Endoscopic therapy in inflammatory bowel diseases (with videos) CME

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Crohn's disease (CD) and ulcerative colitis (UC) are the 2 most common forms of inflammatory bowel disease (IBD). The Montreal Classification System divides CD into nonstricturing/nonpenetrating (B1), stricturing (B2), and penetrating (B3), based on clinical behavior.[1] It is generally believed that stricturing disease develops from prolonged inflammation. CD-related strictures often lead to significant morbidities such as bowel obstruction and the development of fistulas. In contrast, UC is primarily characterized by the extent of colonic involvement with categories, including extensive colitis, left-sided colitis, and proctitis.[2] UC can also be associated with strictures because of cancer,[3] muscularis mucosa hyperplasia,[4] and submucosal fibrosis related to inflammatory cell infiltration.[5]

CD- or UC-associated benign strictures have been treated by medical, endoscopic, and surgical modalities. Patients with strictures who have predominantly active inflammation may be treated with anti–tumor necrosis factor biologics[6] or steroids. However, medical management has a limited role in predominantly fibrotic strictures. It is believed that mechanical strictures need to be managed mainly in mechanical ways, such as by endoscopic or surgical therapy. Of endoscopic therapy for stricturing disease, through-the-scope (TTS) balloon dilation of benign strictures has been studied the most, and this modality has been shown to be effective, particularly for strictures at the surgical anastomosis, colon, or small bowel no more than 4-7 cm in length.[7] Surgical options for these strictures include intestinal resection with anastomosis or stricturoplasty.[8] The choice between endoscopic and surgical therapy depends on the disease course, characteristics of strictures, concurrent IBD-associated adverse events (such as abscesses), medical comorbidities, and local expertise. The advantages and disadvantages of endoscopic versus surgical therapy for IBD benign strictures are listed in Table 1.

Surgical therapy, although effective in IBD-related strictures, has inherent invasiveness and a high frequency of adverse sequelae and disease recurrence. Anastomotic leaks and fistulas are common in IBD patients who undergo surgery. A systemic review by Yamamoto et al[9] noted a 4% rate of post-IBD surgery septic adverse events, including leaks, fistulas, and abscesses. In addition, surgical therapies for both CD and UC are often associated with subsequent strictures at anastomosis sites. Rutgeerts et al[10] reported that strictures occurred at the surgical anastomosis or neoterminal ileum in 46% of patients after surgical intervention for CD. Anastomotic strictures between the ileal pouch body and anal transitional zone have been reported to occur in 10% to 40% of patients after restorative proctocolectomy for UC.[11] These anastomotic strictures are believed to occur because of perioperative reduced vascular flow, bacterial stasis, and high pressure within the intestine.[12] Anastomotic strictures tend to recur, even after surgical resection and reanastomosis or stricturoplasty.[12] For example, a recent study by Wu et al[13] found that among groups of patients who underwent surgical stricturoplasty (N = 16) versus endoscopic dilation (N = 151) of their ileal pouch strictures, there were similar rates of stricture recurrence (56.3% vs 55.0%) after a mean follow-up of 4.1 years. These findings suggest that endoscopic balloon dilation is an effective alternative to surgical intervention.

Despite advances in the diagnosis and management of IBD-related strictures, there is a gap in our knowledge in regard to a structured classification and management of these strictures. Here, we evaluate the current literature in the diagnosis and management of IBD-associated strictures and other adverse events, and with our experience in a tertiary center, we propose a classification system and management algorithm.

IBD-RELATED STRICTURES

A stricture is defined as an abnormal area of narrowing of the intestinal lumen. A stricture can cause a spectrum

Abbreviations: CD, Crohn's disease; CTE, CT enterography; EMR, endoscopic mucosal resection; EUA, exam under anesthesia; GGE, gastrografin enema; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; MRE, magnetic resonance enterography; SEMS, self-expandable metal stent; TTS, through-the-scope; UC, ulcerative colitis.

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TABLE 1. Comparison of endoscopic and surgical therapy for IBD benign strictures

	Endoscopy	Surgery
Invasiveness	+/−	+++
Short-term efficacy	++	+++
Short-term recurrence	++	+/−
Long-term recurrence	+++	+++
Adverse events	+	++

IBD, Inflammatory bowel disease; +, denotes that this therapeutic option has this characteristic; −, denotes that this therapeutic option does not have this characteristic.

of narrowing, from subtle to complete obstruction. The diagnosis of a stricture is usually made by the evaluation of imaging or endoscopy. The main advantage of endoscopic evaluation of a stricture is the ability to obtain tissue samples for histologic assessment and to deliver therapy at the time of the diagnosis. However, abdominal and pelvic imaging is recommended before diagnostic/therapeutic endoscopy to provide the "roadmap" (eg, location, number, and length of strictures).

Diagnosis of strictures

Imaging is essential in the diagnosis of IBD-related strictures. The modalities commonly used to identify strictures include CT enterography (CTE), magnetic resonance enterography (MRE), transabdominal US, small intestinal contrast US, EUS, small bowel follow-through, and water-soluble contrasted gastrografin enema (GGE).

CTE is an important tool in the assessment of small and large bowel disease. This modality is noninvasive, commonly available, and easy to perform, but it requires intravenous contrast and exposes patients to excessive ionizing radiation.[14] The CTE appearance of active CD includes fat stranding, mucosal hyperenhancement, vasa recta engorgement, transmural inflammation, lymphadenopathy, and abscess or fistula.[15] Fibrostenotic disease on CTE has been defined by the presence of narrowing of the intestinal lumen without active inflammation.[15]

MRE is another form of imaging commonly used in the assessment of small and large bowel CD with particular utility for distinguishing between fibrostenotic and active disease. Fibrostenotic disease on MRE appears as creeping fat without mesenteric vascularity or abscess and with mild mural thickness and enhancement.[16] Active disease on MRE appears as mucosal and submucosal edema, engorged vasa recta, mural stratification, and mural enhancement with increased mural thickness as compared with fibrostenotic disease.[16] MRE can distinguish inflammatory strictures from fibrotic strictures. For example, a low intensity on T1 and T2 sequences is characteristic of chronic fibrotic strictures, and a high intensity on fat-suppressed T2 images is a feature of inflammatory edematous strictures.[17]

Various forms of US modalities have been investigated for the diagnosis and differential diagnosis of IBD-related strictures. Transabdominal US and small intestinal contrast US can be used to detect small bowel strictures in CD. In 1 study,[18] transabdominal US was shown to have a sensitivity of 76% in the diagnosis of at least 1 stricture and a sensitivity of 50% in detecting prestenotic luminal dilation; in the same study, small intestinal contrast US had a sensitivity of 94% in the assessment of at least 1 stricture and a sensitivity of 100% in the detection of prestenotic luminal dilation.[18] Despite the high sensitivity, these US techniques are operator-dependent, with the quality of the studies largely influenced by the experience and technical precision of the operator.

Small bowel follow-through, or small bowel enteroclysis, involves the use of orally ingested barium followed by fluoroscopic imaging. The main advantage of this technique is its ability to provide a dynamic picture of the small bowel stricture (rather than the static picture seen on CTE or MRE), which helps to differentiate strictured versus collapsed or peristaltic bowel. In addition, the technique allows for the assessment of functional stenosis as well as peristalsis.[19] However, the modality predisposes the patient to excessive ionizing radiation and is not useful in identifying extraluminal pathologies such as abscesses.[20] Small bowel follow-through is also inaccurate for distinguishing between edematous versus fibrotic strictures, and imaging quality is operator-dependent.[21] For those reasons, small bowel follow-through and small bowel enteroclysis have largely been replaced by CTE or MRE in the diagnostic evaluation of IBD.

GGE is commonly used to assess for distal colonic strictures or fistulas, for ileal pouch-anal anastomosis (IPAA) adverse events including strictures and anastomotic leaks, and for abnormalities at the neoterminal ileum in patients with stomas. It is useful in the detection of the number and length of strictures and their conditions. This radiographic study has been shown to have a sensitivity of 100% in the detection of pouch-anal anastomotic strictures when an anastomotic diameter of no more than 8 mm is used for diagnosis.[22] In addition, GGE has been shown to have a sensitivity of 80% and specificity of 95% for inlet and distal small bowel strictures with a specificity of 93% for outlet strictures in patients with IPAA.[23]

Classification of strictures

Although various studies report some endoscopic characteristics of strictures, no uniform classification of IBD strictures is available in current literature. Strictures have been described by the intestinal location and length in centimeters, by the number of strictures,[24-28] and by the presence of luminal angulation.[27] Van Assche et al[27] classified short strictures as having a maximal length of 5 cm. Here, we propose a comprehensive classification system

TABLE 2. Proposed classification of strictures in inflammatory bowel disease

Criteria	Classification
Etiology	Primary vs secondary (anastomotic); benign vs malignant
Number	Single vs multiple
Degree	High-grade vs low-grade
Shape	Web-like vs spindle-shaped; circumferential vs asymmetric
Length	Short vs long
Location	Esophagus, pylorus, small bowel, ileocecal valve anastomosis, colon, rectum, anus
Associated conditions	Fibrosis, edema, proximal dilation, ulceration, fistula with or without abscess, angulated, prior stricturoplasty

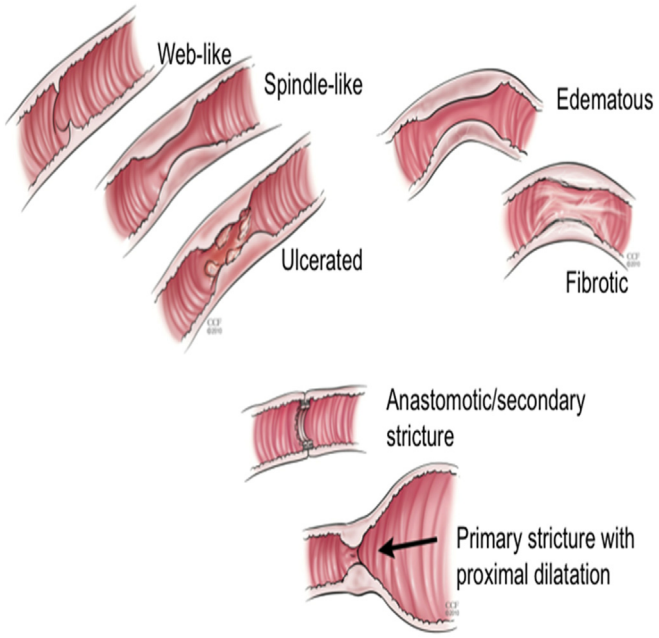

Figure 1. Classification of IBD strictures.

for IBD strictures (Table 2, Fig. 1). Because of the malignant potential of IBD-associated strictures, the initial endoscopic evaluation should include biopsies and/or cytology brushings at the stricture site. A detailed description of the nature of the stricture(s) should be a part of a routine endoscopy report.

Endoscopic balloon dilation therapy

In many cases, endoscopic dilation using a TTS balloon is a viable treatment alternative to surgery for patients with IBD-related benign small bowel, ileocolonic, or colonic strictures. Cases in which this technique is indicated include symptomatic strictures less than 4 to 5 cm without associated fistulous tracts,[24] abscesses, or malignancy. In addition, this technique is indicated to facilitate completion of dysplasia surveillance in cases of prior procedures that were incomplete because of nontraversable strictures.

There are no published standards for the technical details of TTS balloon dilation of IBD strictures, such as the specification of balloon size, duration of balloon insufflation, graded dilation, anterograde versus retrograde dilation, wire guided versus non–wire guided, intralesional injection of long-acting corticosteroids, and the use of fluoroscopy. Multiple studies have been performed with varying diameters of balloon, success rates, and adverse events with heterogeneous results (Table 3). In a systematic review by Hassan et al,[25] including 13 studies with a total of 347 CD patients undergoing TTS balloon stricture dilation, patients in 5 studies were dilated to 18 mm, in 6 studies to 20 mm, and in 2 studies to 25 mm. The reported percentage of successful gastroscope or colonoscope passage after dilation ranged from 45% to 100% among these 13 studies, regardless of the balloon size.[25] In various studies, short-term symptomatic improvement using this technique occurred in 71% to 100% of patients,[26,29-31] with overall long-term improvement (defined as surgery-free in the follow-up period) reported in 50% to 100% of patients.[28,29,31-33] For example, Singh et al[34] reported long-term improvement with endoscopic dilation in 77% of patients with primary strictures and in 72% of patients with anastomotic strictures. However, symptomatic recurrence is common, with a reported frequency ranging from 13% to 100%.[27] The time interval between dilations is quite variable, with some patients requiring only 1 dilation in the study follow-up interval and other patients requiring dilations periodically for symptomatic recurrence; various studies have reported mean intervals between dilations ranging from 5.7 to 32 months in patients requiring repeated dilations.[12,26,28]

Various investigators have also had mixed results when evaluating the efficacy of injection of steroids after endoscopic balloon dilation in improving outcomes and reducing the need for further dilations. In a randomized controlled trial of pediatric patients with CD strictures requiring balloon dilation, 5 of 14 patients receiving placebo intralesional injections after dilation required redilation versus 1 of 15 patients receiving steroid injections; in addition, the mean time free of redilation was significantly longer in the steroid group versus placebo group (11.7 months vs 9.4 months, $P = .048$).[35] Furthermore, in a study by Brooker et al[31] including 14 patients receiving 20 dilations with subsequent steroid intralesional injection, 7 patients did not require further dilations in the follow-up period; in addition, 3 of 4 patients who required additional dilations had a longer interval between dilations than they had previously had with dilation without steroid injection.

TABLE 3. Endoscopic Balloon Dilation of Strictures and Outcomes

Authors	N	Anastomotic stricture	Maximum balloon size (mm)	Steroid injection	Immediate Technical Success*	Clinical Efficacy*	Major adverse events*	Stricture location	Follow-up duration (months)
Dear 2001[120]	22	95%	18	No	45%	73%	0	C, ICA	4 – 90
Sabate 2003[121]	38	68%	25	No	56%	53%	2%	ICA, CCA, C, I, J, ICV	0.2-103
Williams 1991[30]	7	71%	20	No	71%	71%	0	ICA, D, C	21-27
Ferlitsch 2006[53]	46	59%	20	Yes	95%	66%	4%	ICA, C, I ,NI	3-98
Brooker 2003[31]	14	100%	20	Yes	71%	79%	0	ICA, IIA, CCA, IRA	13.2-32.8
Matsui 1997[122]	5	0%	20	No	NR	100%	0	P, PB	10.8-80.4
Thomas-Gibson 2003[123]	59	90%	18	No	60%	41%	1.6%	ICA, ICV, IIA, CCA, C, PIA, IRA, JIA	29.4
Ramboer 1995[29]	13	69%	18	Yes	77%	100%	0	ICA, ICV, NI, C	9-73
Couckuyt 1995[28]	55	59%	25	No	73%	62%	8%	ICA, IRA, NI, TI, ICV, C, CCA	3-80
Morini 2003[124]	43	67%	18	No	91%	63%	0	ICA, ICV, NI, TI	10-168
Blomberg 1991[32]	27	100%	25	No	67%	70%	2%	NR	7-38
Singh 2005[34]	17	35%	20	Yes	97%	76%	10%	C, CCA, ICA, I, D	5-50
Ajlouni 2007[125]	37	37%	20	No	90%	87%	1%	I, ICV, ICA, IIA, C	6-153
Stienecker 2009[26]	25	42%	18	No	97%	84%	3%	C, ICA, ICV, I	54-118
Thienpont 2010[126]	138	84%	18	No	97%	76%	3%	I, ICA, C, IIA	69.6

C, colon; *CCA*, colo-colonic anastomosis; *D*, duodenum; *I*, ileum; *ICA*, ileo-colonic anastomosis; *ICV*, ileocecal valve; *IIA*, ileo-ileal anastomosis; *J*, Jejunum; *JIA*, jejuno-ileal anastomosis; *NI*, neoterminal ileum; *PIA*, pouch-ileal anastomosis; *P*, pylorus; *PB*, postbulbar; *TI*, terminal ileum; *NR*, not reported

*Immediate technical success was defined by successful passage of the endoscope or colonoscope immediately after dilation. Clinical efficacy was defined as the resolution of obstructive symptoms after dilation with the avoidance of surgery. Major adverse events (calculated per number of dilations) included in the calculation were perforations, bleeding requiring transfusion, and intra-abdominal abscesses or fistulas.

Despite the promising results with steroid injection after dilation in these studies, a randomized controlled trial by East et al[36] comparing time to redilation or surgery between patients receiving intralesional triamcinolone versus placebo injection after dilation found in the per-protocol analysis a statistically significant trend toward earlier redilation in patients receiving triamcinolone; in addition, 5 of 7 patients in the steroid group versus 1 of 6 in the placebo group required redilation during the follow-up period.

In the IBD Therapeutic Endoscopy Center at the Cleveland Clinic, we routinely perform graded dilation with an 18-, 19-, and 20-mm TTS balloon (Boston Scientific, Inc, Boston, MA); a balloon with a guidewire is used for angulated strictures or pinhole strictures that are not traversable by a pediatric colonoscope or upper endoscope. Dilation to 18 to 20 mm (3-6 atmospheric pressure) is performed for anastomotic strictures, with dilation to 20 mm (6 atmospheric pressure) for primary strictures. In addition, when feasible, retrograde dilation with the passage of a pediatric colonoscope or gastroscope beyond the stricture and working backward is preferred to blind anterograde dilation with or without guidewire to minimize perforation and other adverse events (Figs. 2 and 3, Video 1, available online at www.giejournal.org).

Endoscopic TTS balloon dilation is also a feasible alternative in patients with IPAA strictures. A prospective study by Shen et al[37] including 150 patients undergoing 646 dilations for IPAA strictures reported a technical success rate (defined as successful passage of endoscope without resistance) of 97.8% with a 97% 5-year pouch retention rate.

Endoscopic needle-knife stricturotomy

The needle-knife is an endoscopic tool that can be used in various clinical settings for therapeutic benefit. It has commonly been used to perform a precut sphincterotomy in patients with difficult biliary cannulation, usually caused by mechanical problems such as bile duct or pancreatic duct fibrosis or stenosis, ampullary tumor, or gallstone impaction.[38] In addition, it has been used for refractory upper endoscopic anastomotic strictures. In a small case series of 9 patients, needle-knife electroincision was used

Figure 2. Retrograde versus antegrade endoscopic balloon dilation of strictures. **A,** Retrograde fashion: The endoscope is passed through the stricture, followed by the introduction of the balloon, withdrawal of the endoscope, and insufflation of the balloon. **B,** Antegrade fashion with guidewire balloon dilation of a stricture not traversable to the endoscope. The guidewire in the balloon is introduced through the stricture, followed by the wire exchange technique (withdrawing the wire while pushing the balloon forward).

to make radial incisions at esophagogastric anastomotic strictures before endoscopic balloon dilation; 8 of 9 patients had improved dysphagia and a reduced frequency of subsequent endoscopic dilations.[39] Furthermore, needle-knife therapy has been used in patients with congenital pyloric stenosis. In a small study, 7 infants with this condition underwent endoscopic pyloromyotomy using a needle-knife and subsequently tolerated oral feeding within 1 to 2 hours of this therapy.[40]

Similar to the latter therapeutic uses of needle-knife during endoscopy, endoscopic needle-knife stricturotomy is a novel therapeutic modality that can be used for ileocolonic and ileal pouch strictures. Endoscopic needle-knife therapy is less costly than surgical treatment modalities and is therefore an attractive therapeutic option in these strictures. At our center, we developed the technique of Doppler US–guided needle-knife therapy for IBD-related strictures. This modality is primarily used for fibrotic strictures refractory to repeated balloon dilations. We illustrated the technique in a previous publication.[41] Briefly, the stricture is scanned with the insertion of a disposable catheter–based Doppler US probe (VTI Vascular Technology, Nashua, NH) through the working channel of an endoscope. The probe is used to localize areas within the stricture without significant vascular structures or high-volume blood flow. Then a needle-knife with the setting of ERCP Endocut (ERBE USA, Marietta, GA) is used to dissect away fibrotic tissue, when possible avoiding the areas with significant vascularity identified by Doppler US (Fig. 4, Video 2, available online at www.giejournal.org). We believe needle-knife stricturotomy is more effective than TTS balloon dilation in refractory IBD-related benign strictures. In experienced hands, it has an acceptable rate of adverse events such as bleeding and perforation.

Endoscopic stent placement

The application of endoscopic stents has been explored in CD strictures. In a small case series of 11 CD patients, the investigators used an enteroscope or colonoscope through an overtube to localize the stricture and then performed a TTS balloon dilation of the stricture; next, radiographic contrast and/or endoclips were used to mark the distal margin of the stenosis. The endoscope was removed, and a guidewire was introduced through the overtube; under fluoroscopy, the biodegradable stent was placed over the wire using an introducer.[42] In this series, 3 patients had stent migration and 1 had stent shortening; the mean time to stent degradation in the other 7 patients was 4 months. No immediate adverse events including perforation occurred in this study.[42] Of note, these biodegradable stents are not available in the United States. However, self-expandable metal stents (SEMSs) are available in the United States, and in a separate case series of 5 patients with CD anastomotic strictures, the investigators successfully placed a SEMS over a guidewire with fluoroscopic guidance. Four patients achieved symptomatic response with no need for repeat intervention within 28 months of follow-up. The fifth patient experienced delayed stent occlusion with subsequent resection and removal of the stent.[43] We believe that stent treatment for CD strictures warrants further evaluation and that the risks and benefits for stent placement in benign diseases, such as CD, should be carefully balanced.

Because of the frequency of SEMS migration that can limit the clinical use of these stents, several investigators

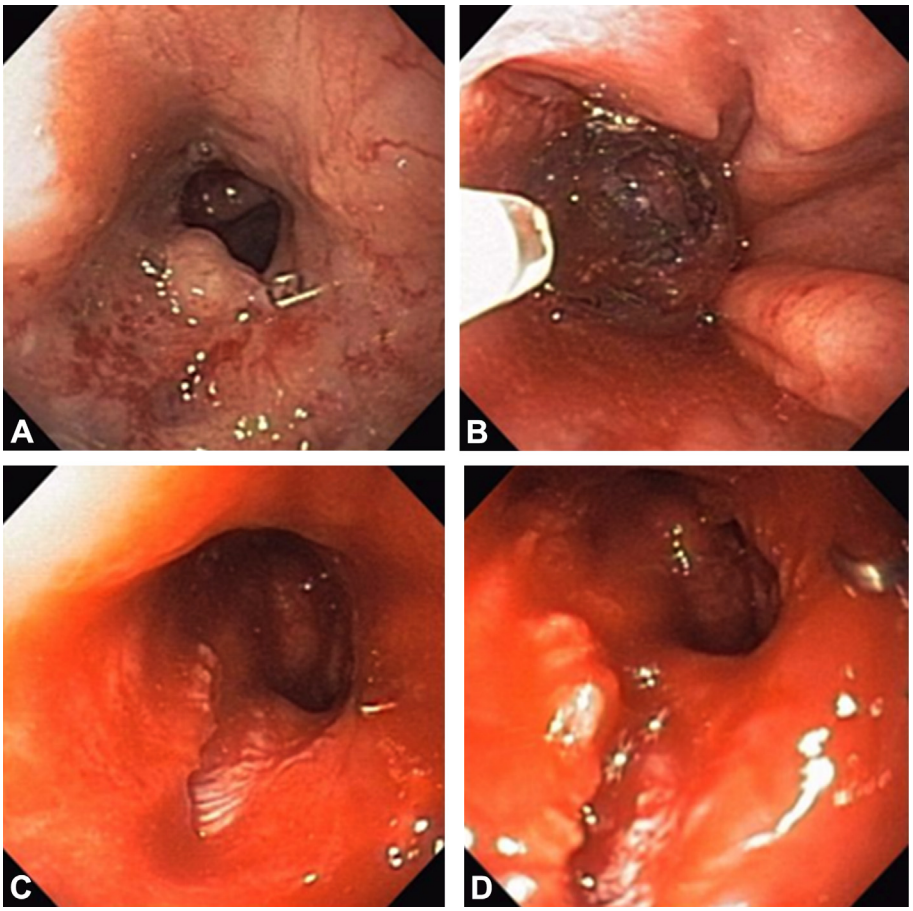

Figure 3. Endoscopic balloon dilatation of an anastomotic stricture from Crohn's disease. **A**, Anastomotic stricture in a Crohn's disease patient. **B**, Balloon dilation of the stricture. **C**, Mucosal tear after balloon dilation. **D**, Dilation effect with enlargement of stricture after balloon dilation.

have evaluated the efficacy of an endoscopic suturing device in the reduction of stent migration. In 1 study, 7 patients with esophageal SEMSs received endoscopic suture fixation of their stents using the overstitch endoscopic suturing device (Apollo Endosurgery, Austin, TX), and no stent migration occurred after the sutures were placed.[44] In another study by Rieder et al,[45] 4 of 5 patients with esophageal SEMSs had no stent migration after endoscopic suturing; the fifth patient experienced stent migration after 4 weeks. Although this method has not been studied for the prevention of stent migration in IBD patients, the technique could potentially be useful and warrants further evaluation in this patient population.

Endoscopic procedure–associated adverse events and their management

Procedure-related perforation is a detrimental adverse event in IBD as well as non-IBD patients. The patients' underlying IBD and concurrent immunosuppressive medications and therapeutic endoscopy interventions may pose additional risks for this adverse event. In a case-control study, hospitalized patients with underlying IBD had a significantly higher rate of perforation than those without IBD (1% vs .6%, $P = .0001$).[46] A meta-analysis showed that 1.9% of CD patients undergoing therapeutic procedures in the included studies experienced perforations. This percentage is higher than the rate of colonoscopic perforation in the general population in large studies (<.1%-.3%).[47] The perforation rate of endoscopic dilation of ileal pouch strictures by an experienced endoscopist was reported to be .46% when calculated by the number of endoscopies with dilation performed.[37] Therefore, endoscopic therapy in IBD patients should be performed by specialized endoscopists, with proper surgical backup.

The treatment of endoscopic procedure–related perforations often requires surgical intervention but can be managed nonoperatively in some instances. A retrospective review including 105,786 colonoscopies reported 35 perforations with 23 managed with surgery and 12 managed without surgery.[48] Conservative nonsurgical therapies include hospitalization with bowel rest, intravenous fluids and antibiotics, and serial abdominal assessments.[49] Surgical repair may include primary closure, resection with diversion and ostomy, or resection with primary anastomosis.[50] Nonoperative management, including closure with large endoclips, is now more feasible in select cases. Although there is a dearth of literature on endoscopic therapy for iatrogenic perforations in IBD therapeutic procedures, we

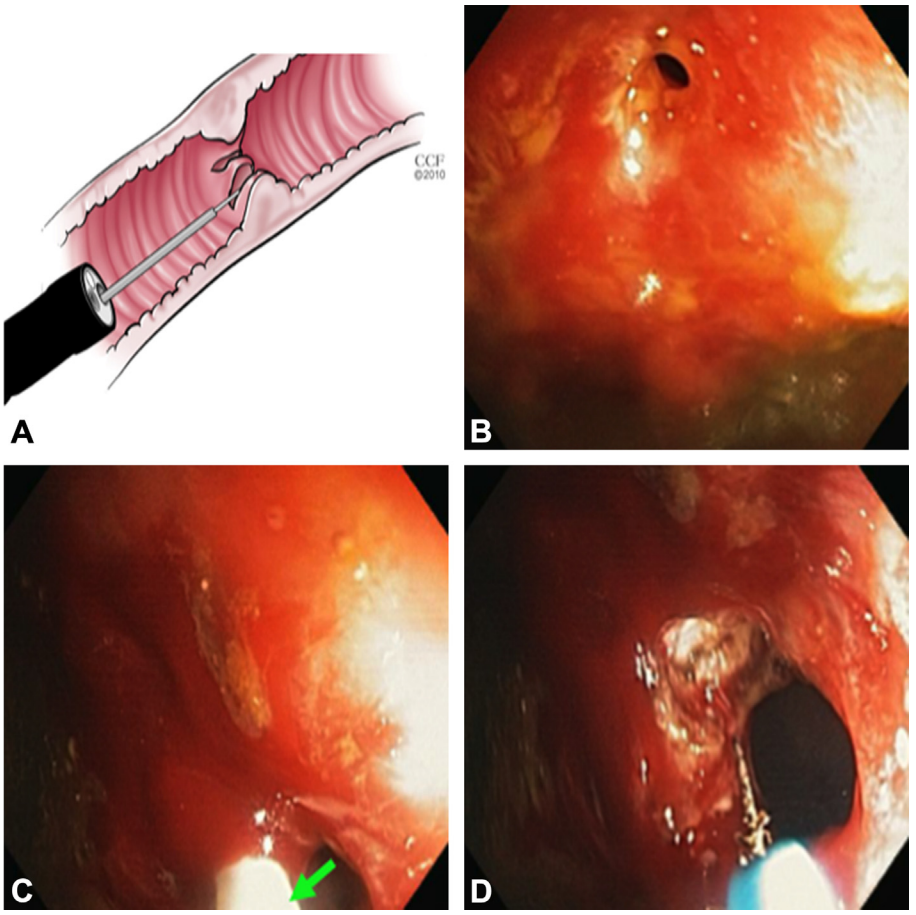

Figure 4. Doppler ultrasound-guided needle-knife stricturotomy. **A,** Artist depiction of the procedure. **B,** A pinhole recurrent anastomotic stricture refractory to balloon dilation therapy. **C,** Doppler ultrasound probe (*green arrow*) being used to identify the area with blood flow. **D,** Needle-knife therapy.

have successfully managed some of these patients using endoclips to close the perforation (Fig. 5). A retrospective review showed that after clip closure of perforation only 24% of patients required surgery, with the remaining 76% treated medically and 59% experiencing positive clinical outcomes.[50]

Over-the-scope clips have also been used in the treatment of perforation, although there is a paucity of literature on the use of this device in IBD patients. In a retrospective review by Baron et al,[51] 4 of 5 patients with iatrogenic endoscopic perforations had successful closure of the perforation with an over-the-scope clip. Another option for the treatment of iatrogenic perforations is the use of enteral fully covered stents. This modality has been widely used for iatrogenic upper GI perforations and is now becoming an option for colonic perforations. In a prospective cohort study, 9 patients (including 2 patients with UC) with breaks in the bowel wall including perforation, postoperative fistula or leak, and complete anastomotic disunion received fully covered SEMSs.[52] Evidence of significant healing of the bowel wall was present in all patients at follow-up endoscopy 3 to 8 weeks after stent placement, and no patients required surgery.[52]

Excessive bleeding is another major adverse event related to endoscopic stricture dilation in IBD strictures, with frequency ranging from 0% to 1.41% of dilations in various studies.[12,29,53] Bleeding was successfully treated with a heater probe without the need for transfusion in 1 study[12] and was managed with transfusion alone in another study.[53] In our experience, most bleeding can be successfully managed with endoscopic clips. Per the ASGE guidelines, endoscopic dilation is considered a procedure with a higher risk of bleeding, and, as such, consideration should be given to holding clopidogrel or ticlopidine 7 to 10 days before endoscopy; in addition, warfarin should be held before the procedure with bridging therapy instituted in patients at high risk of thromboembolic events.[54]

IBD-RELATED FISTULA

A fistula is a chronic communication between epithelialized areas in which both ends of the tract remain open.[55] Among the common areas connected by fistulous tracts in IBD are the intestine and cutaneous tissue (enterocutaneous fistula), the intestine and the vagina (entero- or rectovaginal fistula), the intestine and the bladder

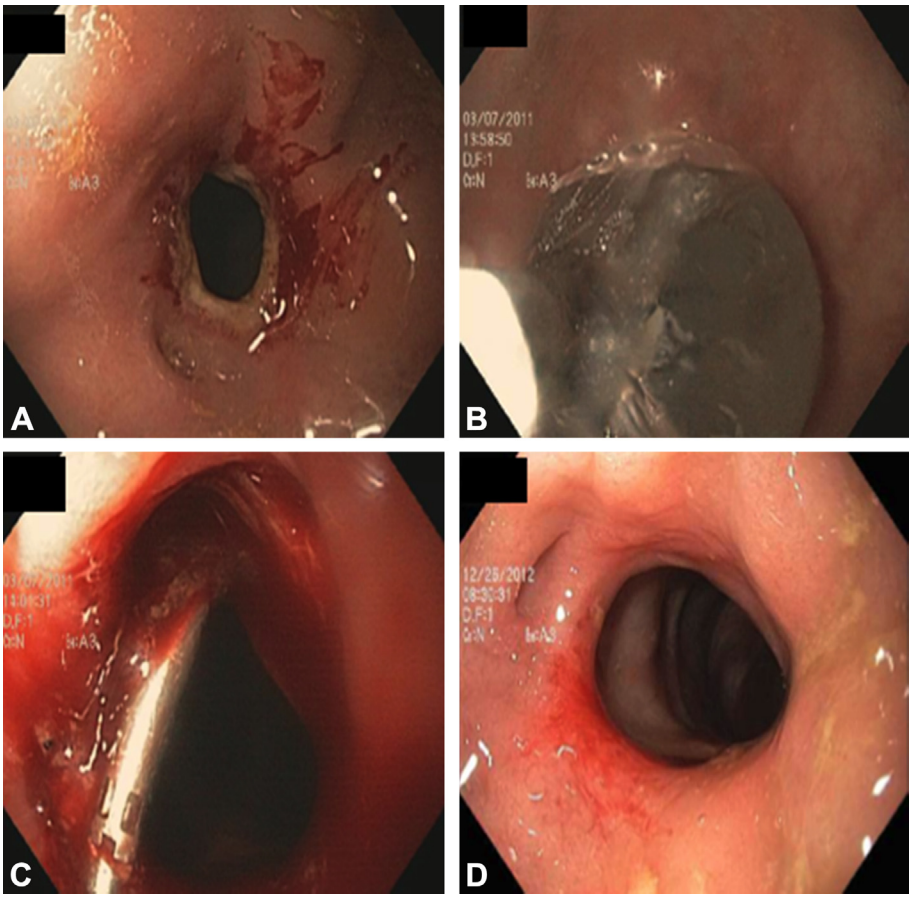

Figure 5. Treatment of endoscopy-associated perforation. **A** and **B,** Endoscopic balloon (size 20 mm) dilation of an ileosigmoid anastomotic stricture. **C,** Treatment of perforation from the dilation with an endoclip. **D,** More patent anastomosis at the 1-year follow-up (Figures 5A-C reprinted with permission from Gastroenterology & Hepatology).

(enterovesicular fistula), and the intestine and intestine (enteroenteric fistula).[56] In addition to CD, other disease conditions that can be associated with fistulas include HIV infection, bowel surgery, radiation, tuberculosis, pilonidal disease, trauma, and cancer.[57] Because of the location, length, and complexity of CD or IBD surgery-related fistulas, a combined assessment of clinical, endoscopic, and imaging features is often needed.

Diagnosis and classification of CD-associated fistulas

Fistulizing disease is a common clinical phenotype of CD, with possible mechanisms including transmural inflammation, infection of the anal glands, or fissures or ulcers that penetrate from the anus or rectum into adjacent areas. Clinically, patients with perianal, vaginal, or vesicular fistulas may present with drainage from perianal openings, anal discomfort, painful passage of bowel movements,[58] air or stool discharge from vagina, pneumaturia, or frequent urinary tract infections.

Although several classifications of symptoms have been proposed, a widely accepted system reported by Sandborn et al[55] in an American Gastroenterological Association technical review classifies fistulas into simple and complex groups. Simple fistulas usually have 1 orifice externally, are located distal to the dentate line, are not associated with discomfort, have no indication of connection with the vagina, and have no associated anorectal stricture. Complex fistulas usually cause discomfort, are proximal to the dentate line, have more than 1 external opening, may be associated with abscess, may have a connection to the vagina, and may have anorectal strictures.[55] Another widely used system, the Parks System, classifies fistulas based on the origin of the fistulous tract into intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric categories. Intersphincteric fistulas are located between the internal and external anal sphincters, whereas transsphincteric fistulas extend through the external anal sphincter into the ischiorectal fossa; in addition, suprasphincteric fistulas pass superior to the sphincters and eventually into the intersphincteric space, and extrasphincteric extend over the sphincters and through the levator ani without passing through the sphincters.[59]

Fistulas can be diagnosed by imaging, examination under anesthesia (EUA), or anorectal EUS. Imaging modalities useful in the detection of fistulas include MRI, CT, GGE, and EUS. MRI with fistula protocol, using endoanal coils

or phased array, has been reported to have a diagnostic accuracy ranging from 76% to 100%.[60-68] Diagnostic accuracy of other imaging modalities is lower, making these modalities less useful; 1 study reported a diagnostic accuracy of US and barium radiography in the detection of fistulas as 85% with the accuracy of CT at 77% in patients with fistulas with septic adverse events.[69] Another useful method for diagnosis of fistulas is EUA, which consists of assessment for fistulas by visualization, palpation, and probes advanced into tracts by a colorectal surgeon in the operating room; accuracy has been reported at 90%.[55] Anorectal EUS has also been used for evaluation of suspected fistulas and has an accuracy of 56% to 100% in the diagnosis of fistulas in various studies.[68,70-76]

The combined assessment of radiographic, endoscopic, and clinical features is surely helpful to diagnose and characterize fistulas. Among the characteristics used to classify fistulas are etiology, location, length, complexity, and associated conditions (Table 4).

Medical management of CD fistulas

Medical therapies that have been used for CD fistulas include antibiotics, immunomodulators, and anti–tumor necrosis factor agents. Antibiotics, including ciprofloxacin and metronidazole, and immunomodulators, such as 6-mercaptopurine and azathioprine, have not been shown to treat CD fistulas significantly more effectively than placebo in controlled trials with primary endpoints of fistula healing.[55] However, a meta-analysis of 5 trials showed that among patients on 6-mercaptopurine or azathioprine, 54% experienced fistula response (defined as decreased fistular discharge or complete healing of the fistula) versus 21% in the placebo group.[77] Biological agents, including infliximab,[78] adalimumab,[79] certolizumab,[80] and maybe natalizumab,[81] have been shown to be effective in reducing fistula drainage or, in some cases, closing fistulas. Despite the benefits of some of these medical treatments as compared with placebo, none is very effective in fistula closure in the long term. Therefore, other modalities are necessary in the treatment of these patients. Among these alternative modalities is endoscopic injection of various substances into the fistulas.

Endoscopic fistular injection

Injection of various substances has been used for the management of CD fistulas. One of these substances is doxycycline; in our practice, we inject 10 mL of liquid doxycycline directly into the fistula during endoscopy (Fig. 6). This antibiotic results in local inflammation with subsequent fibrin extravasation and tissue adhesion[82]; because of this effect, it has also been used in pleurodesis for malignant pleural effusions.[83] Use of this medication for fistula closure has been reported in a small case series of postoperative lymphatic fistulas in which 4 of 5 patients had closure of fistulas within 2 days of injection, with the fifth patient having closure after a second injection of doxycycline.[82] In addition, a clinical trial by Rogler et al[84] investigating CD fistula closure after injection of doxycycline and acetylcysteine is ongoing.

Highly concentrated sugars have also been used in the management of wound healing, including the healing of fistulas in a case report.[85] At the Cleveland Clinic, we inject 50% dextrose into the fistula tract to promote fistula closure. Natural medicine practitioners have used honey for years for various medical purposes, including for wound healing.[85] In an assessment of available evidence for the use of honey in wound healing, Molan[86] noted that honey was beneficial in wound care in 17 randomized controlled trials with 1965 patients. A case report by Vlcekova et al[85] noted that after 6 months of honey injected into the patient's multiple gluteofemoral fistulas, most of the fistulas were closed.

Fibrin glue has also been used for the treatment of fistulas because it results in mechanical closure of the tract via formation of a fibrin clot. Del Rio et al[87] reported their successful treatment of fistulas in 7 patients with endoscopic placement of fibrin glue. In addition, a case series including 15 patients with non-IBD GI fistulas treated with fibrin glue instilled during endoscopy noted successful closure of 86.6% of the fistulas with reopening of 1 fistula in follow-up ranging from 2 months to over 3 years.[88] Despite this success, one issue with fibrin glue is the durability of this treatment. In a study by Loungnarath et al,[89] only 31% of patients with fistulas injected with fibrin glue in the operating room had persistent closure of the fistulas beyond the early postoperative period; of note, this study included primarily complex and chronic fistulas. Despite the low long-term success rate of fibrin glue, the authors advocated the use of fibrin glue, particularly for complex fistulas, because the therapy has low morbidity and may provide some benefit.[89]

A newly developed therapeutic option being studied for fistulas is endoscopic injection of stem cells. A recent cases series of 24 patients was reported.[90] In this series, patients received 20 million units of expanded adipose-derived mesenchymal stem cells injected into a fistulous tract; if the fistula was not completely closed at week 12, a second injection of 40 million units of stem cells was administered.[90] In this study at week 24, all fistulous tracts were closed in 30% of patients, the treated fistula was sealed in 56%, and fewer fistulas with drainage were seen in 69% of patients.[90] A phase III, randomized, multicenter clinical trial including 200 patients compared fistular injection of autologous stem cells, fibrin glue, and the combination of stem cells and fibrin glue in the closure of fistulas.[91] Although the 24- to 26-week healing rate was the highest in patients receiving both stem cells and fibrin glue, the 1-year healing rate at 57% was highest in the group receiving only stem cells; neither of these rates was significantly higher than the rates in the other groups.[91] Despite the promising results of this novel therapeutic technique, a major challenge to its use is the concern of theoretical increased risk of cancer associated with the injection of stem cells.

TABLE 4. Proposed classification of IBD-related fistulas

Criteria	Classification
Etiology	Primary (directly related to disease course of IBD) vs secondary (iatrogenic or surgery-related, radiation, cryptogenic) vs malignant transformation
Location	Enteroenteric vs enterocutaneous vs perianal vs gut-to-adjacent hollow organs (such as bladder and vagina) vs intersphincteric vs transsphincteric vs extrasphincteric vs suprasphincteric
Length	Short vs long
Complexity	Simple vs branched vs multiple
Associated conditions	Mucosal inflammation of gut; stricture vs abscess; cancer; infections, including tuberculosis and HIV; radiation; pilonidal disease

IBD, Inflammatory bowel disease.

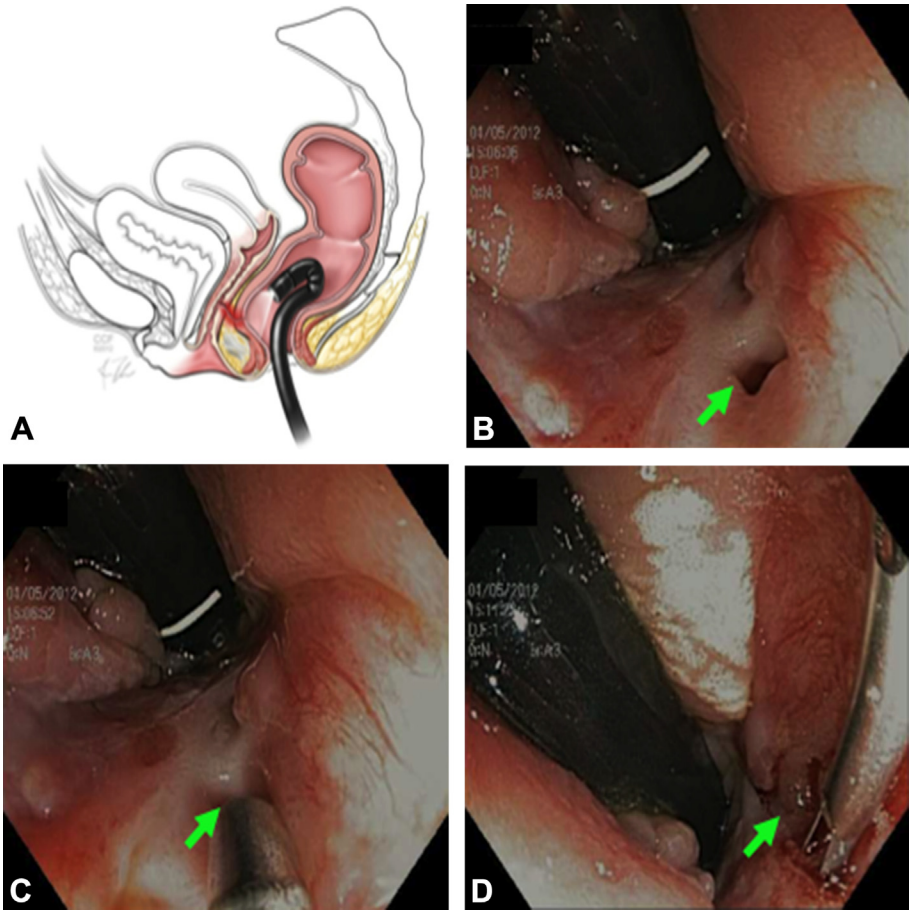

Figure 6. Endoscopic treatment of a rectovaginal fistula. **A,** Artist depiction of a rectovaginal fistula with retroflexed endoscopy. **B,** Endoscopic view of the fistular orifice *(green arrows)*. **C,** Endoscopic injection of liquid doxycycline into the fistula. **D,** Deployment of an endoscopic endoclip at the fistular orifice.

IBD SURGERY–ASSOCIATED ADVERSE EVENTS

IBD surgeries can be an important part of the management of IBD patients, but these surgeries can have adverse events. Adverse events associated with stricturoplasty[92] and bowel resection[93] for CD include anastomotic leaks, abscesses, fistulas, wound infections, bleeding, prolonged ileus, and small bowel obstruction.[92,93] Among these surgery-associated adverse events after restorative colectomy with IPAA for UC are pouch leak, small bowel

obstruction, hemorrhage, fistula, anastomotic stricture, de novo CD of the pouch, and pouchitis.[11] These adverse events can lead to additional consequences, such as abscesses, pelvic sepsis, peritonitis, pouch failure, and reduced fertility.[11] Surgical options to treat these adverse events and consequences can include laparotomy, diverting ileostomy, and surgical pouch removal with ileostomy or pouch revision.[94] However, many of these adverse events can be treated endoscopically with avoidance of surgery (Table 5).

TABLE 5. Classification of IBD surgery–associated adverse events amenable to endoscopic therapy

Criteria	Classification
Bowel blockage	Anastomotic stricture vs bezoars
Extravasation of gut luminal content	Acute anastomotic leak vs sinus vs fistula
Anastomotic bleeding	Acute vs chronic intermittent

IBD, Inflammatory bowel disease.

Diagnosis of IBD surgery–associated adverse events

Common operative interventions for CD, including intestinal resections or stricturoplasties, can have postoperative septic adverse events such as anastomotic leaks and intra-abdominal abscesses.[95] An anastomotic leak has been defined as leakage of stool because of the lack of a seal between 2 surgically opposed segments of bowel.[96] The imaging modalities most often used in the diagnosis of anastomotic leaks are GGE and CT; a review comparing the 2 modalities showed that a water-soluble enema was superior to CT, especially in the diagnosis of distal leaks.[97] Abdominal abscess is typically diagnosed with CT[14] or MRI.[17]

Patients can also develop strictures after CD surgeries. Recurrence of CD strictures within 15 years of surgery has been reported in more than 50% of patients, and recurrence of endoscopic evidence of CD has been noted in up to 70% of patients within 1 year after surgery.[98] In a recent study by Khoury et al,[99] 34 patients required early reoperation within a median 21.6 months, with 23.6% of these patients having stricturing that developed since their last surgery as the operative indication. MRE is useful in the diagnosis of these strictures,[17] as is CTE.[14]

Among the adverse events of IPAA for UC amenable to endoscopic therapy are strictures and fistulas. Strictures occur at the pouch-anal anastomosis (pouch outlet), pouch body–afferent limb junction (pouch inlet), or former ileostomy site[11] and are diagnosed by imaging modalities such as GGE[22] or by endoscopy. A subset of patients can develop strictures because of de novo CD of the pouch. CTE, MRE, or GGE is the first-line radiographic modality for inflammatory or fibrostenotic CD of the pouch. If previous endoscopic and radiographic workup fails to yield a conclusive diagnosis, EUA should be performed.[100] Fistulas can also occur at the anastomosis or in the pouch body, and evaluation of these patients includes EUA with consideration of injection of hydrogen peroxide or methylene blue, pouchoscopy, and contrasted radiographic pouch assessment.[11]

Patients can also develop anastomotic leaks or sinuses as adverse events related to IPAA. Anastomotic leaks tend to become evident immediately postoperatively, whereas pouch sinuses become evident later. Pelvic MRI, GGE, or EUA is useful in localizing and characterizing the leak.[101]

Pouch sinuses are blind-ending tracts or cavity with an opening within the pouch; these sinuses can be diagnosed on imaging, EUA, and endoscopy.[102] They occur at the pouch-anal anastomosis and represent a delayed presentation of an earlier leak. Contrasted enema and MRI of the pelvis as well as pouchoscopy and EUA are all used in diagnosis.[101]

Endoscopic treatment of anastomotic leak and sinus

Anastomotic leaks occurring after colorectal surgery can be treated endoscopically with covered stents. In a study by DiMaio et al,[103] 5 non-IBD patients with postoperative colorectal anastomotic leaks received covered SEMS. In this study, 4 of 5 patients experienced clinical success and improved endoscopic and radiographic appearance of the leak, but 1 of these 4 patients experienced stent migration after 1 week.[103] In addition, in a study by Chopra et al,[104] patients received endoscopic management or traditional surgical management of their postoperative anastomotic leaks. Among the 13 endoscopically managed patients were 6 patients who received endoscopic debridement followed by placement of a covered self-expandable plastic stent for a median of 9 days; in this study, the overall time to healing of the anastomotic leak was shorter in the endoscopic group versus the surgical group (median 105 days vs mean 173 days, $P < .05$).[104] Although there is a paucity of literature in the use of this modality in IBD patients, the technique could likely be applied in this patient population; however, further studies are needed in IBD patients.

When treating anastomotic sinuses, surgeons sometimes use a procedure known as anastomotic sinus unroofing, which involves the use of electrocautery scissors during laparoscopy or anoscope to cut the shared wall between the sinus and the intestine.[105] Traditionally, asymptomatic pouch anastomotic sinuses have been treated initially with fecal diversion with subsequent observation for spontaneous resolution of the sinus.[105] Those patients without resolution of the sinus then receive operative or percutaneous management, including pouch revision or pouch advancement procedure.[105]

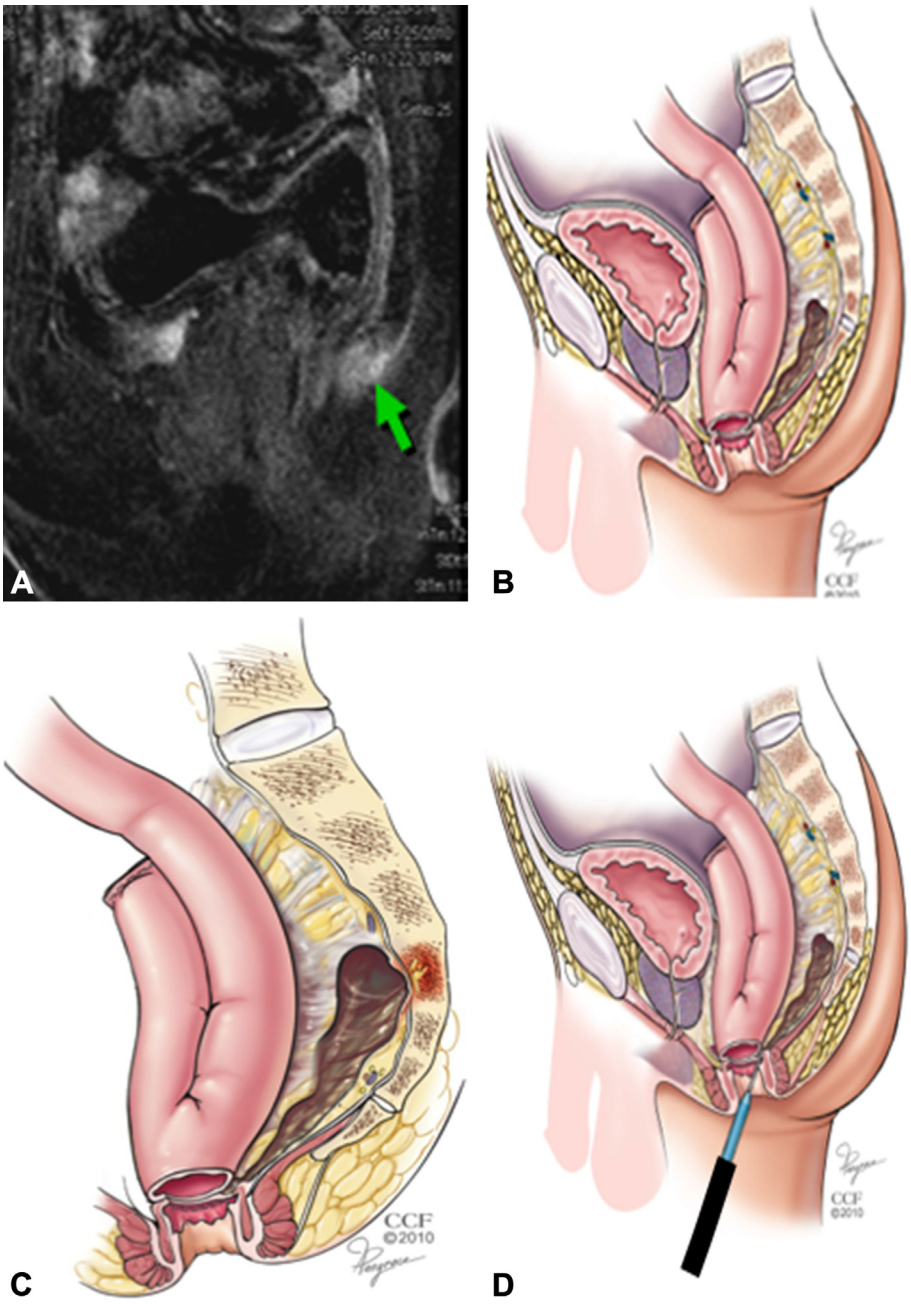

Figure 7. Endoscopic sinusotomy or unroofing of a sinus. **A,** Coronal MRI showing a presacral sinus *(green arrow)*. **B,** Artist depiction of a presacral sinus. **C,** Artist depiction of a presacral sinus with a closer view **D,** Artist depiction of endoscopic unroofing of the sinus (Figure 7D reprinted with permission. © 2012 The Authors. Colorectal Disease © 2012. The Association of Coloproctology of Great Britain and Ireland).

However, in our practice, we found that endoscopic needle-knife therapy is also a safe, viable option for the treatment of presacral sinuses. We previously reported this technique with video.[106] Our technique involves the use of a triple-lumen needle-knife with an ERCP "Endocut setting" on the ERBE system (USA Incorporated Surgical Systems, Marietta, GA) to open the sinus to create a diverticulum with epithelialization of the chronic leak (Figs. 7 and 8, Video 3, available online at www.giejournal.org). A study by our group including 65 patients with pouch sinuses who underwent needle-knife therapy showed that after a median of 2 sessions, 43.1% had a complete response and an additional 41.5% had a partial response.[107]

Endoscopic treatment of bezoars in the ileal pouch reservoir

Bezoars occurring in the ileal pouch reservoir can be successfully treated endoscopically. A case report by Lian et al[108] noted a pill bezoar in the Koch pouch

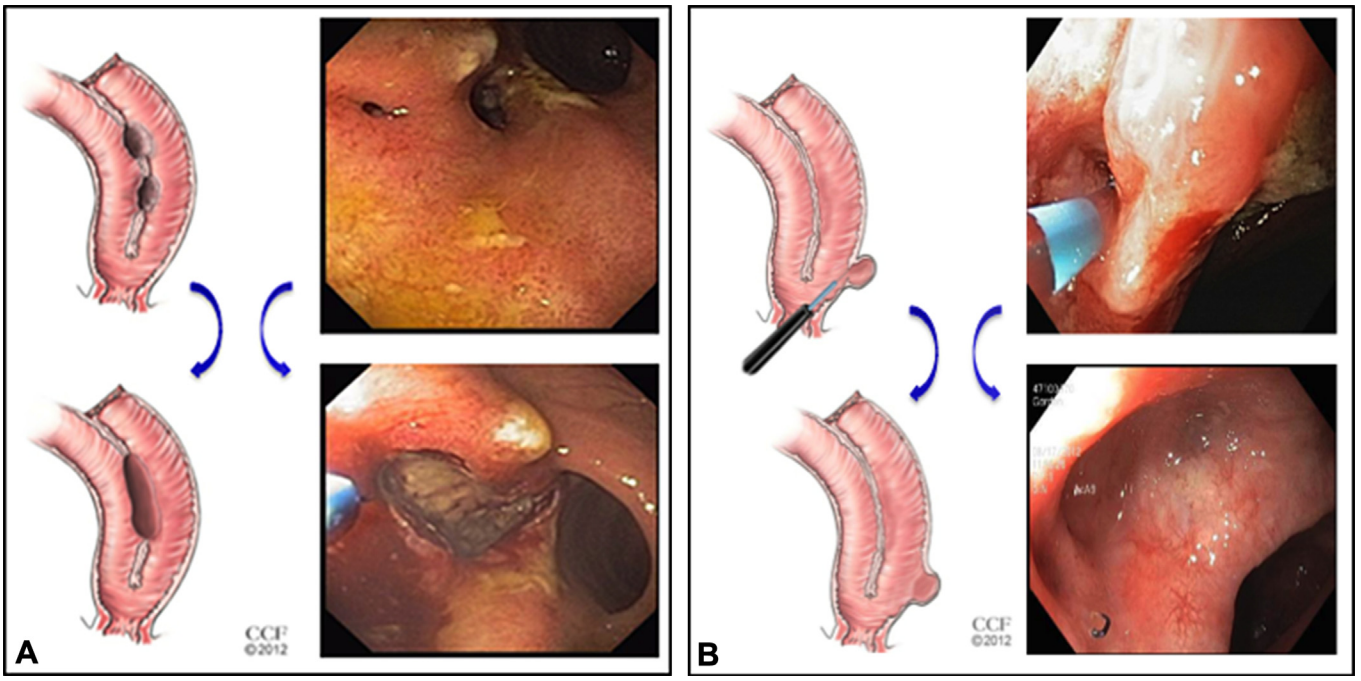

Figure 8. Endoscopic needle-knife sinusotomy for a chronic suture line leak in a patient with a J pouch. **A,** Unroofed compartmentalized sinus. **B,** Needle-knife sinusotomy followed by injection of 50% of glucose, resulting in complete epithelialization of the sinus.

TABLE 6. Classification of IBD-associated neoplasia

Criteria	Classification
Histologic feature	Indefinite for dysplasia; low-grade dysplasia; high-grade dysplasia; cancer
Macrophologic or endoscopic feature	Flat (unifocal vs multifocal) vs adenoma-like lesion vs non–adenoma-like lesion vs dysplasia-associated mass or lesion

IBD, Inflammatory bowel disease.

reservoir with nipple valve stricture; after balloon dilation of the stricture to 18 mm, 224 pills were removed in a piecemeal fashion using Tripod (Endoscopy Support Service America, Brewster, NY), retrieval baskets (Olympus America, Melville, NY), and RothNet (US Endoscopy, Mentor, OH).[108] Another case report by Shenoy et al[109] noted the removal of more than 50 pills located proximal to the ileostomy pouch by laparotomy and enterotomy. Finally, our group[110] reported on 8 patients with bezoars within their pouches, including lithobezoars, phytobezoars, a foreign object, and a pharmacobezoar; in half of these patients, endoscopic techniques were successfully used in the removal of the bezoar(s) or object.

COLITIS-ASSOCIATED NEOPLASIA

Colitis in both UC and extensive CD has been associated with neoplasia. There are areas of controversy in the classification, definitions, and management of this colitis-associated neoplasia. However, based on the current available literature and our experience, we propose a classification system based on histologic, macrophologic, and endoscopic features of this colitis-associated neoplasia (Table 6). Management of this colitis-associated neoplasia can include endoscopic polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection.

Colonoscopic polypectomy

Patients with IBD are predisposed to the development of colitis-associated neoplasia and can have various lesions within the colon. These lesions have traditionally been characterized as flat or raised, as assessed endoscopically.[111-113] A raised lesion with associated dysplasia is referred to as dysplasia-associated lesion or mass,[114] which should be differentiated from an adenoma-like lesion resembling a sporadic adenoma without adjacent flat dysplasia.[115] A non–adenoma-like lesion is typically an ulcerated, broad-based, irregular lesion.[116] Although an adenoma-like lesion can be managed with polypectomy, a non–adenoma-like lesion generally requires colectomy.[116] Biopsy samples of mucosa surrounding the lesion should be sent separately for pathology assessment. In most cases, for flat dysplasia in the colon, total proctocolectomy should be discussed

with the patient.[117] If biopsy specimens adjacent to the polyp do not reveal dysplasia and if there is complete resection of the polyp, colonoscopy should be repeated within 6 months.[117] Patients with multifocal flat low-grade dysplasia, repetitive low-grade dysplasia, or high-grade dysplasia should be referred for total colectomy.[117] Of note, the diagnosis of all dysplasia needs to be confirmed by at least 2 expert GI pathologists.

EMR and endoscopic submucosal dissection

EMR and endoscopic submucosal dissection are emerging treatment modalities for the removal of specific lesions in UC. Hurlstone et al[118] used EMR in chronic UC patients for complete removal of 79 flat Paris O-II lesions; this group had 2.4% recurrence at 3 months with no additional lesions diagnosed in the rest of the 4-year study period. In addition, 3 lateral spreading tumors in the cecum were removed by extended piecemeal EMR, and 4 lateral spreading tumors in the rectum or rectosigmoid colon were removed by cap-associated endoscopic submucosal dissection; this group with lateral spreading tumors had recurrence in 14% of patients with a median follow-up of 4 years.[118] In another study, Smith et al[119] used a combined EMR/cap-assisted endoscopic submucosal dissection technique in 67 UC patients with an adenoma-like mass with an overall cure rate of 98% at 18 months; in this study, there was a 10% bleeding rate and a 3% perforation rate.

SUMMARY

Endoscopic therapies are important modalities in the treatment of IBD, adjunct to medical and surgical approaches. These therapeutic techniques are particularly useful in the management of IBD-associated or IBD surgery–associated strictures, fistulas, and sinuses and colitis-associated neoplasia. Although the main focus of endoscopic therapies in IBD has been on balloon stricture dilation and ablation of adenoma-like lesions, new endoscopic approaches are emerging, including needle-knife stricturotomy, needle-knife sinusotomy, endoscopic stent placement, and fistula tract injection. Risk management of endoscopy-associated adverse events is also evolving. The application of endoscopic techniques in novel ways in the treatment of IBD is just beginning and will likely expand rapidly in the near future.

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