Practical guidelines on endoscopic treatment for Crohn's disease strictures

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Title: **Practical Guideline on Endoscopic Therapy of Crohn's Disease Strictures: An Expert Consensus from the Global Interventional Inflammatory Bowel Disease Group**

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ABSTRACT

Stricture formation is the most common complication of Crohn's disease, resulting from the disease process, surgery, or medications.. Endoscopic balloon dilation plays an important role in the management of these strictures, with emerging techniques such as endoscopic electroincision and stenting. The underlying disease process, altered bowel anatomy from disease or surgery, and concurrent use of immunosuppressive medications can make these endoscopic procedures more challenging. An urgent need exists for the standardization of these procedures and peri-procedural management. The consensus group proposes detailed guidance in all aspects of principle and techniques for these procedures.

KEYWORDS

Balloon Dilation; Bleeding; Crohn's disease; Consensus; Electroincision; Guideline; Perforation; Stricture; Strictureplasty; Stricturotomy; Technique

ABBREVIATIONS

APAGE, the Asian Pacific Association of Gastroenterology; APSDE, the Asian Pacific Society for Digestive Endoscopy; ASGE, the American Society for Gastrointestinal Endoscopy; BSG, the British Society of Gastroenterology;; CO_2,carbon dioxide; CTE, computed tomography enterography; EBD, endoscopic balloon dilatation; EL, evidence level; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; ESGE, the European Society of Gastrointestinal Endoscopy; ET, endoscopic treatment; GA, general anesthesia; GI, gastrointestinal; GR, grade of recommendation; IBD, inflammatory bowel disease; MAC, monitored anesthesia care; MRE, magnetic resonance enterography; MRI,

magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; SEMS, self-expandable metallic stent; TNF, tumor necrosis factor ;

INTRODUCTION

The majority of patients with Crohn's disease eventually develop complications, including strictures, fistulas, abscesses, and colitis-associated neoplasia. Stricture formation is the most common complication, resulting from the underlying disease, surgical anastomosis or strictureplasty. In a population-based study in Olmsted County, MN, USA, 249 patients presented with inflammatory phenotype at diagnosis in the diagnosed between 1970 and 2004, the cumulative risk of developing a stricturing or penetrating intestinal complication was 19% at 90 days, 22% at 1 year, and 51% at 20 years after diagnosis.[1] Review of population-based cohort studies showed 56% to 81% of patients with CD presented with inflammatory phenotype, 5% to 24% with stricturing phenotype, and 4% to 23% with penetrating disease.[2]

For diagnosis, disease monitoring, and treatment, a comprehensive classification of inflammatory bowel disease (IBD)-related strictures, has been proposed, which is based on the etiology, clinical presentation, underlying and associated conditions, malignant potential, composition (inflammatory vs. fibrotic), length, location, degree, number, and complexity (**Table 1**).[3]

Early and effective medical therapy may delay or prevent the development of complications,while the role medical therapy for the management of fibrostenotic and anastomotic strictures is being explored.. Mechanical modalities of therapy are necessary in view of the structural nature of stricture. Bowel resection and strictureplasty are effective to treat primary or secondary (i.e. anastomotic) strictures. However, this invasive nature risks postoperative complications and disease recurrence, making surgical approaches a last resort. Alternative need to provide greater efficacy and durability than medical therapy, and lower cost and risks than

surgery. Endoscopic treatment (ET) with balloon dilation (EBD), electroincision, or stent placement have emerged as important options in the management of stricturing Crohn's disease.[4]

Endoscopic therapy for Crohn's disease can be technically challenging, due to underlying disease factors, anatomic alteration by disease or surgery, frequently in the setting of immunosuppression. A survey study of medical IBD specialists detailed considerable variation in practice of EBD.[5] Initial guidelines documented clinical efficacy, safety, and contraindications of EBD and concurrent use of corticosteroids or anti-tumor necrosis factor (TNF).[6] Standardization of the technical approaches to ET is needed.

METHODS

Perspectives

These consensus statements were developed to address the general and technical aspects of endoscopic management of Crohn's disease strictures.

Data source

The steering committee (B.S., G.K., U.N.) first performed a review of the medical l literature using relevant references for each statement. A systematic literature search of MEDLINE, Google Scholar, EMBASE (from 1999), and CENTRAL (Cochrane Central Register of Controlled Trials) was performed. Key search terms included Crohn's disease, inflammatory bowel disease, stenosis, stricture, obstruction, balloon dilation (dilatation), complications, bleeding, perforation, and procedure. Inclusion criteria were: (1) Crohn's disease with primary or secondary (i.e. anastomotic stricture) strictures; and (2) ET with EBD, electroincision, or stent placement. Published articles or abstracts for evaluation met the following criteria were: (1) case

series describing EBD must exceed 50 cases for lower gastrointestinal (GI) tract stricture, 25 cases for upper GI stricture, or 15 cases of stricture therapy for ileoscopy via stoma, pelvic pouches, or Kock pouches; (2) controlled studies describing EBD must exceed 20 cases; (3) case series describing endoscopic electroincision or stricturotomy mush exceed 15 cases; or (4) case series describing stent placement must exceed 5 cases. The most recent publications from serial authors were used. The lack of high-quality clinical trials, i.e. randomized controlled trials, in the endoscopic management of Crohn's disease-associated strictures, necessitated inclusion of expert opinions.

We adopted the Oxford Center for Evidence Medicine methodology to generate treatment recommendations (http://www.cebm.net/index.aspx?o=1025) (**Table 2**).

Consensus Process

The Delphi method guided the preparation of documents. The consensus group consisted of leading IBD experts, advanced endoscopists, gastrointestinal (GI) radiologists, and IBD surgeons. The initial questionnaire and statement were developed and circulated by the steering committee. A face-to-face consensus meeting with the first-round voting process was convened during the annual Digestive Disease Week in San Diego, CA, in May 2019, to conduct the first voting round. The participants voted anonymously on their agreement with the statements, provided comments and suggested revisions. The second round of web-based voting process for the revised documents was performed within a month of the face-to-face meeting. A statement was accepted if >80 % of participants agreed with the statement. The manuscript was drafted, reviewed, and approved by all members of the consensus group.

The guidelines were categorized based on published literature as well as consensus among expert participants in the group. The guidelines were organized in the following categories: pre-procedural preparation, balloon dilation, other ET modalities, post-procedure care, outcome measures, and damage controls.

Funding Source

The process was largely self-funded, with participants devoting time and efforts. A total of less than $10,000 of unrestricted grants were provided by Boston Scientific (Marlborough, MA, USA) and OVESCO (Cary, NC, USA), for the meeting space.

REPORTS

The consensus statements are listed in **Table 3**.

1. *PRE PROCEDURAL PREPARATION*

Prior to endoscopic intervention, or strictures, it is essential to delineate the number, severity, type (inflammatory vs. fibrotic), and length of strictures, and the presence or absence of associated conditions (fistulas or abscesses), or proximal disease (Recommendation **Table 3-1-1**).[7] Major published studies used pre-procedural cross-sectional imaging.[8,9,10,11,12,13, 14,15] CTE or MRE is generally considered to be more accurate to assess intraluminal, bowel wall, and extra-luminal structures than conventional computed tomography (CT) or conventional magnetic resonance imaging (MRI), although the true advantages of CTE or MRE over conventional CT or MRI are yet to be verified.[16] MRE with various techniques, such as diffusion-weighted and delayed enhancement is preferred, as MRE is the preferred technique to diagnose strictures and to

differentiate fibrotic from inflammatory components and to measure length of stricture.. [17] Ultrasound elasticity has been increasing been used for the evaluation of intestinal strictures, particularly in Europe and Australia.[17] Enteroclysis or contrast enemas via the anus or stoma provide dynamic images to delineate stricture characteristics. However, use of small bowel follow through or small bowel enteroclysis for Crohn's disease is waning. Three key components have been proposed for the detection of stricture, luminal narrowing, wall thickening, and prestenotic dilation.[17]Most Crohn's strictures are of mixed type and distinction between inflammatory and fibrotic stricture has been difficult with biomarkers, endoscopy, or histology.[6] The complexities in the management of Crohn's disease require multidisciplinary team approach, including GI radiologists, as well as IBD specialists, endoscopists, and colorectal surgeons.[18,19]

It is imperative that the bowel be optimally prepared via standard oral route to reduce procedure time and complication (Recommendation **Table 3-1-2**).[20] Unfortunately, scant data exist regarding the bowel preparation prior to ET for Crohn's disease.[12,21,22] Standard bowel preparation recommended [23,24] typically consists of polyethylene glycol-based regimen utilizing a balanced electrolyte solution and split dose regimen or equivalent approved preparations. Adequate bowel preparation is also critical to minimize electrocautery-associated colonic gas explosion.[25] Bowel preparation can be challenging in patients with bowel strictures. Prolonged preparation (i.e. more than 12 – 24 hours) or additional doses of the prep agent may be needed. Oral bowel preparation may be avoided in patients undergoing ileoscopy via stoma, lower GI endoscopy for diverted colon, diverted rectum, or ileal pouch.

Sedation is routinely used in IBD patients undergoing endoscopy procedures. Methods range from conscious sedation to general anesthesia (GA).[8,10,11,21, 26 , 27] Conscious sedation generally suffices in the most settings[8,26,27] Monitored anesthesia care (MAC) or GA should be

performed in the setting of significant comorbidities, or when contemplating prolonged procedure time for complex strictures, angulated or multiple strictures, or strictures in the deep small bowel (Recommendation **Table 3-1-3**).[15] The American Society of Anesthesiologists classification should guide sedation method, based on functional status.

The majority of ET procedures can be safely performed in an outpatient. A few studies report outpatient-based ET.[28,29] Anatomy altered by underlying disease process or surgery can present challenges during ET. For prolonged procedures, hospital admission may be preferred. Procedures on hospitalized patients or those at high risk for perforation may be performed in the operating room where immediate surgical backup is available (Recommendation **Table 3-1-4**).

Fluoroscopic may be needed in certain ET procedure in IBD patients..[21,30] Maintaining hydrostatic pressure and/or documenting waist obliteration by fluoroscopy portend a successful dilation when treating non-Crohn's disease strictures. However, the majority of therapeutic endoscopy procedures can be performed without on-site fluoroscopic guidance,[30] especially when pre-procedural abdominal imaging is available to guide ET. Complex strictures (as defined in **Table 1)**, angulated, long, or multiple strictures, or the presence of pre-stenotic luminal dilation, may benefit from onsite fluoroscopy, when bowel anatomy has been significantly altered by underlying disease or surgery (Recommendation **Table 3-1-5**).

The advantages of carbon dioxide (CO_2) insufflation are documented.[31] The use of CO_2 was reported in previous case-control studies in interventional IBD.[28,29,] Compared to room air, CO_2 insufflation reduces procedure-associated pain or discomfort, procedure time, post-procedural ileus, aspiration, and embolism (Recommendation **Table 3-1-6**).

The role of antibiotic prophylaxis in ET of Crohn's disease strictures has not been defined. Few studies reported the use of pre-procedural antibiotics.[8,26] ASGE guidelines regarding peri-

procedural antibiotic prophylaxis did not specify use of `its application in ET for Crohn's disease strictures.[32] The 2017 American Heart Association guidelines stated that the administration of prophylactic antibiotics to prevent infectious endocarditis was no longer recommended for patients undergoing GI endoscopy.[33] No published data exist on the frequency of bacteremia in Crohn's disease patients following EBD, endoscopic electroincision, or stenting, while the reported rate of bacteremia following esophageal bougie dilation ranged from 12% to 22%,[34,35,36] and declined to 6.3% after therapeutic colonoscopy procedures such as stent insertion.[37] Group consensus states that endoscopic intervention in immunocompromised patients, or in those with a central intravenous line, diverted colon, rectum, or ileal pouch may pose a risk for bacterial translocation; and therefore prophylactic antibiotics may be useful (**Figure 1**) (Recommendation **Table 3-1-7**).

The use of topically (i.e. budesonide) and systemically active corticosteroids was mentioned in the majority of cited studies.[8,9,10,11,13,14,15,28,29,30] However, the impact of steroid use on efficacy and adverse events was not specified in those studies. IBD patients undergoing colonoscopy, especially EBD, exhibited a higher risk for procedure-associated perforation than non-IBD or non-intervention controls.[38] Current surgical literature suggests that high dose of systemic corticosteroids may attenuate systemic inflammatory responses, improve pulmonary function, and increase postoperative pain control without increasing infections or wound dehiscence.[39,40,41] However, corticosteroids, especially when combined with other immunosuppressive agents, may increase postoperative complication risk in ulcerative colitis and Crohn's disease.[42,43,44,45] Systemic steroid use has been implicated with a higher risk for procedure-associated complications in patients undergoing diagnostic or therapeutic endoscopy.[46] Perforation occurring in steroid users may increase risk of bowel resection, intensive care unit admission, or need for stoma.[47]

Steroid avoidance, discontinuation, or tapering in patients undergoing therapeutic endoscopy remains controversial. Surgical literature covering Crohn's disease management defines high-dose steroid use as taking more than 20 mg prednisone-equivalents for ≥ 6 weeks.[48] While this definition may be applied in interventional IBD, the group did not reach consensus for either dose or duration of pre-procedural systemic steroid use precluding ET in Crohn's disease patients. The absence of guidelines regarding steroid use before colorectal surgery also impacts diagnostic or therapeutic endoscopy. The consensus group believes that ET in IBD is generally less invasive than surgery and therefore steroid use imparts a lower risk. Nonetheless, the group agreed that systemic steroid therapy heightens risk of procedure-associated complications or adverse events of bowel resection and a diverting ostomy for perforation. The group suggests that endoscopists balance risks and benefits of ET procedure if a patient take ≥ 20 mg prednisone equivalent and taper steroids prior to elective ET, if possible (Recommendation **Table 3-1-8**).

Concurrent or prior use of biological agents ranged from 5.6% to 86.3% patients.[8,9,10,11,14,15,21,22,26,28,29,30,47] No published data exist associating the efficacy or adverse events of EBD with concurrent biological agent use (Recommendation **Table 3-1-9**).

Bleeding is a significant complication for ET in Crohn's disease. Fortunately, ET procedures for Crohn's disease are elective; and urgent ET is not recommended. In summary, aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may be continued for EBD or stent placement; warfarin should be discontinued for at least 5 days prior to EBD, electroincision, or stent placement; and thienopyridines should be held for at least 5 days (Recommendation **Table 3-1-10**). Detailed information on the use antithrombotics in GI endoscopy and relevant society guides are listed in **Supplement.**

2. *BALLOON DILATION*

Stricture is generally defined as the narrowing of the lumen of GI tract. Luminal narrowing that prevents the non-resistant passage of an endoscope indicate a clinically significant stricture. Proper categorization of Crohn's disease strictures is important for the delivery of proper ET. The consensus group has proposed a classification system to categorize IBD-strictures (**Table 1**).[3]

Strictures may be found incidentally in asymptomatic patients on abdominal imaging or endoscopy. It is controversial whether asymptomatic patients with incidental strictures need to be treated endoscopically. Some only treated symptomatic strictures,[9,10,11,12,13,27,30] while others treated both symptomatic and asymptomatic patients.[8,21,26,28,29] The rationale offered for treating asymptomatic patients is that symptomatology is not necessarily correlated with the objective finding of strictures on imaging or on endoscopy;[49] treatment of asymptomatic strictures may help defer or prevent the development of symptomatic strictures, and evaluate postoperative recurrence after resection and anastomosis or neoplasia in the bowel proximal to the stricture. Symptomatic strictures demonstrated worse response to EBD and a higher risk for subsequent surgery.[50] Incidentally found strictures may impact the severity of disease courses, leading to acute partial small bowel obstruction and formation of pre-stenotic dilation or fistula/abscess. Later ET may not be feasible. Lack of pre-procedural imaging should not preclude ET of the incidental strictures (Recommendation **Table 3-2-1**).

Endoscope preference varies among endoscopists. Light-weight endoscopes would assist with scope maneuverability, maintaining scope orientation, and fatigue reduction (Recommendation **Table 3-2-2**). Gastroscopes are routinely used to treat patients with strictures at the upper GI tract,[15] conventional ileostomies,[51] continent ileostomies,[52] or ileoanal pouches.[53]

Graded dilation is recommended for the index or initial EBD to reduce the risk of bleeding and perforation. Various definitions of "graded dilation" have been used in the current literature.[8,9,10,11,13,14,15,21,22,26,28,29] Graded dilation is normally performed with controlled radial expansion balloons, with inflation and partial or complete deflation in between each size. Inspection of the balloon-treated area should be taken after each dilatation. A goal of the size 18-20 mm should pursued, as shown in foundational studies, even with multiple sessions of ET (Recommendation **Table 3-2-3**).[8,9,10,11,15,21,22,26,27,28,29,30]

The efficacy of EBD may be tied with balloon size employed,[14] although a pooled analysis failed to correlate balloon size and surgery-free survival. [54] No literature exists correlating balloon size and complication risk, but the consensus group cautioned that balloon size may yet impact procedure-associated complication risks. Therefore, the consensus group recommends that the integrated guide wire should be advanced beyond balloon tip for the duration of insufflation. This technique is particularly useful for high-grade, angulated, and tight strictures (**Figure 2**) (Recommendation **Table 3-2-4**). It is imperative for the endoscopist to secure the position of the balloon, as the balloon tends to slip forward (**Figure 3**). Retrograde dilation is preferred over antegrade dilation, if the stricture is initially traversable (Recommendation **Table 3-2-5**). Disagreement exists regarding optimal duration of balloon insufflation due to a lack of evidence on which to base this recommendation. No special recommendation was provided from the group (Recommendation **Table 3-2-6**). The consensus group supported taking a second look at the treated stricture after EBD, to ascertain the degree of tearing, to assess disease status of the proximal bowel, and to evaluate bleeding or perforation in which case rescue therapy should be delivered (**Figure 3; Figure 7**) (Recommendation **Table 3-2-7**). Additionally, attempts traverse the treated stricture should be made in order. Direct through-the-balloon visualization to detect endoscopic

tearing during balloon dilation is suggested (Recommendation **Table 3-2-8**). More detailed information regarding EBD techniques please see attached **Supplement.**

EBD is efficacious and safe in primary or anastomotic strictures < 4 – 5 cm in length (Recommendation **Table 3-3-9**). The length of the stricture can be measured with endoscopy or imaging (**Figure 4** and **Figure 5**). The threshold for dividing short vs. long strictures has been defined at 4-5 cm.[15,29,54,**Error! Bookmark not defined.**,55] Current literature suggests that EBD efficacy decreases being when treating strictures > 4-5 cm, without impacting procedure-associated complications.[29] Every 1 cm increase in stricture length increases the need for surgery by 8%.[54] Despite these findings, the endoscopist may still attempt EBD. Patients with poor immediate response or lack of long-term efficacy may benefit from alternative endoscopic therapy (e.g. electroincision) or surgery. A short interval between endoscopic interventions predicts an imminent need for surgical intervention.[29]

EBD is more efficacious and safe for a small number of strictures (< 4) in a close proximity (Recommendation **Table 3-3-10**). EBD should be avoided for strictures with deep ulcerations (Recommendation **Table 3-3-11**). Few reported results of EBD for multiple strictures.[11,13,22,26,28,29,30] EBD of multiple strictures in the ileocolonic segment (>3) performed poorly and often required surgical resolution.[56] The consensus group speculates that multiple strictures in a *short* segment of bowel may benefit more from surgical resection and anastomosis or stricturoplasty. These cases often involve angulation of the stenotic bowel, increasing procedural difficulty and attendant perforation risks. However, EBD may be attempted when multiple strictures are present in a *long* segment of bowel, such as concurrent strictures in the terminal ileum, ileocecal valve, and distal rectum.

The presence of inflammatory activity on the stenotic segment and concomitant use of anti-inflammatory agents do not appear to impact efficacy of EBD efficacny.[10] But the impact of ulceration in stricture on EBD is unknown. The consensus group presumes that deep ulcers in strictures suggests active inflammation, which may indicate a higher risk for EBD-associated perforation[38] or bleeding (**Figure 6**) (Recommendation **Table 3-2-11**). However, superficial ulceration in strictures should not preclude EBD.

The presence of prestenotic luminal dilation indicates a long-standing disease or high-grade stenosis, raising the possibility of a poor response to EBD (**Figure 5**) (Recommendation **Table 3-2-12**). In Crohn's disease, patients with ileocolonic anastomosis strictures with prestenotic dilation demonstrated poor responses to EBD,[28,50]although this may not hold for Crohn's disease strictures in the upper GI tract.**Error! Bookmark not defined.**

Patients with concurrent fistula or abscess (except in the case of perianal abscess) were excluded for undergoing EBD in large case series.[12,13,21,27,28,29] EBD of strictures in this setting could theoretically disrupt of nearby fistula track or abscess, causing bowel perforation. Therefore, EBD is not recommended in this setting (Recommendation **Table 3-2-13**).

Neoplasia associated with chronic inflammatory disease in Crohn's disease can present within strictures, although ulcerative colitis-associated strictures harbor neoplasia more commonly than Crohn's disease. Cumulative frequency of Crohn's disease-associated neoplasia ranged from 1.2% to 6.4%.[57,58,59,60,61,62,63] The risk appears to be the highest in the anal strictures, followed by rectal strictures, then colon and small bowel strictures, respectively (**Figure 8**). Crohn's disease-associated colorectal cancer presents at more advanced stages than ulcerative colitis-associated cancer.[63] Few studies of Crohn's disease strictures describe the use of tissue biopsy during EBD.[21] The role biopsy plays in determining inflammatory vs. fibrotic nature is unclear. Nonetheless, the

consensus group recommends that endoscopic biopsy of primary or anastomotic strictures should be conducted after undertaking EBD or other measures before completing the treatment session (Recommendation **Table 3-2-14**).

Therapeutic role of intralesional injection of corticosteroid adjunct to EBD is not clear. Two small randomized clinical trials provide conflicting results regarding benefits of intralesional injection of long-acting corticosteroids and outcomes of EBD.[12,64,65] Intralesional steroid injection during EBD has also been reported in multiple case series, case-control studies,[26,28,29,30] a metaanalysis,[65] and a pooled analysis.[54] Consensus opinion holds that the intralesional injection of long-acting corticosteroids offers no additional benefit to EBD. The risk added by intralesional steroid injection after EBD is unknown increases EBD-associated complications is not known. At this point, the consensus group recommends against routine use of intralesional injection (Recommendation **Table 3-2-15**).

Several case series report on efficacy and feasibility of intralesional anti-TNF injection for stricture treatment.[66,67,68,69] Currently, the consensus group has no recommendation regarding this practice pending further studies (Recommendation **Table 3-2-16**).

3. *OTHER ENDOSCOPIC TREATMENT MODALITIES*

The past decade has witnessed an emerging role of endoscopic electroincision and stent placement for managing primary and anastomotic Crohn's disease strictures.[3,70,71,72] The consensus group endorses efforts to standardize the terminology. Current publications were from few tertiary-care center. These techniques need to perfection and their routine application requires training of the endoscopist.

Endoscopic stricture electroincision in the treatment of stricturing lesions involves opening or removing strictured tissue with electrocautery. Electroincision can be performed in either radial, circumferential, or horizontal orientations (**Figure 9**). Incisions progressively widen the stenotic bowel lumen, hence, the term endoscopic stricturotomy. Selected strictures may benefit from endoscopic clipping after endoscopic stricturotomy, to enhance the short- and long- term luminal efficacy. Short-length (0.5 – 1.5 cm) strictures undergoing radial or horizontal stricturotomy may also be treated with endoscopic clipping after the incision with clips serving as spacers. Endoscopic clipping involves application of through-the-scope clips to the edges of electroincised strictures, in a fashion resembling surgical stricturoplasty. The technique used in endoscopic electroincision defines to its categorization into either (1) stricturotomy, i.e. widening of the stenotic lumen of the GI tract by incision alone; or (2) strictureplasty, i.e. widening of the stenotic lumen of the GI tract by incision, assessed by endoscopic clipping (**Figure 9**) (Recommendation **Table 3-3-1**). Information on techniques of endoscopic electroincision in Crohn's disease strictures is listed in **Supplement.**

The role of endoscopic stricturotomy or strictureplasty has yet to be defined. In the current literature, 23-50% of Crohn's disease patients with primary or anastomotic strictures who underwent endoscopic stricturotomy or strictureplasty had been previously treated with EBD.[29,70] Endoscopic stricturotomy and stricturoplasty appear to be more effective than EBD in treating ileocolonic anastomotic strictures in Crohn's disease. Endoscopic electroincision may be particularly useful for fibrotic, anastomotic, or anal or distal bowel strictures (Recommendation **Table 3-3-2**). While endoscopic electroincision provides greater efficacy than EBD and a lower perforation risk, it can cause delayed bleeding.[29,70,71,72] Bleeding typically results from a

protuberant vessel in the ulcer created by electrocautery. These technically challenging procedures should be performed by expert endoscopists.

The consensus group agreed that endoscopic electroincision is particularly applicable to the treatment of anorectal strictures in Crohn's disease (Recommendation **Table 3-3-3**). Compared with bougie or balloon dilation, circumferential stricturotomy at the posterior wall of the strictures allows for precise control of orientation (parallel to anal sphincters), depth, and location of the ablation. Electroincision may reduce the risk of anal sphincter damage or iatrogenic vaginal fistula seen EBD or bougie dilation (**Figure 10**). Electroincision may be conducted with various knives using a power setting of endoscopic retrograde cholangiopancreatography (ERCP) Endocut (Recommendation **Table 3-3-4**).

Endoscopic stenting has been used to treat both benign and malignant strictures in the lower GI tract. Due to its questionable sustain efficacy and safety concern, the role of endoscopic stent is yet to be defined (Recommendation **Table 3-3-5**). More information on endoscopic stent please see attached **Supplement**.

4. *POST-PROCEDURE CONSIDERATION*

Patients undergoing EBD or endoscopic electroincision should be considered at risk for developing procedure-associated complications. In addition to heightened procedural precautions, equal attention must be devoted to post-procedural care. If any concern for adverse events exists, the patient should undergo clinical and radiographic evaluation (Recommendation **Table 3-4-1**). Extreme precautions should be taken for monitoring and early intervention for procedure-associated perforation. Intra- and post- procedure intravenous antibiotics should be administered to patients with suspected or at risk for perforation (Recommendation **Table 3-4-2**).

Most patients undergoing endoscopic stricture therapy require repeat interventions.[8,9,10,11,13,14,15,21,22,28,29,50,56,65,70,71,72] Defining risk factors that predict the need for endoscopy re-intervention or surgical intervention may identify patients requiring more frequent ET. The following items may identify the need for early follow-up endoscopy: (1) failure to achieve dilation goal (e.g. size of balloon or improvement in symptom) at initial endoscopy;[29] (2) smoking;[27] (3) multiple [56] or long[54] strictures; (4) strictures in the duodenum, jejunum, or proximal ileum;[54,65] (5) strictures with prestenotic luminal dilation;[28,29,50] (6) short intervals between endoscopic interventions;[50] and (7) a short interval from the disease diagnosis to need for intervention.[29,50]

In addition to following symptoms, endoscopic assessment of treatment response is often needed. Therefore, the consensus group suggests that all patients receiving ET undergo follow up endoscopy within a year to monitor treatment response and deliver repeat treatment, if needed. The presence of risk factors for poor response or stricture recurrence should prompt a shorter follow-up interval (Recommendation **Table 3-4-3**)

5. *OUTCOME MEASURES*

The consensus group believe that there is a need for performance measures in therapeutic endoscopic in IBD, similar to general endoscopy.[73] In addition to rate of quality bowel preparation, rate of intubation of the targeted segment of the bowel, and patient experience, short- and long-term efficacy and safety should be measured.

One of the goals of ET for strictures is the successful passage of the endoscope through the area of luminal narrowing after treatment. However, current reports loosely define “technical or immediate success” as the passage of the endoscope after EBD, endoscopic stricturotomy, or

endoscopic strictureplasty.[8,9,10,11,13,15,22,26,27,28,29,30,54] This implies that all strictures were not endoscopically traversable prior to ET, and left out the class of strictures which were traversed, but with resistance. These still need treatment. Thus, the term "traversable" needs fine-tuning. The consensus group suggests that the term "traversable to the scope" indicates passage of a pediatric colonoscope. Otherwise, the endoscopist must specify the type of scope used to traverse the lesion (i.e. gastroscope or adult colonoscope) (Recommendation **Table 3-5-1**).

Various measurements have been used for reporting outcomes of ET for Crohn's disease strictures. Endoscopic intervention-free survival and surgery-free survival have been most commonly used.[8,9,10,11,12,14,15,21,26,27,28,29,30,70,71,72] Other outcome measures include stricture-associated emergency department visits or hospitalization.[28,29]

Long-term efficacy of endoscopic therapy is defined as surgery free-survival for 1 year after any endoscopic treatment (Recommendation **Table 3-5-2**). The one-year surgery-free survival is not a perfect criterion. Symptoms correlate poorly with objective findings in stricturing Crohn's disease. Additionally, the threshold for surgical intervention varies according to patient, treating physician, and surgeon preferences. It appears that severity of stricture at the index EBD may affect the subsequent need of additional EBD.[30] It should also be pointed out that persistent symptoms in a patient who avoids an operation within one year) does not define a successful ET, and *vice versa*.

6. *PROCEDURE-ASSOCIATED ADVERSE EVENTS AND THEIR MANAGEMENT*

Mild intraluminal bleeding often occurs after applying mechanical force (e.g. balloon dilation) or electric power (e.g. stricturotomy and strictureplasty) to tissue. Inspection for bleeding during the delivery of ET should be mandatory. Patients undergoing therapeutic endoscopy

procedures may be placed on a clear liquid diet for 12-24 hours after recovery from sedation or general anesthesia, in case endoscopic re-intervention is needed to control bleeding or perforation. In most cases, mild bleeding will cease spontaneously. Significant intra-procedure bleeding is defined as the presence of associated hemodynamically instability (Recommendation **Table 3-6-1**). Significant post-procedure bleeding has been defined as hemorrhage requiring blood [74] transfusion.[28,29,51,52,53,56, 75] (Recommendation **Table 3-6-2**) Patients undergoing endoscopic electroincision may carry a higher risk for delayed bleeding.[28,29,52,56,70,70,72] In most cases of significant post-procedure bleeding, repeat endoscopy is needed to evaluate bleeding source and deliver endoscopic hemostasis, supplementary to fluid resuscitation and blood transfusion.

Intra-procedure bleeding or delayed-onset bleeding can be associated with EBD or electroincision. In most cases, intra- and post- procedure bleeding can be controlled by endoscopic clips, mechanical pressure, or epinephrine or hypertonic glucose injection or spray at the site (Recommendation **Table 3-6-3**). In rare cases, angiography with embolization or surgery may be needed. Patients with significant intra-procedure bleeding should be closely monitored and observed. Unfortunately, there is limited literature on the endoscopic management of the procedure-associated bleeding and perforation (**Figure 11**).

Clear liquid diet for 12-24 hours may be considered after the therapeutic endoscopic intervention (Recommendation **Table 3-6-4**). Patients with suspected perforation and/or frank perforation should be considered as a medical emergency. Urgent evaluation and surgical consult should be obtained (Recommendation **Table 3-6-5**). Intra-procedure perforation recognized at the time of endoscopy may benefit from endoscopic interventions to close the defect (Recommendation **Table 3-6-6**). Endoscopic maneuvers may be attempted to close the defect for any intra-procedure perforation recognized at the time of endoscopy (Recommendation **Table 3-**

6-7). Information on endoscopic management of procedure-associated bleeding and perforation is listed **Supplement**.

SUMMARY

We are witnessing the emergence of interventional endoscopy in IBD, particularly ET of strictures of Crohn's disease as a major treatment modality. The goals of ET are to relieve obstruction and symptoms, delay or prevent surgery, preserve bowel by reducing surgeries, and improve patients' quality of life. A multidisciplinary approach requires a team of IBD specialists, IBD interventionalists, colorectal surgeons, nutritionists, GI radiologists, and GI pathologists to manage complex IBD, including stricturing Crohn's disease. The lack of high-quality data, e.g. large randomized controlled trials, has prevented this consensus group from making strong (**GR-A**) recommendations. However, the available data and \vast experience of the participants provide a sound foundation for this technical guideline, which is the first step in standardizing and individualizing the treatment of strictures in patients with Crohn's disease.

FIGURE LEGENDS

Figure 1. Literature and inclusion.

Figure 2. Fecal diversion-associated distal rectum stricture and inflammation in a patient with ileostomy. **A.** Pinhole stricture at the distal rectum (Green Arrow) was treated with endoscopic stricturotomy; **B.** Severe diversion proctitis with friable mucosa, which is prone to bacterial translocation with the endoscopic therapy.

Figure 3. Retrograde and antegrade balloon dilation of distal ileum strictures. **A & B.** Retrograde dilation with first passage of endoscope through the stricture, introduction of balloon sheath and guide wire, withdrawal of endoscope and anchoring of balloon across the stricture, and insufflate the balloon; **C & D.** Antegrade dilation with sequential introduction of balloon sheath and guidewire, exchange of the wire with sheath, and insufflation of balloon, and passage of endoscope through the treated stricture.

Figure 4. Through-the-balloon direct visualization during dilation. **A.** Disruption of bowel wall seen through the balloon (Green Arrow); **B.** Post-dilation inspection of balloon-dilated stricture showing a deep tearing.

Figure 5. Post-balloon dilation inspection of the proximal bowel. **A & B.** Balloon dilation of an ileal stricture; **C.** Large ulcers in the proximal bowel; **D.** A fecal bezoar in the lumen of the proximal bowel.

Figure 6. Short terminal ileum stricture. **A & B.** Non-ulcerated stricture with normal bowel proximal to the stricture; **C.** The short stricture on CTE.

Figure 7. Long-terminal ileum stricture. **A & B.** Non-ulcerated, mixed inflammatory and fibrotic stricture with prestenotic luminal dilation; **C.** The long stricture on CTE.

Figure 8. Ulcerated strictures. **A & B.** Ileocolonic anastomosis stricture with superficial ulcers, which was treated with balloon dilation; **C & D.** Ileal stricture with deep ulceration, which was treated with balloon dilation, resulting in significant bleeding.

Figure 9. Crohn's disease-associated cancer. **A & B.** Anorectal malignant strictures (adenocarcinoma) in two patients with long-standing Crohn's disease.

Figure 10. Endoscopic stricturotomy and strictureplasty. **A.** Endoscopic electroincision of an ileorectal anastomosis stricture (stricturotomy); **B.** Endoscopic electroincision of an ileocolonic anastomosis stricture followed by the placement of endoclips to facilitate the maintenance of luminal patency (strictureplasty).

Figure 11. Electroincision of anal stricture in Crohn's disease. **A.** Tight anal stricture; **B.** Status post treatment with insulated-tip knife endoscopic stricturotomy.

Figure 12. Endoscopy balloon dilation-associated bleeding and control. **A & B.** Bleeding after balloon dilation of ileocolonic anastomosis stricture, which was controlled by the deployment of endoclips; **C & D.** Bleeding after balloon dilation of an ileal stricture, which was controlled by spray of 50% dextrose.

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