Current and Emerging Approaches to the Diagnosis and Treatment of Crohn’s Disease Strictures

Briton Lee, MD,1 Bari Dane, MD,2 and Seymour Katz, MD3

1Department of Medicine, NYU Langone Medical Center, New York, New York
2Department of Radiology, NYU Langone Medical Center, New York, New York
3Department of Gastroenterology, NYU Langone Medical Center, New York, New York

Abstract: The management and understanding of Crohn’s disease (CD) continues to evolve quickly. Intestinal strictures were previously thought to be an inevitable result of irreversible fibrosis caused by chronic inflammation. However, increased understanding of the dynamic nature of strictures and of the pathophysiology of this condition has highlighted emerging targets for potential treatment. In the diagnosis of strictures, a distinction must be made between inflammatory and fibrotic types, as the former may respond to medical therapy. Emerging technologies, such as dual-energy computed tomography enterography and iodine density, have allowed more accurate characterization of strictures. Surgical and endoscopic treatment remains the mainstay for fibrotic strictures, but developments in systemic and intralesional biologic therapy have shown efficacy. This article reviews the pathophysiology of this debilitating complication of CD as well as current and emerging diagnostics and treatments.

The pathogenesis of Crohn’s disease (CD) requires an understanding of the diagnosis and treatment of intestinal fibrosis, which has been insufficiently characterized. Approximately 75% of CD patients develop complications, with 50% as fibrostenotic strictures,1 one of the main indications for CD-associated surgery.2 Despite advances in biologics and small molecule therapeutics for CD, a lack of specific antifibrotic treatments remains.3,4 Additionally, differentiating between inflammatory and fibrotic strictures continues to be a significant challenge. This article outlines the pathophysiology of CD strictures, along with current and emerging diagnostics and therapeutics.

Pathophysiology

Strictures are thought to be caused by chronic inflammation that is characteristic of CD, which leads to the upregulation and excessive deposition of an extracellular matrix (ECM) owing to the complex interplay between cellular and inflammatory regulators.5,6 Mesenchymal cells (including
fibroblasts, myofibroblasts, and smooth muscle cells) play a major role in the induction of ECM production by regulating profibrotic factors. Although mesenchymal cell proliferation had been thought to arise from specific local precursors, there is evidence that these fibrogenic cells emerge from multiple sources, such as recruitment of bone marrow–derived fibroblasts, cellular transdifferentiation (epithelial-to-mesenchymal transition and endothelial-to-mesenchymal transition), and stellate cell differentiation. Important mediators of intestinal fibrosis include inflammatory cytokines such as interleukin (IL)−1β and IL−17, and transforming growth factor β (TGF-β). In particular, TGF-β plays a well-characterized role in the regulation of inflammation, and its associated pathway is a key fibrogenic factor and regulator of cell transdifferentiation to profibrotic mesenchymal cells. IL−36 is also thought to play an important role in fibrosis, owing to fibrotic mucosal and submucosal tissue from CD patients found to have elevated levels of this cytokine.

Fibrosis is a dynamic process between profibrotic and antifibrotic factors that is caused by an imbalance of ECM deposition and degradation, and provides potential treatment targets for established fibrotic strictures. This balance is maintained by matrix metalloproteinases, which break down ECM, and tissue inhibitors of matrix metalloproteinases. Recent evidence shows that myofibroblasts differentiate into smooth muscle cells, resulting in smooth muscle hyperplasia and hypertrophy, which play a significant role in creating strictures. A histologic analysis of fibrostenotic lesions found that smooth muscular hyperplasia and hypertrophy positively correlated with chronic inflammation and negatively correlated with fibrosis, suggesting that strictures may also arise via a pathway of nonfibrotic smooth muscle–mediated narrowing.

**Epidemiology**

The prevalence of CD is approximately 0.3% in Western countries, with up to 28% of patients presenting with strictures in industrializing countries. Moreover, 50% of patients with CD developed clinically significant strictures in long-term follow-up. Progression of CD occurs even with modern biologic therapy. However, improvement in stricture management and prevention is evidenced by a decrease in surgical resection during the past 2 decades.

**Diagnosis**

Differentiating inflammatory from fibrotic strictures is critically important because fibrotic strictures require surgical or endoscopic intervention, whereas inflammatory strictures may respond to medical treatment. However, a major challenge remains in distinguishing the two on cross-sectional imaging.

Stricturing disease usually occurs with postprandial abdominal pain, nausea, vomiting, and/or distention, but may be clinically silent. Clinical activity indices such as the Crohn’s Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI) are nonspecific and have poor correlation with endoscopic findings of strictures. Objective markers of disease activity (eg, fecal calprotectin, C-reactive protein) and endoscopic findings have been incorporated by the Simple Endoscopic Score for Crohn’s Disease (SES-CD) and Crohn’s Disease Endoscopic Index of Severity scoring systems, yet biomarkers of inflammation correlate poorly. No biomarker for fibrosis in CD is widely used, although promising genetic, serologic, and epigenetic markers have been reported. Currently, no validated scoring system incorporates these biomarkers.

**Imaging**

Cross-sectional imaging is an indispensable tool for evaluating CD complications, including strictures and penetrating disease, particularly in disease affecting the small bowel. Cross-sectional enterography can identify small bowel inflammation or intramural disease in approximately 50% of CD patients with normal ileocolonoscopy. A recent consensus statement from the Society of Abdominal Radiology and the American Gastroenterological Association described recommendations for the interpretation of enterography examinations in patients with small bowel CD. According to this consensus statement, strictures, defined as persistent luminal narrowing with greater than 3 cm upstream bowel dilation, are to be interpreted as strictures with or without imaging findings of active inflammation. Active inflammation is indicated by mural enhancement, edema, or restricted diffusion on magnetic resonance (MR) imaging. However, strictures lie on a spectrum of inflammation and fibrosis, with inflammation and fibrosis often coexisting. Structures can also be evaluated on cross-sectional imaging for soft tissue extending into the adjacent mesentery, a finding suggestive of a neoplasm. Computed tomography enterography (CTE) and MR enterography (MRE) are among the most commonly utilized imaging modalities in the evaluation of CD and associated strictures, and both will be further discussed (Table 1).

**Computed Tomography Enterography**

CTE is a readily available imaging modality in the evaluation of CD strictures and requires the administration of intravenous and neutral oral contrast. Adequate small bowel distention with steadily consumed neutral oral contrast is critical to avoid false-positive stricture
diagnoses from underdistended small bowel. Luminal narrowing with upstream small bowel dilation greater than 3 cm is used to avoid misdiagnosing peristalsing bowel as a stricture.\textsuperscript{36}

Strictures with active inflammation are frequently diagnosed using mural hyperenhancement, with greater than 109 Hounsfield units indicating active disease.\textsuperscript{43} A study evaluated 39 CD patients with dual-energy CTE (DECTE) and found significant differences in iodine concentration in patients with active CD (3.39 ± 1.05 mg/mL) compared with patients in remission (2.00 ± 0.70 mg/mL).\textsuperscript{44} Another study evaluated 22 patients with CD and found that patients with minimum iodine density greater than 2.6 mg/mL, or maximum iodine density greater than 4.7 mg/mL, correlated with clinically active disease.\textsuperscript{45} Compared with CDAI and HBI based on histopathologic comparison, iodine density from DECTE was shown to identify CD active inflammation with higher sensitivity (100% for iodine density vs 53%-59% for clinical parameters) and accuracy (92% for iodine density vs 60%-64% for clinical parameters).\textsuperscript{46} An example of the diagnosis of an equivocal stricture as inflammatory on DECTE is provided in Figure 1.

**Magnetic Resonance Enterography**

MRE is another commonly utilized imaging modality for evaluating patients with CD, and has the benefit of not utilizing ionizing radiation. Because MRE can be more sensitive as images are acquired over longer periods of time compared with CTE, areas of persistent luminal

<table>
<thead>
<tr>
<th>Table 1. Available Imaging Modalities for Detecting Strictures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technique</strong></td>
</tr>
</tbody>
</table>
| Dual-energy computed tomography enterography            | • Easily accessible
 • Iodine mapping
 • Improves differentiation of inflammatory vs fibrotic strictures | • Iodine exposure
 • Radiation
 • Accessibility |
| Magnetic resonance enterography                          | • No radiation
 • High resolution
 • Standard of care | • Cost
 • Long acquisition time
 • Accessibility |
| Ultrasound ± contrast                                    | • No radiation
 • Easily accessible
 • Cost | • Less standardized
 • Technician dependent
 • No consensus on diagnostic criteria |

![Figure 1. Coronal (A) and axial (B) images from dual-source, dual-energy abdominopelvic computed tomography performed with intravenous and oral contrast showing terminal ileum narrowing (white arrow in each image) with upstream small bowel dilation up to 4.8 cm, compatible with stricture. The upstream dilated small bowel shows small bowel feces sign and pseudosacculation along the antimesenteric border (red arrow in A), a finding of chronicity. However, iodine density analysis showed iodine density of 4.0 mg/mL and 55.1% aorta enhancement within the stricture, findings compatible with active inflammation despite the 83.8 Hounsfield unit measurement, which does not meet the threshold for active inflammation. This stricture was new from the study performed 8 months prior and demonstrated severe active inflammation on ileocolic resection, which was confidently diagnosed preoperatively using dual-energy computed tomography iodine density analysis.](image)
narrowing but with upstream bowel dilation less than 3 cm can be diagnosed as probable strictures on MRE. Without ionizing radiation, MRE permits the acquisition of multiple postcontrast time points, such as during the enterography or delayed phases of contrast administration. A stricture with active inflammation shows early enhancement on dynamic contrast-enhanced MRE and intramural edema manifested by hyperintense signal on T2 fat-saturated images. On the other hand, predominantly fibrotic strictures show progressive enhancement on delayed phases of dynamic contrast-enhanced MRE and show hypointense signal on T2 fat-saturated images. An example of MRE-based diagnosis of an inflammatory stricture is provided in Figure 2.

Ultrasound
Ultrasound (US) is an accessible, affordable, and non-invasive modality without ionizing radiation that is particularly useful because many CD patients are diagnosed at a younger age, when they are more susceptible to radiation and have a longer time horizon to develop radiation-associated malignancy. Comparison of US and MRE findings in a pediatric population has shown that the diagnostic agreement between the modalities was substantial to almost perfect for strictures, penetrating disease, and abscesses. Another study found comparable test characteristics for US and MRE in detecting CD, with sensitivity and specificity greater than 90% for both. However, when assessing extent of disease and detecting penetrating complications, US was found to be significantly less accurate than MRE. Contrast-enhanced US is a newer technique that requires the injection of intravenous US-specific contrast to help quantify mesenteric perfusion and visualize bowel enhancement characteristics. Additionally, US elastography can measure tissue elasticity, and was shown to successfully differentiate fibrotic and nonfibrotic tissue in 10 patients with CD strictures. However, there remains no consensus on the US criteria to differentiate fibrosis and inflammation; CTE and MRE remain the mainstay for the imaging of patients with CD.

Endoscopy
Strictures are endoscopically defined as an inability to pass a colonoscope through the narrowed area without prior endoscopic dilation or applying a reasonable amount of pressure. Most strictures occur in the ileocolonic region.
accessible by endoscopy. However, because CD has significant skip lesions in areas of the digestive tract not accessible by endoscopy, disease activity can be missed. Video capsule endoscopy in the diagnosis of strictures in areas of the small bowel not accessible by traditional endoscopy can lead to the retention of up to 13.2% of capsules, which limits its use in diagnosing and differentiating strictures.

Treatment

Management of strictures depends on distinguishing inflammatory from fibrotic strictures and identifying the extent of fibrosis, location, proximal dilation, and symptoms. This article will further discuss the different medical and endoscopic treatment modalities available (Table 2).

**Medical Management**

Anti-inflammatory medications may contribute to the treatment of complicated stricturing disease when combined with endoscopic dilation. Anti–tumor necrosis factor (anti-TNF) agents had been thought to worsen strictures owing to an accelerated healing process worsening fibrosis, but subsequent studies have shown regression of fibrosis using biologics, with improved endoscopic findings and decreased hospital admission rates. A retrospective study evaluating bowel resection in patients given biologic therapy found a significant decrease in progression to surgery (9.3% with biologics vs 12.1% with no biologics). The majority of surgery in this study occurred within 1 year of starting biologics, which suggests that the efficacy may be reduced by the delayed start of biologic therapy. Another study randomized 52 patients with evidence of inflammatory symptomatic strictures to intensive treat-to-target adalimumab and thiopurine treatment and 25 patients to standard adalimumab treatment. The intensive therapy resulted in significantly less treatment failure compared with standard treatment (10% vs 28%), and both groups showed a reduction in stricture-associated inflammation and greater improvement in stricture morphology with no significant differences between groups. Early and intensive intervention with these agents may prevent fibrosis, which may be self-propagating and independent of concurrent inflammation once established.

Medical therapy for CD is targeted at clinical and endoscopic remission, with a presumed benefit of preventing strictures. No antifibrotic regimen is currently available for treating established strictures. Studies addressing antifibrotic therapy in CD utilize therapies for fibrosis in other organ systems, such as renal interstitial nephritis, pulmonary fibrosis, cirrhosis, and systemic sclerosis. Pirfenidone (Esbriet, Genentech), an antifibrotic agent for treatment of idiopathic pulmonary fibrosis, has shown promise in inhibiting fibroblasts in patients with active CD and attenuating fibrosis in murine models.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical management</td>
<td>Delay/avoids invasive interventions</td>
<td>No antifibrotic agents</td>
</tr>
<tr>
<td></td>
<td>Increases time to surgery</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Regression of fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevents strictures</td>
<td></td>
</tr>
<tr>
<td>Endoscopic balloon dilation</td>
<td>Well established</td>
<td>High recurrence rate</td>
</tr>
<tr>
<td></td>
<td>High technical success rate</td>
<td>Poor success with asymmetric strictures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity of procedures</td>
</tr>
<tr>
<td>Stents</td>
<td>Delay surgery in refractory cases</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High adverse event rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent procedure needed for removal</td>
</tr>
<tr>
<td>Endoscopic stricturotomy</td>
<td>Localized and directed</td>
<td>Logistic barriers to learn technique</td>
</tr>
<tr>
<td></td>
<td>Low risk of perforation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymmetric strictures</td>
<td></td>
</tr>
<tr>
<td>Intrallesional injection</td>
<td>Low risk of perforation</td>
<td>Corticosteroid injections possibly harmful</td>
</tr>
<tr>
<td></td>
<td>Adjunct to dilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible evolving use of anti–tumor necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>factor agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No consensus recommendation for use</td>
<td></td>
</tr>
</tbody>
</table>
Endoscopy

Endoscopic treatment includes endoscopic balloon dilation (EBD), stents, stricturotomy, and intralesional corticosteroid injections. Examples of EBD and stricturotomy are depicted in Figure 3. The goals of endoscopic treatment include symptom relief, surgery prevention, and minimizing risk of stricture-related complications.

Endoscopic Balloon Dilation  EBD is an invasive, well-established modality for treating symptomatic CD and delaying surgery. However, its use is limited by heterogeneity in stricture lengths, balloon diameters, and duration of inflation. Balloon dilation is performed in a retrograde or antegrade fashion using progressively larger balloons, typically starting with an 18-mm balloon. Although EBD can be attempted with larger strictures, a pooled analysis found that complications requiring surgical intervention, such as perforations, increase 8% for every 1-cm increase in stricture length. Further, the same study found that increased balloon diameters conferred higher technical success but did not improve clinical efficacy or decrease the need for surgery. Duodenal strictures may be more likely than ileocolonic strictures to require earlier surgery after dilation.

Ninety-seven percent of EBD procedures achieve immediate technical success, but up to 70% result in clinically significant obstructive symptoms on follow-up and approximately 40% ultimately require surgery. Predictors of successful intervention include nonulcerated, straight, short segments (<4-5 cm in length) without any adjacent abscess or fistula. Although repeat dilations are commonly performed, their outcomes and complications do not significantly differ from those following the first dilation. Data regarding double balloon

Figure 3. Images before and after different endoscopic therapies. Crohn’s disease stricture before (A) and after (B) endoscopic balloon dilation. Crohn’s disease stricture before (C) and after (D) endoscopic isolated-tip knife stricturotomy. All images provided courtesy of Dr Bo Shen, Columbia University, New York, New York.
enteroscopy dilation of strictures of the small bowel are scarce. A systematic review of 13 studies of 310 patients found that 80% of patients avoided surgery during the average follow-up of 32 months.87 Furthermore, medical therapy with a combination of an immunomodulator and anti-TNF agents is associated with a decreased need for repeat dilations.88

**Stents** Self-expanding metal stents (SEMS) are an effective, nonsurgical alternative treatment for malignant obstruction as both a palliative measure and a bridge to surgery. Stents should be 3 cm to 4 cm longer than the stricture because they may shorten by 40% after placement, which makes shorter strictures more favorable for intervention.90 Stent efficacy has been evaluated in strictures refractory to EBD as an alternative to repeat dilation or surgery. A retrospective study of 17 CD patients treated with SEMS for symptomatic refractory strictures found that 65% of patients did not need repeat intervention for a mean follow-up of 67 weeks.90 In this study, stents were maintained for an average of 28 days before removal. Surgery was required for 1 patient with proximal stent migration. One retrospective cohort of 5 patients with SEMS placed for an average of 9.7 months found 80% clinical success at a mean follow-up of 28 months.91 In this study, 1 patient had significant re-obstruction requiring surgical intervention. A prospective cohort of 11 patients receiving SEMS demonstrated a 60% clinical success rate; however, the adverse event rate was 73%, including 2 patients requiring surgery related to the procedure and 6 patients with migrating stents.92 Despite the high rate of adverse events, distal stent migrations may be considered a natural course of efficient dilation, which may support earlier stent removal before stents have a chance to migrate.

Most recently, a study selected 21 patients using a multidisciplinary team that included gastroenterologists, radiologists, and colorectal surgeons to determine ideal candidates (strictures ≤6 cm with no fistulas, abscesses, or highly active disease) for stent placement.95 Given the high rate of adverse events noted previously, stents remained for only 7 days before removal. Eighty-one percent of patients reported symptom improvement. There was a 21% adverse event rate (events included abdominal pain and asymptomatic stent migration), and no patients required surgery. Another study randomized 80 patients with predominantly fibrotic symptomatic strictures to stent placement or EBD and found that the stent group had a significantly higher proportion of patients who required a new therapeutic intervention at 1 year (49% vs 20%).96 Given these data, stent placement may be a safe alternative or adjunct to EBD in carefully selected patients.

Biodegradable stents obviate the need for a subsequent procedure for removal. Currently, no biodegradable stents are designed for bowel strictures, but they have been evaluated for esophageal strictures. A prospective study evaluated polydioxanone monofilament stents, which provide approximately 6 to 8 weeks of radial force prior to degradation, in a cohort of 11 patients naive to EBD.93 The polydioxanone monofilament stents demonstrated a technical success rate of 91% and resulted in no adverse events other than 3 patients with early stent migration. Another study evaluated the same biodegradable stent in 6 patients with strictures refractory to EBD, with clinical success in 1 patient.94 Failures were owing to mucosal overgrowth and stent collapse. Pending advances in biodegradable stents, there is not enough evidence to promote their regular use.

**Endoscopic Strictures** Endoscopic stricturotomy has been used to treat upper gastrointestinal tract strictures, with increased use in inflammatory bowel disease–related lower gastrointestinal strictures. A retrospective study evaluating 85 patients who underwent endoscopic stricturotomy for primary and secondary strictures found that 60% of patients required additional endoscopic intervention and 15% of patients required surgery over a mean follow-up of 1 year.95 Although data were limited to a single institution and lack significant follow-up, they suggest improved rates of surgical delay or avoidance. The procedure was safely tolerated with a low rate of adverse events (3.7%) and 100% technical success.

**Intralesional Injection** Corticosteroid injections may be an adjunct to EBD and have been shown to significantly delay time to repeat intervention.98 However, there are studies showing a trend toward harm,99 and given the limited and contradictory findings, there is no clear support for the routine use of these injections.100

There has been interest in intralesional injection of anti-TNF agents. A study assessed the injection of infliximab in 3 patients with obstructive symptoms refractory to biologic therapy.101 These patients experienced symptomatic relief with endoscopic evidence of improvement with no adverse events for a median of 10 months of follow-up. Another study evaluated 5 patients with inflammatory strictures (on imaging or endoscopy) refractory to EBD who underwent serial balloon dilation at 0, 2, and 6 weeks with intralesional injection subsequent to each procedure.102 In all 5 patients, there was a clear reduction in SES-CD without any adverse events. Although local anti-TNF therapy seems well tolerated, long-term follow-up data and randomized trials would better demonstrate its efficacy. Ultimately, there is no consensus recommendation for any form of intralesional injection.
Conclusion

Strictures remain a common and debilitating complication of CD; however, therapeutics and understanding of the condition continue to evolve in the pursuit of prevention and reversal of strictures. The ability to better characterize strictures as inflammatory or fibrotic facilitates the tailoring of therapies and standardizing of effective treatments (Figure 4). Early diagnosis and intervention may prevent complications and decrease morbidity associated with strictures. Emerging technologies such as DECTE and iodine density are promising in stratifying patient populations for specific medical and invasive therapeutics.

In reviewing the diagnosis and management of fibrostenosing strictures, this article aims to give providers an overview of the landscape of stricturing CD and inform future treatment and innovation.

Disclosures

The authors have no relevant conflicts of interest to disclose.

References


38. Gastroenterology & Hepatology  Volume 18, Issue 4  April 2022