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Practical Approach to Stricture Management in Crohn's Disease



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Strictureing complications are an important and common event during the course of Crohn's disease (CD) and may lead to significant disability. It is a leading indication for surgery among patients with CD. Strictures are diagnosed most commonly during colonoscopy or on cross-sectional imaging, appear as a narrowing in the bowel lumen and may be associated with a variety of concomitant features, such as internal penetrating disease. Standardized radiologic diagnostic criteria have been proposed by the CONSTRICT group. Abdominal cross-sectional imaging is crucial in the evaluation of strictures and helps guide treatment. Management of strictures is often multidisciplinary and involves a combination of medical, endoscopic and surgical options. However, despite recent advances in medical therapies, the progression to strictureing complications has not been significantly altered and only a subset of patients improve on medical therapy temporarily, highlighting the need for durable treatment options. Anti-fibrotics are being evaluated in this setting and further data are eagerly awaited.

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are immune-mediated conditions leading to chronic relapsing and remitting inflammation of the gastrointestinal tract. Although the pathophysiology of IBD has not yet been fully elucidated, it appears to be due to a combination of environmental, microbial and genetic factors.¹

While ulcerative colitis only affects the colon, Crohn's disease can affect any part of the gastrointestinal (GI) tract. It is also a transmural disease and involves deeper layers of the bowel. It therefore can lead to a variety of manifestations, depending on the location of the disease, and can lead to several types of complications and phenotypes due to its transmural nature. It is a progressive disease with accumulating bowel damage over time.¹ Complications may include strictures (narrowing of the bowel lumen) as well as fistulas (tracts communicating between different bowel segments or from the GI tract to another organ) and infectious complications such as abscesses. Malnutrition, vitamin deficiencies and extra-intestinal manifestations are also common.

Strictureing complications are an important and common event in the course of the disease, and are associated with significant morbidity. This review will aim to provide an overview of Crohn's disease strictures and propose a practical approach to management.

Epidemiology and natural history of stricturing Crohn's disease

Up to 29% of patients with Crohn's disease may present with a complication at the time of diagnosis, including 21% with strictures.² In patients without complications at diagnosis, approximately 10% of patients are estimated to develop stricturing complications at 5 years,² and about 21% by 20 years.³

Strictureing disease, in addition to penetrating disease, are the most common indications for surgery in CD and account for up to 70% of surgical interventions during the first 10 years of disease.⁴ Unfortunately, CD recurs postoperatively and repeat surgery is required in about 35% of patients within 10 years of the initial resection.⁵ Strictures

can recur at the site of anastomosis (anastomotic strictures).

Although strictures manifest anywhere along the gastrointestinal tract, they are most commonly found in the small bowel. Colon strictures are less common than small bowel strictures but are associated with a higher rate of dysplasia.⁶ Colonic strictures can also occur in patients with ulcerative colitis in up to 11% of patients.⁷ Although most of them are benign, they harbor risk for malignancy. It is therefore important to monitor patients with colonic strictures closely and a lower threshold for surgery should be considered.

Patients with strictures can also have associated internal penetrating disease, including abscesses, phlegmon and abdominal fistulas. In fact, most patients with internal fistulizing disease have an associated stricture.⁸ One study assessing surgically resected segments with fistulas found that 96.3% of specimens had an underlying stricture.⁹ This has led to the hypothesis – although not supported by prospective data – that fistulas may arise in the area of pre-stricture dilation, which is considered a 'high pressure zone' of the intestinal lumen.

Unfortunately, the progression towards stricturing complications has not been significantly modified by current medical treatment options, perhaps because tissue damage may already have developed by the time CD is diagnosed.^{8,10}

Clinical manifestations of stricturing Crohn's disease

Patients with Crohn's disease may present with a variety of symptoms depending on disease severity, location and complications. General clinical features of CD include abdominal pain, diarrhea, unintentional weight loss, anorexia, rectal bleeding, fatigue, in addition to extra-intestinal features in up to 50% of patients such as ocular, joint or skin manifestations.¹ Strictures can often be clinically "silent" without obvious obstructive symptoms. In a recent cohort study assessing patients with CD-associated small bowel strictures, up to 40% had no obstructive symptoms at the time of baseline assessment.¹¹ When present, symptoms suggestive of obstruction may include post-prandial abdominal pain, change in food intake, nausea, vomiting, bloating, and abdominal distention.¹² Careful

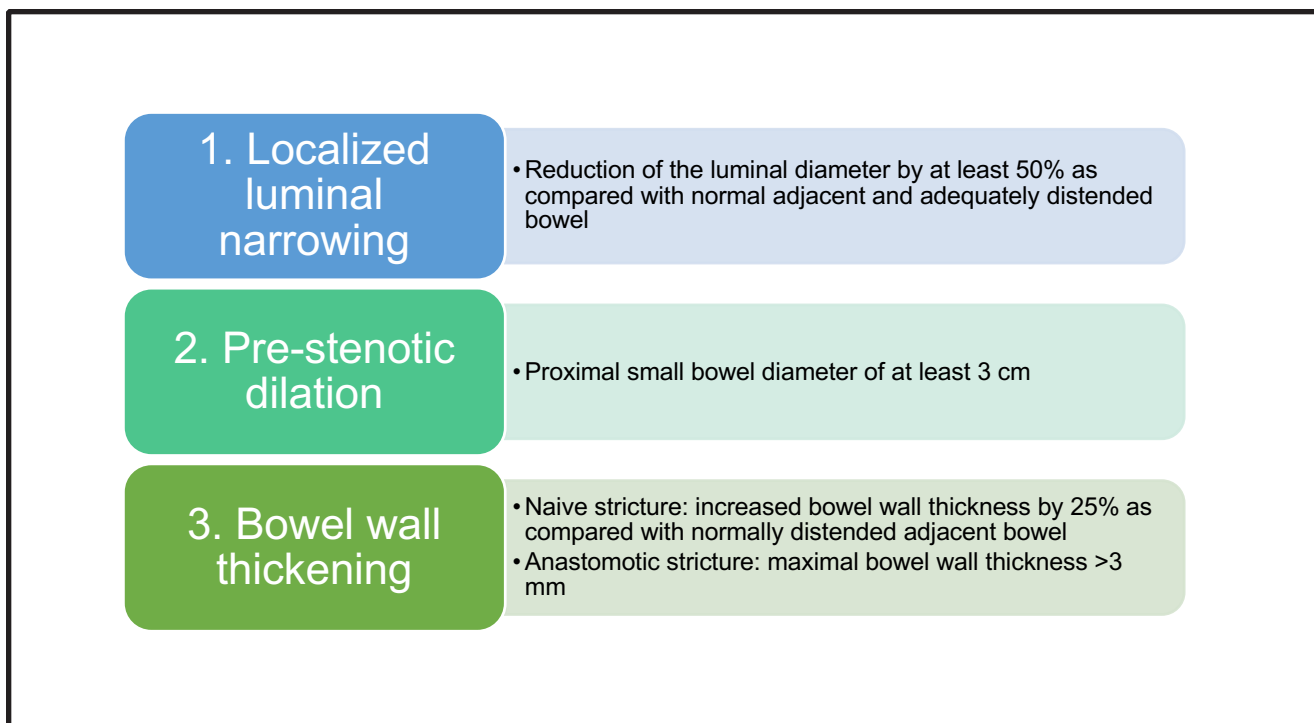


Figure 1. Radiologic stricture definition according to the CONSTRICT¹² criteria.

Two out of the three criteria are required for diagnosis in clinical practice, while all three are required for stricture diagnosis in the setting of clinical trials

history-taking is important as patients may not complain of specific symptoms other than tight dietary restrictions in order to avoid symptoms.

Diagnosis of stricturing Crohn's disease

Several endoscopic and imaging modalities can help in the diagnosis of strictures. Endoscopically, strictures appear as a narrowing of the bowel lumen and are difficult or impossible to traverse with a regular endoscope or colonoscope.¹³ Biopsies of the stenosed areas should be obtained in order to evaluate for associated dysplasia or malignancy. However, histopathologic changes can be patchy and involve deeper layers of the bowel wall. Dysplasia and malignancy, therefore, cannot be entirely ruled out despite negative biopsies.

Cross-sectional imaging is fundamental in the diagnosis and management of strictures. It provides important information regarding the presence of concomitant complications such as penetrating disease (abscesses, fistulas) or malignancy. In addition, it allows assessment of proximal disease or lesions and helps characterize the location, length of strictures and their associated features such as

signs of inflammation or bowel wall thickening, pre-stenotic dilatation, etc., thereby ultimately guiding management.¹⁴

Several types of imaging modalities are available for stricture diagnosis. Abdominal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can diagnose strictures with sensitivity ranging from 75% to 100%. Specificity ranges from 91% to 100% for CT and MR enterography. MR enterography, when available, is usually favored given its high diagnostic accuracy and the absence of ionizing radiation.¹²

In order to standardize the definition of strictures on cross-sectional imaging, a set of diagnostic criteria has been proposed by the Crohn's disease anti-fibrotic STRICTure therapies (CONSTRICT) expert consensus¹² and can be found in **Figure 1**.

Management

General approach to strictures

Several different treatment modalities are available in the management of stricturing CD, including

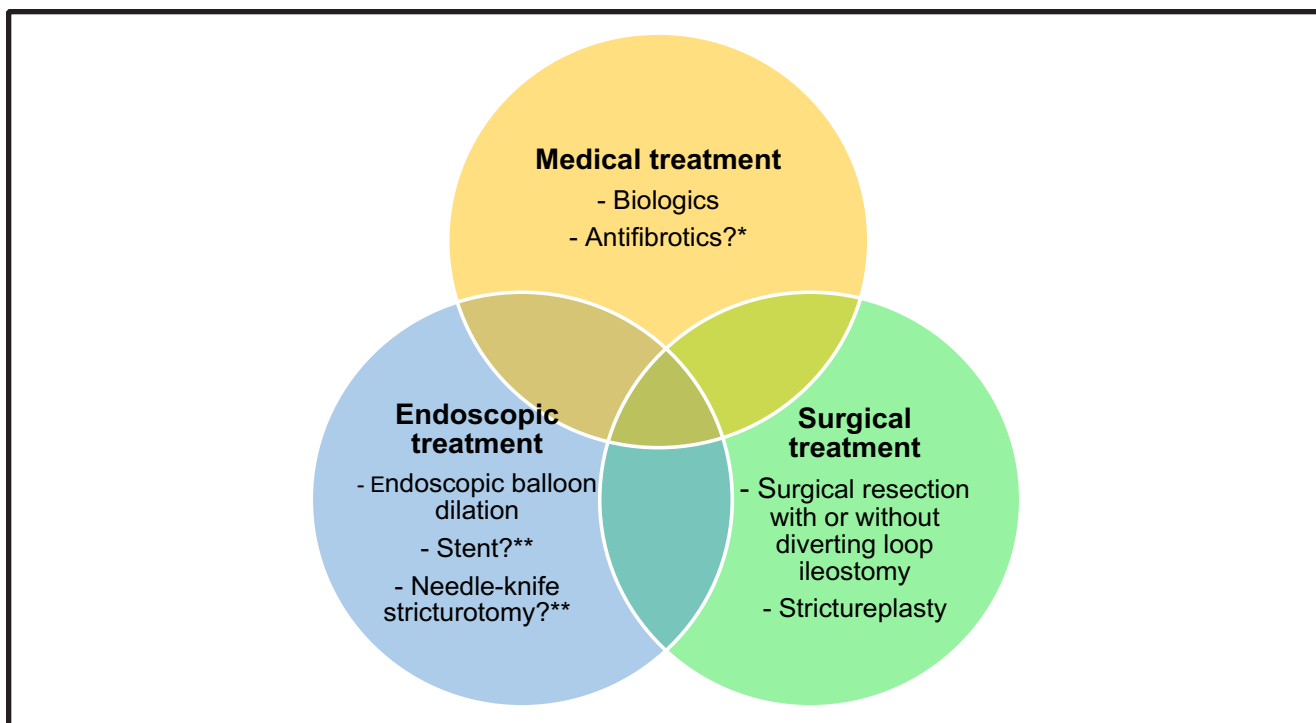


Figure 2. Overview of current and possible future treatment options in the management of Crohn's disease strictures.

**Currently being evaluated in randomized controlled trials **These techniques are not routinely used in clinical practice pending further safety and efficacy data*

medical, endoscopic and surgical options (Figure 2). Strictures are therefore best addressed in a multidisciplinary approach, with involvement from gastroenterologists, radiologists, surgeons and other IBD team members as needed. Ultimately, treatment will depend on stricture and disease characteristics, complications (fistula, abscess, etc.) and patient preference.

Acute small bowel obstruction

Patients with Crohn's disease presenting with a suspected acute small bowel obstruction (SBO) should be urgently assessed. Symptoms suggestive of an acute SBO include severe abdominal pain and distention, vomiting, high-pitched bowel sounds, along with inability to pass flatus and/or stool. Cross-sectional imaging should be obtained promptly in order to rule out complications such as perforation, fistulizing disease or abscess. Patients should be initially kept nil per os (NPO) and hydrated adequately. Nasogastric tube insertion might be necessary, particularly with recurrent vomiting or persistent obstruction.⁸

Serial imaging with abdominal x-rays should be obtained. Intravenous corticosteroids are widely used in such cases, despite limited evidence to support their use in this setting. In a small study, 25 out of 26 patients with CD with an acute SBO improved clinically at 72 hours.¹⁵ However, more than 70% of patients had recurrent obstruction during follow-up, highlighting the importance of a durable treatment strategy, as outlined below. In case of persistent obstruction, endoscopic balloon dilation or surgery may be required urgently.

Overview of treatment options in stricturing Crohn's disease

Medical therapy:

Immunomodulators have been evaluated in this setting. In a randomized controlled trial (RCT) of 72 patients with CD and ileal stricturing disease comparing mesalamine and azathioprine, the latter was found to be associated with a reduced rate of surgery and hospitalization during follow-up.¹⁶ Of note, methotrexate has never been evaluated

specifically for the treatment of strictures in Crohn's disease.

Anti-tumor necrosis factor (anti-TNF) agents have been widely used in the management of fibrostenosing CD. Most of the evidence supporting their use stems from retrospective and single-arm prospective studies.¹⁷ There is only very limited evidence on the use of non-anti-TNF drugs such as vedolizumab and ustekinumab in this setting and further data are awaited.

In a prospective single arm observational study (the "CREOLE" study) evaluating adalimumab treatment in patients with CD-associated small bowel strictures, drug persistence was 64% at 24 weeks and 29% at 4 years.¹⁸ About half of the cohort had surgery during the 4-year follow-up. Some of the predictors of adalimumab persistence were the use of immunomodulators at treatment onset, a high obstructive symptom score, pre-stenotic bowel dilation, stricture shorter than 12cm, obstructive symptom onset of less than 5 weeks at baseline, and the absence of underlying fistulas.

A systematic review of available studies evaluating systemic medical treatment in stricturing CD found a pooled rate of up to 28.3% (95% CI: 18.2%–41.3%) of patients requiring surgery over a median follow-up of 23 months.¹⁷

A recent open-label RCT from Australia compared an intensive high-dose adalimumab regimen combined with azathioprine with a "treat-to-target" approach to a standard adalimumab regimen in patients with intestinal CD strictures.¹⁹ Although rates of radiologic improvement on MRI as measured by the MaRIA score at 12 months were significantly higher in the intensive regimen arm, the improvement in obstructive symptoms was not statistically significant. In addition, surgery rates, intestinal ultrasound findings and biomarkers were not significantly different among the groups.¹⁹

Although these findings - in line with the above

literature - suggest a role for biologic treatment in stricturing disease, they do highlight the need for alternative and more effective treatment options in this setting. The problem may lie in the fact that once fibrosis is present, the damage may be "too far gone" for anti-inflammatory agents to help.^{10,11,20} Targeting intestinal fibrosis is a promising avenue and randomized controlled trials of antifibrotics are under way to help address this unmet need (National Clinical Trial registration number NCT05013385).

Endoscopic treatment

Endoscopic options are available for patients with persistent obstructive symptoms with strictures that are amenable to endoscopic interventions. Endoscopic balloon dilation (EBD) is the most established endoscopic intervention for strictures and involves dilating the stricture while inflating a through-the-scope balloon.⁸ This procedure can be performed in small bowel, colonic or upper gastrointestinal tract locations and in both naïve and anastomotic (postoperative) strictures. Strictures amenable to EBD should be endoscopically accessible, shorter than 5 cm and should never be associated with an underlying abscess, fistula or suspected malignancy. Technical success rates (i.e. successful dilation during endoscopy) are estimated to approach close to 90% while clinical efficacy rates (improvement in clinical symptoms) are around 80%.²¹ Complications are estimated to occur in 2.8% of patients and include fever, bleeding and perforation.²¹ Of note, a significant portion of patients (about 42% at 2 years) still require surgery given recurrent or persistent symptoms.²¹

Additional endoscopic techniques have been studied, including intralesional anti-TNF or corticosteroid injection into the stricture, stent insertion as well as needle-knife stricturotomy, which involves slicing open the stenotic area using an endoscopic knife. However, these have not yet been incorporated into routine clinical practice given limited safety and controlled efficacy data.²²

Surgery

Surgery is indicated in patients with persistent obstructive symptoms with strictures that are felt

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to be either not amenable or refractory to medical and/or endoscopic intervention,²³ as well as in cases where penetrating disease or malignancy are suspected. Several surgical options are available. Resection of the stenotic segment is the most commonly used procedure along with bowel anastomosis and possibly a temporary diverting loop ileostomy in certain cases.²³

Strictureplasty is another surgical option that involves widening of the narrowed area without resecting the affected segment. Given its bowel-sparing nature, strictureplasty is particularly helpful in patients with multiple prior surgical resections and at risk for short bowel syndrome, as well as in the setting of multifocal strictures separated by long segments of normal bowel.²³ Several types of strictureplasty techniques are used depending on the length of the stricture. Of note, since strictures are not resected and are left in situ, this procedure should be avoided in patients with suspected malignancy or dysplasia or any other complication such as perforation, penetrating disease or malnutrition.²³

Importantly, regardless of the selected surgical technique, preoperative nutritional status should be optimized and smoking cessation should be addressed to prevent complications and postoperative recurrence. Postoperatively, patients should be closely observed for disease recurrence and patients at high risk of recurrence should be started or continued on a biologic treatment with monitoring of their response.^{8,24,25}

Identifying patients at risk for intervention

The natural history of stricturing CD and factors associated with the need for endoscopic or surgical intervention have been studied but have remained poorly defined given heterogeneity of patient populations, the absence of a standardized definition of strictures, inclusion of patients with concomitant fistulizing disease or colonic strictures. In a recent well-defined US cohort looking at the disease course of established CD strictures as defined by the CONSTRUCT criteria,¹² stricture length, duration and obstructive symptoms were found to be independent and validated predictors for the need of intervention (combined endpoint of EBD and/or surgery).¹¹ In this cohort, 26% and

45% of patients required intervention at 1 and 4 years, respectively. An online risk calculator was developed to help clinicians estimate the need for intervention and thereby guide patient discussions and shared-decision making.¹¹ The calculator can be accessed at: riskcalc.org/CrohnsDiseaseSmallBowelStricture.

CONCLUSION

Stricturing disease is an important and common complication in patients with Crohn's disease. A combination of different treatment modalities are available including medical, endoscopic and surgical options. However, strictures are still a leading indication for surgery in CD, and the frequency of progression to stricturing complications has not been significantly altered over the last few years despite considerable advances in the medical treatment landscape. Important goals in the management of CD over the next few years will therefore be to attempt to target fibrosis through antifibrotics, but also ultimately to continue to work on preventing the development of fibrosis. The Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium, a group of experts in stricturing CD, have been working on determining appropriate endpoints and definitions in stricturing CD in order to help pave the way for further research and clinical trials of anti-fibrotic agents, which are under way. ■

References

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017;389(10080):1741-1755.
2. Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut*. 2019;68(3):423-433.
3. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV, Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology*. 2010;139(4):1147-1155.
4. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut*. 2013;62(7):1072-1084.
5. Frolkis AD, Lipton DS, Fiest KM, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. *Am J Gastroenterol*. 2014;109(11):1739-1748.
6. Fumery M, Pineton de Chambrun G, Stefanescu C, et al. Detection of Dysplasia or Cancer in 3.5% of Patients With Inflammatory Bowel Disease and Colonic Strictures. *Clin Gastroenterol Hepatol*. 2015;13(10):1770-1775.

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 e346.
8. El Ouali S, Click B, Holubar SD, Rieder F. Natural history, diagnosis and treatment approach to fibrostenosing Crohn's disease. *United European Gastroenterol J*. 2020;8(3):263-270.
9. Oberhuber G, Stangl PC, Vogelsang H, Schober E, Herbst F, Gasche C. Significant association of strictures and internal fistula formation in Crohn's disease. *Virchows Arch*. 2000;437(3):293-297.
10. Jeuring SF, van den Heuvel TR, Liu LY, 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.
11. El Ouali S, Baker ME, Lyu R, et al. Validation of stricture length, duration and obstructive symptoms as predictors for intervention in ileal stricturing Crohn's disease. *United European Gastroenterology Journal*. 2022;10(9):958-972.
12. 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.
13. 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.
14. Sleiman J, Chirra P, Gandhi NS, et al. Crohn's disease related strictures in cross-sectional imaging: More than meets the eye? *United European Gastroenterology Journal*. 2022;10(10):1167-1178.
15. Yaffe BH, Korelitz BI. Prognosis for nonoperative management of small-bowel obstruction in Crohn's disease. *J Clin Gastroenterol*. 1983;5(3):211-215.
16. de Souza GS, Vidigal FM, Chebli LA, et al. Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients. *Med Sci Monit*. 2013;19:716-722.
17. Lu C, Baraty B, Lee Robertson H, et al. Systematic review: medical therapy for fibrostenosing Crohn's disease. *Alimentary Pharmacology & Therapeutics*. 2020;51(12):1233-1246.
18. Bouhnik Y, Carbonnel F, Laharie D, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. *Gut*. 2018;67(1):53-60.
19. 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. *The Lancet Gastroenterology & Hepatology*. 2022;7(4):318-331.
20. Lazarev M, Ullman T, Schraut WH, Kip KE, Saul M, Regueiro M. Small bowel resection rates in Crohn's disease and the indication for surgery over time: experience from a large tertiary care center. *Inflamm Bowel Dis*. 2010;16(5):830-835.
21. 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 Stricture Crohn's Disease. *Inflamm Bowel Dis*. 2017;23(1):133-142.
22. Sleiman J, El Ouali S, Qazi T, et al. Prevention and Treatment of Stricture Crohn's Disease – Perspectives and Challenges. *Expert Review of Gastroenterology & Hepatology*. 2021;15(4):401-411.
23. Lightner AL, Vogel JD, Carmichael JC, et al. The American Society of Colon And Rectal Surgeons clinical practice guidelines for the surgical management of Crohn's disease. *Diseases of the Colon & Rectum*. 2020;63(8):1028-1052.
24. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99(4):956-963.
25. Regueiro M, Velayos F, Greer JB, et al. American Gastroenterological Association Institute technical review on the management of Crohn's disease after surgical resection. *Gastroenterology*. 2017;152(1):277-295. e273.

