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, MD[3]

[1]Department of Medicine, NYU Langone Medical Center, New York, New York

[2]Department of Radiology, NYU Langone Medical Center, New York, New York

[3]Department of Gastroenterology, NYU Langone Medical Center, New York, New York

Corresponding author:
Dr Briton Lee
550 First Avenue
NBV 16 North 30
New York, NY 10016
Tel: (212) 263-5506
Fax: (720) 405-4497
E-mail: briton.lee@nyulangone.org

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.

Keywords
Inflammatory bowel disease, inflammatory, fibrosis, dual-energy computed tomography enterography, magnetic resonance enterography, biologics

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.[7,8] 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.[7,9] Important mediators of intestinal fibrosis include inflammatory cytokines such as interleukin (IL)-13 and IL-17,[10,11] and transforming growth factor β (TGF-β).[12] 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.[13] 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.[14]

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.[15] This balance is maintained by matrix metalloproteinases, which break down ECM, and tissue inhibitors of matrix metalloproteinases.[16,17] 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.[18] 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.[18]

Epidemiology

The prevalence of CD is approximately 0.3% in Western countries, with up to 28% of patients presenting with strictures in industrializing countries.[19-21] Moreover, 50% of patients with CD developed clinically significant strictures in long-term follow-up.[1] Progression of CD occurs even with modern biologic therapy.[22,23] However, improvement in stricture management and prevention is evidenced by a decrease in surgical resection during the past 2 decades.[24,25]

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.[26] However, a major challenge remains in distinguishing the two on cross-sectional imaging.[27]

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.[28-32] 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,[33,34] 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.[35] Currently, no validated scoring system incorporates these biomarkers.[3]

Imaging

Cross-sectional imaging is an indispensable tool for evaluating CD complications, including strictures and penetrating disease, particularly in disease affecting the small bowel.[36] Cross-sectional enterography can identify small bowel inflammation or intramural disease in approximately 50% of CD patients with normal ileocolonoscopy.[37] 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.[36] 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.[7,38-41] Strictures can also be evaluated on cross-sectional imaging for soft tissue extending into the adjacent mesentery, a finding suggestive of a neoplasm.[42] 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

Table 1. Available Imaging Modalities for Detecting Strictures

Technique	Advantages	Disadvantages
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

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.[36]

Strictures with active inflammation are frequently diagnosed using mural hyperenhancement, with greater than 109 Hounsfield units indicating active disease.[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).[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.[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).[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

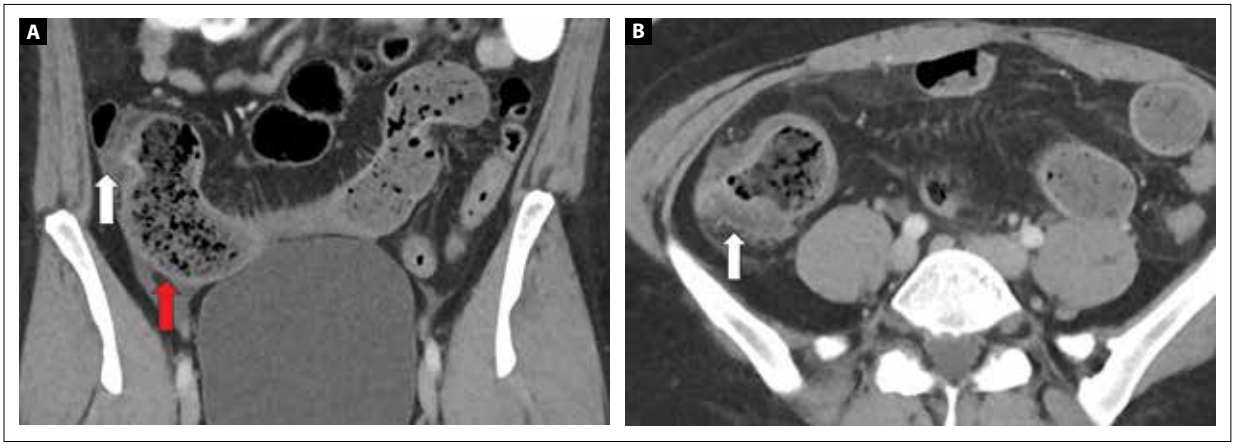

Figure 1. Coronal (**A**) and axial (**B**) images from dual-source, dual-energy abdominopelvic computed tomography performed with intravenous and oral contrast showing terminal ileum narrowing (white arrow in each image) with upstream small bowel dilation up to 4.8 cm, compatible with stricture. The 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.

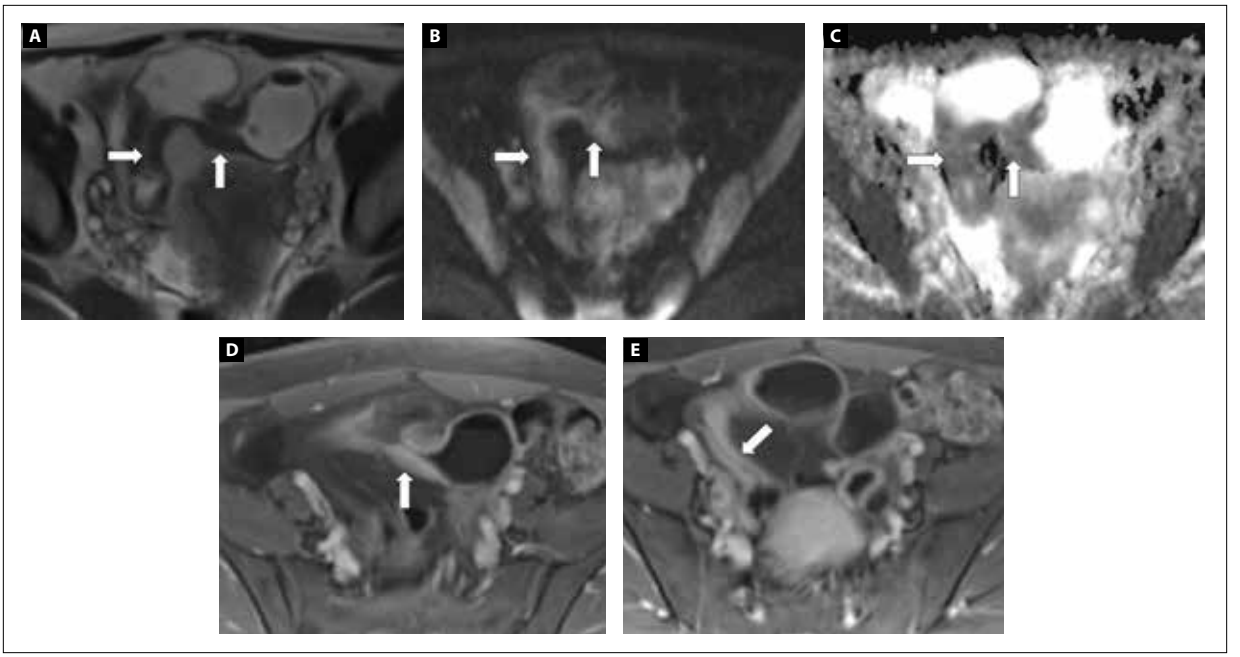

Figure 2. A 27-year-old woman with Crohn's disease underwent 1.5-Tesla magnet magnetic resonance enterography (Avanto, Siemens). Axial half-Fourier acquisition single-shot turbo spin-echo image (**A**) demonstrates 2 adjacent strictures (white arrows) measuring 2 cm in length with upstream dilation to 3 cm, compatible with stricture. Axial diffusion-weighted image (**B**) shows high mural signal within the same strictures (white arrows), and the corresponding axial attenuated diffusion coefficient image (**C**) shows low signal (white arrows), compatible with active inflammation. Axial T1-weighted fat-suppressed Golden-Angle Radial Sparse Parallel image (**D**, **E**) shows mural stratification and early enhancement on dynamic postcontrast imaging within the stricture (white arrows), compatible with active inflammation.

narrowing but with upstream bowel dilation less than 3 cm can be diagnosed as probable strictures on MRE.[36] 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.[47] An example of MRE-based diagnosis of an inflammatory stricture is provided in Figure 2.

Ultrasound

Ultrasound (US) is an accessible, affordable, and noninvasive 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.[48] Another study found comparable test characteristics for US and MRE in detecting CD, with sensitivity and specificity greater than 90% for both.[49] However, when assessing extent of disease and detecting penetrating complications, US was found to be significantly less accurate than MRE.[49] 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.[50] Additionally, US elastography can measure tissue elasticity, and was shown to successfully differentiate fibrotic and nonfibrotic tissue in 10 patients with CD strictures.[51] 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.[52] Most strictures occur in the ileocolonic region

Table 2. Advantages and Disadvantages of Available Treatment Modalities for Strictures

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

accessible by endoscopy.[53] However, because CD has significant skip lesions in areas of the digestive tract not accessible by endoscopy, disease activity can be missed.[37] 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.[54,55]

Treatment

Management of strictures depends on distinguishing inflammatory from fibrotic strictures and identifying the extent of fibrosis, location, proximal dilation, and symptoms.[56] 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.[57-59] 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).[60] 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.[61] 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.[62]

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.[63] Studies addressing antifibrotic therapy in CD utilize therapies for fibrosis in other organ systems,[64] such as renal interstitial nephritis,[65,66] pulmonary fibrosis,[67-69] cirrhosis,[70-73] and systemic sclerosis.[74,75] Pirfenidone (Esbriet, Genentech), an antifibrotic agent for treatment of idiopathic pulmonary fibrosis, has shown promise in inhibiting fibroblasts in patients with active CD[76] and attenuating fibrosis in murine models.[77,78]

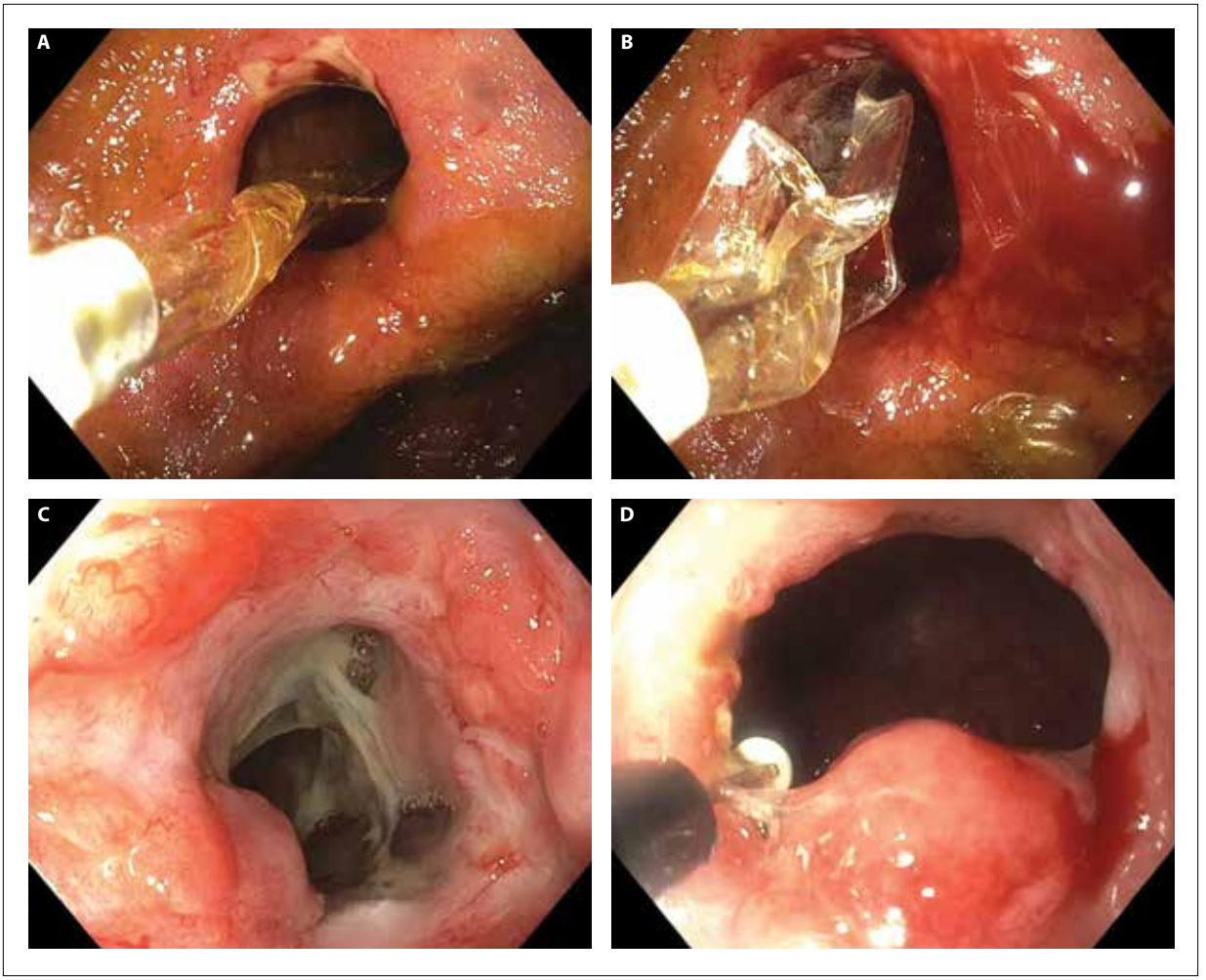

Figure 3. Images before and after different endoscopic therapies. Crohn's disease stricture before (**A**) and after (**B**) endoscopic balloon dilation. Crohn's disease stricture before (**C**) and after (**D**) endoscopic isolated-tip knife stricturotomy. All images provided courtesy of Dr Bo Shen, Columbia University, New York, New York.

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.[79,80] Balloon dilation is performed in a retrograde or antegrade fashion using progressively larger balloons, typically starting with an 18-mm balloon.[81] 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.[82] 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.[82]

Ninety-seven percent of EBD procedures achieve immediate technical success, but up to 70% result in clinically significant obstructive symptoms on follow-up[83] and approximately 40% ultimately require surgery.[82] Predictors of successful intervention include nonulcerated, straight, short segments (<4-5 cm in length) without any adjacent abscess or fistula.[84,85] Although repeat dilations are commonly performed, their outcomes and complications do not significantly differ from those following the first dilation.[83,86] Data regarding double balloon

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.[89] 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.[93] 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%).[94] 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.[95] 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.[96] 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 Stricturotomy 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.[97] 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.

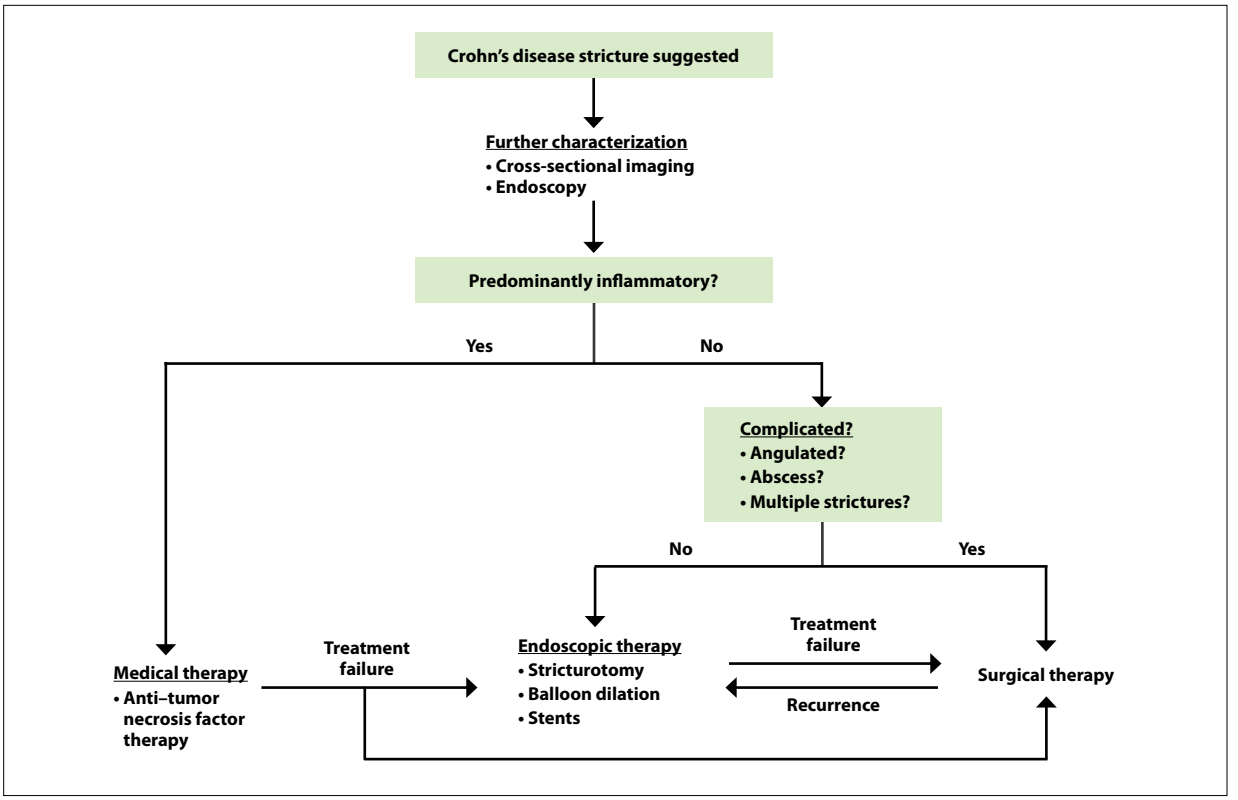

Figure 4. Algorithm of medical, endoscopic, and surgical treatments for Crohn's disease strictures. Adapted with permission from Dr Bo Shen, Columbia University, New York, New York.

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

1. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8(4):244-250.
2. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut*. 2013;62(7):1072-1084.
3. Bettenworth D, Rieder F. Medical therapy of stricturing Crohn's disease: what the gut can learn from other organs—a systematic review. *Fibrogenesis Tissue Repair*. 2014;7(1):5.
4. Ma C, Jairath V, Click B, et al; Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium. Targeting anti-fibrotic pathways in Crohn's disease—the final frontier? *Best Pract Res Clin Gastroenterol*. 2019;38-39:101603.
5. Alfredsson J, Wick MJ. Mechanism of fibrosis and stricture formation in Crohn's disease. *Scand J Immunol*. 2020;92(6):e12990.
6. Crespi M, Dulbecco P, De Ceglie A, Conio M. Strictures in Crohn's disease: from pathophysiology to treatment. *Dig Dis Sci*. 2020;65(7):1904-1916.
7. Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. *Gastroenterology*. 2017;152(2):340-350.e6.
8. Usunier B, Benderitter M, Tamarat R, Chapel A. Management of fibrosis: the mesenchymal stromal cells breakthrough. *Stem Cells Int*. 2014;2014:340257.
9. Pariente B, Hu S, Bettenworth D, et al. Treatments for Crohn's disease-associated bowel damage: a systematic review. *Clin Gastroenterol Hepatol*. 2019;17(5):847-856.
10. Fichtner-Feigl S, Fuss IJ, Young CA, et al. Induction of IL-13 triggers TGF-beta1-dependent tissue fibrosis in chronic 2,4,6-trinitrobenzene sulfonic acid colitis. *J Immunol*. 2007;178(9):5859-5870.
11. Biancheri P, Pender SL, Ammoscato F, et al. The role of interleukin 17 in Crohn's disease-associated intestinal fibrosis. *Fibrogenesis Tissue Repair*. 2013;6(1):13.
12. Vallance BA, Gunawan MI, Hewlett B, et al. TGF-beta1 gene transfer to the mouse colon leads to intestinal fibrosis. *Am J Physiol Gastrointest Liver Physiol*. 2005;289(1):G116-G128.
13. Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. *FASEB J*. 2004;18(7):816-827.
14. Nishida A, Hidaka K, Kanda T, et al. Increased expression of interleukin-36, a member of the interleukin-1 cytokine family, in inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22(2):303-314.

15. Zorzi F, Calabrese E, Monteleone G. Pathogenic aspects and therapeutic avenues of intestinal fibrosis in Crohn's disease. *Clin Sci (Lond)*. 2015;129(12):1107-1113.
16. Heuschkel RB, MacDonald TT, Monteleone G, Bajaj-Elliott M, Smith JA, Pender SL. Imbalance of stromelysin-1 and TIMP-1 in the mucosal lesions of children with inflammatory bowel disease. *Gut*. 2000;47(1):57-62.
17. Lakatos G, Hritz I, Varga MZ, et al. The impact of matrix metalloproteinases and their tissue inhibitors in inflammatory bowel diseases. *Dig Dis*. 2012;30(3):289-295.
18. Chen W, Lu C, Hirota C, Iacucci M, Ghosh S, Gui X. Smooth muscle hyperplasia/hypertrophy is the most prominent histological change in Crohn's fibrostenosing bowel strictures: a semiquantitative analysis by using a novel histological grading scheme. *J Crohns Colitis*. 2017;11(1):92-104.
19. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778.
20. Chan WPW, Mourad F, Leong RW. Crohn's disease associated strictures. *J Gastroenterol Hepatol*. 2018;33(5):998-1008.
21. Cheifetz AS. Management of active Crohn disease. *JAMA*. 2013;309(20):2150-2158.
22. Jeuring SFG, van den Heuvel TRA, Liu LYL, et al. Improvements in the long-term outcome of Crohn's disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL cohort. *Am J Gastroenterol*. 2017;112(2):325-336.
23. Lazarev M, Huang C, Bitton A, et al. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. *Am J Gastroenterol*. 2013;108(1):106-112.
24. Ma C, Moran GW, Benchimol EI, et al. Surgical rates for Crohn's disease are decreasing: a population-based time trend analysis and validation study. *Am J Gastroenterol*. 2017;112(12):1840-1848.
25. Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut*. 2014;63(10):1607-1616.
26. Rimola J, Capozzi N. Differentiation of fibrotic and inflammatory component of Crohn's disease-associated strictures. *Intest Res*. 2020;18(2):144-150.
27. Bettenworth D, Bokemeyer A, Baker M, et al; Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium. Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review. *Gut*. 2019;68(6):1115-1126.
28. Jørgensen LGM, Fredholm L, Hyltoft Petersen P, Hey H, Munkholm P, Brandslund I. How accurate are clinical activity indices for scoring of disease activity in inflammatory bowel disease (IBD)? *Clin Chem Lab Med*. 2005;43(4):403-411.
29. Lahiff C, Safaie P, Awais A, et al. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2013;37(8):786-794.
30. Leake I. IBD: a score to settle—measuring Crohn's disease activity. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):564.
31. Lewis JD, Rutgeerts P, Feagan BG, et al. Correlation of stool frequency and abdominal pain measures with simple endoscopic score for Crohn's disease. *Inflamm Bowel Dis*. 2020;26(2):304-313.
32. Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology*. 2002;122(2):512-530.
33. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60(4):505-512.
34. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut*. 1989;30(7):983-989.
35. Pellino G, Pallante P, Selvaggi F. Novel biomarkers of fibrosis in Crohn's disease. *World J Gastrointest Pathophysiol*. 2016;7(3):266-275.
36. Bruining DH, Zimmermann EM, Loftus EV Jr, Sandborn WJ, Sauer CG, Strong SA; Society of Abdominal Radiology Crohn's Disease-Focused Panel. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Radiology*. 2018;286(3):776-799.
37. Samuel S, Bruining DH, Loftus EV Jr, et al. Endoscopic skipping of the distal terminal ileum in Crohn's disease can lead to negative results from ileocolonoscopy. *Clin Gastroenterol Hepatol*. 2012;10(11):1253-1259.
38. Latella G, Di Gregorio J, Flati V, Rieder F, Lawrance IC. Mechanisms of initiation and progression of intestinal fibrosis in IBD. *Scand J Gastroenterol*. 2015;50(1):53-65.
39. Chiorean MV, Sandrasegaran K, Saxena R, Maglinte DD, Nakeeb A, Johnson CS. Correlation of CT enteroclysis with surgical pathology in Crohn's disease. *Am J Gastroenterol*. 2007;102(11):2541-2550.
40. Barkmeier DT, Dillman JR, Al-Hawary M, et al. MR enterography-histology comparison in resected pediatric small bowel Crohn disease strictures: can imaging predict fibrosis? *Pediatr Radiol*. 2016;46(4):498-507.
41. Rimola J, Planell N, Rodríguez S, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. *Am J Gastroenterol*. 2015;110(3):432-440.
42. Weber NK, Fletcher JG, Fidler JL, et al. Clinical characteristics and imaging features of small bowel adenocarcinomas in Crohn's disease. *Abdom Imaging*. 2015;40(5):1060-1067.
43. Bodily KD, Fletcher JG, Solem CA, et al. Crohn disease: mural attenuation and thickness at contrast-enhanced CT enterography—correlation with endoscopic and histologic findings of inflammation. *Radiology*. 2006;238(2):505-516.
44. Kim YS, Kim SH, Ryu HS, Han JK. Iodine quantification on spectral detector-based dual-energy CT enterography: correlation with Crohn's Disease Activity Index and external validation. *Korean J Radiol*. 2018;19(6):1077-1088.
45. Dane B, Duenas S, Han J, et al. Crohn's disease activity quantified by iodine density obtained from dual-energy computed tomography enterography. *J Comput Assist Tomogr*. 2020;44(2):242-247.
46. Dane B, Sarkar S, Nazarian M, et al. Crohn disease active inflammation assessment with iodine density from dual-energy CT enterography: comparison with histopathologic analysis. *Radiology*. 2021;301(1):144-151.
47. Ream JM, Doshi A, Lala SV, Kim S, Rusinek H, Chandarana H. High spatiotemporal resolution dynamic contrast-enhanced MR enterography in Crohn disease terminal ileitis using continuous golden-angle radial sampling, compressed sensing, and parallel imaging. *AJR Am J Roentgenol*. 2015;204(6):W663-W669.
48. Dillman JR, Smith EA, Sanchez R, et al. Prospective cohort study of ultrasound-ultrasound and ultrasound-MR enterography agreement in the evaluation of pediatric small bowel Crohn disease. *Pediatr Radiol*. 2016;46(4):490-497.
49. Castiglione F, Mainenti PP, De Palma GD, et al. Noninvasive diagnosis of small bowel Crohn's disease: direct comparison of bowel sonography and magnetic resonance enterography. *Inflamm Bowel Dis*. 2013;19(5):991-998.
50. Ripollés T, Martínez-Pérez MJ, Blanc E, et al. Contrast-enhanced ultrasound (CEUS) in Crohn's disease: technique, image interpretation and clinical applications. *Insights Imaging*. 2011;2(6):639-652.
51. Baumgart DC, Müller HP, Grittner U, et al. US-based real-time elastography for the detection of fibrotic gut tissue in patients with stricturing Crohn disease. *Radiology*. 2015;275(3):889-899.
52. Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther*. 2018;48(3):347-357.
53. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut*. 2001;49(6):777-782.
54. Chetcuti Zammit S, Ellul P, Sidhu R. The role of small bowel endoscopy for Crohn's disease. *Curr Opin Gastroenterol*. 2019;35(3):223-234.
55. Yang DH, Keum B, Jeen YT. Capsule endoscopy for Crohn's disease: current status of diagnosis and management. *Gastroenterol Res Pract*. 2016;2016:8236367.
56. Gomollón F, Dignass A, Annese V, et al; ECCO. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis*. 2017;11(1):3-25.
57. Pallotta N, Barberani F, Hassan NA, Guagnozzi D, Vincoli G, Corazziari E. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. *World J Gastroenterol*. 2008;14(12):1885-1890.
58. Danese S, Sandborn WJ, Colombel JF, et al. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. *Gastroenterology*. 2019;157(4):1007-1018.e7.
59. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology*. 2018;155(4):1045-1058.
60. Khoudari G, Mansoor E, Click B, et al. Rates of intestinal resection and colectomy in inflammatory bowel disease patients after initiation of biologics: a cohort study [published online October 14, 2020]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2020.10.008.
61. Schulberg JD, Wright EK, Holt BA, et al. Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures (STRIDENT): an open-label, single-centre, randomised controlled trial. *Lancet*

Gastroenterol Hepatol. 2022;7(4):318-331.
62. Johnson LA, Luke A, Sauder K, Moons DS, Horowitz JC, Higgins PDR. Intestinal fibrosis is reduced by early elimination of inflammation in a mouse model of IBD: impact of a "top-down" approach to intestinal fibrosis in mice. *Inflamm Bowel Dis*. 2012;18(3):460-471.
63. Rieder F, Latella G, Magro F, et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis*. 2016;10(8):873-885.
64. Rogler G. New therapeutic avenues for treatment of fibrosis: can we learn from other diseases? *Dig Dis*. 2014;32(suppl 1):39-49.
65. Trachtman H, Fervenza FC, Gipson DS, et al. A phase 1, single-dose study of fresolimumab, an anti-TGF-β antibody, in treatment-resistant primary focal segmental glomerulosclerosis. *Kidney Int*. 2011;79(11):1236-1243.
66. El-Agroudy AE, El-Baz MA, Ismail AM, Ali-El-Dein B, El-Dein ABS, Ghoneim MA. Clinical features and course of Kaposi's sarcoma in Egyptian kidney transplant recipients. *Am J Transplant*. 2003;3(12):1595-1599.
67. King TEJ, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083-2092.
68. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib. *N Engl J Med*. 2015;372(13):1189-1191.
69. Meier R, Lutz C, Cosín-Roger J, et al. Decreased fibrogenesis after treatment with pirfenidone in a newly developed mouse model of intestinal fibrosis. *Inflamm Bowel Dis*. 2016;22(3):569-582.
70. Arthur MJP. Reversibility of liver fibrosis and cirrhosis following treatment for hepatitis C. *Gastroenterology*. 2002;122(5):1525-1528.
71. Kweon YO, Goodman ZD, Dienstag JL, et al. Decreasing fibrogenesis: an immunohistochemical study of paired liver biopsies following lamivudine therapy for chronic hepatitis B. *J Hepatol*. 2001;35(6):749-755.
72. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology*. 2004;39(6):1647-1654.
73. Czaja AJ, Carpenter HA. Decreased fibrosis during corticosteroid therapy of autoimmune hepatitis. *J Hepatol*. 2004;40(4):646-652.
74. Kuhn A, Haust M, Ruland V, et al. Effect of bosentan on skin fibrosis in patients with systemic sclerosis: a prospective, open-label, non-comparative trial. *Rheumatology (Oxford)*. 2010;49(7):1336-1345.
75. Duarte AC, Santos MJ, Cordeiro A. Anti-fibrotic nintedanib—a new opportunity for systemic sclerosis patients? *Clin Rheumatol*. 2018;37(4):1123-1127.
76. Kadir SI, Wenzel Kragstrup T, Dige A, Kok Jensen S, Dahlerup JF, Kelsen J. Pirfenidone inhibits the proliferation of fibroblasts from patients with active Crohn's disease. *Scand J Gastroenterol*. 2016;51(11):1321-1325.
77. Kurahara LH, Hiraishi K, Hu Y, et al. Activation of myofibroblast TRPA1 by steroids and pirfenidone ameliorates fibrosis in experimental Crohn's disease. *Cell Mol Gastroenterol Hepatol*. 2017;5(3):299-318.
78. Li G, Ren J, Hu Q, et al. Oral pirfenidone protects against fibrosis by inhibiting fibroblast proliferation and TGF-β signaling in a murine colitis model. *Biochem Pharmacol*. 2016;117:57-67.
79. Morar PS, Faiz O, Warusavitarne J, et al; Crohn's Stricture Study (CroSS) Group. Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures. *Aliment Pharmacol Ther*. 2015;42(10):1137-1148.
80. Bettenworth D, Lopez R, Hindryckx P, Levesque BG, Rieder F. Heterogeneity in endoscopic treatment of Crohn's disease-associated strictures: an international inflammatory bowel disease specialist survey. *J Gastroenterol*. 2016;51(10):939-948.
81. Chen M, Shen B. Endoscopic therapy in Crohn's disease: principle, preparation, and technique. *Inflamm Bowel Dis*. 2015;21(9):2222-2240.
82. Bettenworth D, Gustavsson A, Atreja A, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis*. 2017;23(1):133-142.
83. Thienpont C, D'Hoore A, Vermeire S, et al. Long-term outcome of endoscopic dilatation in patients with Crohn's disease is not affected by disease activity or medical therapy. *Gut*. 2010;59(3):320-324.
84. Shen B, Kochhar G, Navaneethan U, et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol*. 2020;5(4):393-405.
85. Hoffmann JC, Heller F, Faiss S, et al. Through the endoscope balloon dilation of ileocolonic strictures: prognostic factors, complications, and effectiveness. *Int J Colorectal Dis*. 2008;23(7):689-696.
86. Atreja A, Aggarwal A, Dwivedi S, et al. Safety and efficacy of endoscopic dilation for primary and anastomotic Crohn's disease strictures. *J Crohns Colitis*. 2014;8(5):392-400.
87. Baars JE, Theyventhiran R, Aepli P, Saxena P, Kaffes AJ. Double-balloon enteroscopy-assisted dilatation avoids surgery for small bowel strictures: a systematic review. *World J Gastroenterol*. 2017;23(45):8073-8081.
88. Ding NS, Yip WM, Choi CH, et al. Endoscopic dilatation of Crohn's anastomotic strictures is effective in the long term, and escalation of medical therapy improves outcomes in the biologic era. *J Crohns Colitis*. 2016;10(10):1172-1178.
89. Loras Alastruey C, Andújar Murcia X, Esteve Comas M. The role of stents in the treatment of Crohn's disease strictures. *Endosc Int Open*. 2016;4(3):E301-E308.
90. Loras C, Pérez-Roldan F, Gornals JB, et al. Endoscopic treatment with self-expanding metal stents for Crohn's disease strictures. *Aliment Pharmacol Ther*. 2012;36(9):833-839.
91. Levine RA, Wasvary H, Kadro O. Endoprosthetic management of refractory ileocolonic anastomotic strictures after resection for Crohn's disease: report of nine-year follow-up and review of the literature. *Inflamm Bowel Dis*. 2012;18(3):506-512.
92. Attar A, Maunoury V, Vahedi K, et al; GETAID. Safety and efficacy of extractible self-expandable metal stents in the treatment of Crohn's disease intestinal strictures: a prospective pilot study. *Inflamm Bowel Dis*. 2012;18(10):1849-1854.
93. Das R, Singh R, Din S, et al. Therapeutic resolution of focal, predominantly anastomotic Crohn's disease strictures using removable stents: outcomes from a single-center case series in the United Kingdom. *Gastrointest Endosc*. 2020;92(2):344-352.
94. Loras C, Andújar X, Gornals JB, et al; Grupo Español de Trabajo de la Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). Self-expandable metal stents versus endoscopic balloon dilation for the treatment of strictures in Crohn's disease (ProtDilat study): an open-label, multicentre, randomised trial. *Lancet Gastroenterol Hepatol*. 2022;7(4):332-341.
95. Rejchrt S, Kopacova M, Brozik J, Bures J. Biodegradable stents for the treatment of benign stenoses of the small and large intestines. *Endoscopy*. 2011;43(10):911-917.
96. Karstensen JG, Christensen KR, Brynskov J, Rønholt C, Vilmann P, Hendel J. Biodegradable stents for the treatment of bowel strictures in Crohn's disease: technical results and challenges. *Endosc Int Open*. 2016;4(3):E296-E300.
97. Lan N, Shen B. Endoscopic stricturotomy with needle knife in the treatment of strictures from inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(4):502-513.
98. Di Nardo G, Oliva S, Passariello M, et al. Intralesional steroid injection after endoscopic balloon dilation in pediatric Crohn's disease with stricture: a prospective, randomized, double-blind, controlled trial. *Gastrointest Endosc*. 2010;72(6):1201-1208.
99. East JE, Brooker JC, Rutter MD, Saunders BP. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol*. 2007;5(9):1065-1069.
100. Bevan R, Rees CJ, Rutter MD, Macafee DAL. Review of the use of intralesional steroid injections in the management of ileocolonic Crohn's strictures. *Frontline Gastroenterol*. 2013;4(4):238-243.
101. Swaminath A, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. *Inflamm Bowel Dis*. 2008;14(2):213-216.
102. Hendel J, Karstensen JG, Vilmann P. Serial intralesional injections of infliximab in small bowel Crohn's strictures are feasible and might lower inflammation. *United European Gastroenterol J*. 2014;2(5):406-412.