenbroek *et al.*[191] prospectively evaluated 63 CD patients with ileocaecal CD, of whom 21 and 42 received single-port and multiport laparoscopic resection, respectively. The authors showed that single-port ileocaecal resection resulted in reduced postoperative pain compared with conventional laparoscopy. Advantages in terms of cosmetic results were reported in two other retrospective series.[192,193]

Current Practice Position on Fibrosis 25:

Smoking is a risk factor for postoperative recurrence after resection or strictureplasty for fibrostenosing Crohn's disease [EL4]

Smoking is the strongest and a widely accepted risk factor for postoperative recurrence after resection or strictureplasty for fibrostenosing CD.[122,194] Smoking must therefore be strongly discouraged.

After surgical resection, optimisation of the medical treatment guided by a timely endoscopy is important to prevent recurrence of disease complications. Consideration should be given to following the ECCO consensus guidelines for follow-up after surgery and the medical management of CD in this situation.[122]

Conflict of Interest

No study sponsors had any involvement in study design, data collection, interpretation or writing of the manuscript.

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of JCC, but also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of authors.

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Disclaimer Text

The ECCO Topical Review Projects are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Topical Reviews. The European Crohn´s and Colitis Organisation and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO Topical Reviews.

Author Contributions

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