

The multidisciplinary health care team in the management of stenosis in Crohn's disease

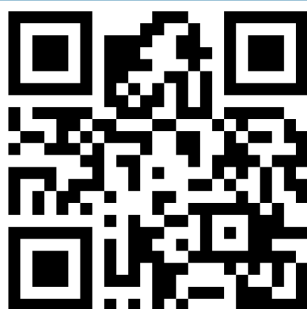
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Background: Stricture formation is a common complication of Crohn's disease (CD), occurring in approximately one-third of all patients with this condition. Our aim was to summarize the available epidemiology data on strictures in patients with CD, to outline the principal evidence on diagnostic imaging, and to provide an overview of the current knowledge on treatment strategies, including surgical and endoscopic options. Overall, the unifying theme of this narrative review is the multidisciplinary approach in the clinical management of patients with stricturing CD.

Methods: A Medline search was performed, using "Inflammatory Bowel Disease", "stricture", "Crohn's Disease", "Ulcerative Colitis", "endoscopic balloon dilatation" and "strictureplasty" as keywords. A selection of clinical cohort studies and systematic reviews were reviewed.

Results: Strictures in CD are described as either inflammatory or fibrotic. They can occur de novo, at sites of bowel anastomosis or in the ileal pouch. CD-related strictures generally show a poor response to medical therapies, and surgical bowel resection or surgical strictureplasty are often required. Over the last three decades, the potential role of endoscopic balloon dilatation has grown in importance, and nowadays this technique is a valid option, complementary to surgery.

Conclusion: Patients with stricturing CD require complex clinical management, which benefits from a multidisciplinary approach: gastroenterologists, pediatricians, radiologists, surgeons, specialist nurses, and dieticians are among the health care providers involved in supporting these patients throughout diagnosis, prevention of complications, and treatment.

Keywords: Crohn's disease, endoscopic balloon dilatation, multidisciplinary team, stricture, strictureplasty

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gut, which includes conditions such as Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified. Endoscopy and histological examination of the gastrointestinal biopsies represents the gold standard for the diagnosis of IBD. It allows us to assess the extent of IBD, to estimate the success of treatments, to monitor the disease course, and to treat some of its complications.^{1,2} The Vienna Classification first described three distinct groups of CD behavior: inflammatory, stricturing, and penetrating. An association between disease location and behavior is demonstrated, and stricturing disease mostly involves the terminal ileum and the ileocolonic locations.³

Stricture formation is a common complication of CD, occurring in approximately one-third of all patients with this condition.⁴ Such complication is the result of chronic

inflammation within the intestinal walls and the continuous healing response, which can lead to a progressive narrowing of the lumen and an increased pressure gradient around the stricture.⁵ CD-related strictures are defined as a persistent luminal narrowing, which can remain clinically silent or manifest with prestenotic dilatation and obstructive symptoms, such as abdominal bloating, distention, and pain.^{5,6} Strictures in CD are described as either inflammatory or fibrotic. They can occur de novo, at sites of bowel anastomosis or in the ileal pouch.⁵

Fibrosis is the result of complex interactions among inflammatory mediators including growth factors (ie, transforming growth factor β , insulin-like growth factor, platelet-derived growth factor, and basic fibroblast growth factor) and cytokines (ie, interleukin [IL]-13 and IL-17), which are all involved in driving changes in tissue architecture and function. This can ultimately impact the structure and function of the small intestine and colon and can result in clinical symptoms.⁷

In the last two decades, the medical therapy for CD has improved remarkably, and the introduction of biologics has dramatically changed the therapeutic approach in both adults and children. However, CD strictures generally show a poor response to medical therapies, and surgical bowel resection or surgical strictureplasty are often required.^{8,9} Over the last three decades, the role of endoscopic balloon dilation in this clinical setting has increased vastly. Nowadays, it represents a valid complementary option.⁴

Epidemiology

At the time of diagnosis, intestinal strictures may occur in about 5%–10% of patients with CD.^{6,7} Up to one-third of the patients will develop intestinal strictures within 10 years of disease activity (mainly at the terminal ileum, ileocolonic, and colonic level).^{8,9}

Though inflammatory strictures have the option of other medical treatments, 60%–70% of these patients will nevertheless require surgery at follow-up.¹⁰ Moreover, a high rate of post-surgical relapses is observed: 40% at 4 years after bowel resection, and 50% at 10–15 years after ileocecal resection. Strictureplasty has also been associated with a risk of stricture relapse in 34% of the cases at 7.5 years. This implies that up to one-third of CD patients will undergo more than one surgery in their life course.¹¹ Patients with early onset of disease have an increased risk of surgical relapse and a need of repeated resections, which may result in a short bowel syndrome.⁶

Factors that affect stricture formation can be broadly categorized into clinical presentation parameters, serologic markers, and genetic susceptibility.⁴ Parameters that have been proved to correlate with stricturing CD behavior and worse disease outcome include smoking, lower educational level, and younger age at diagnosis.¹² As outlined by the data from the TREATTM registry (the Crohn's therapy, resource, evaluation, and assessment tool), other factors that are associated with stricture formation include CD severity at the time of disease onset, CD duration, ileal disease, and use of corticosteroids.¹¹

The role of serologic markers in predicting disease course in IBD is currently not completely defined, though generally perinuclear anti-neutrophil cytoplasmic antibody (pANCA) positivity is thought to correlate with a more benign, "UC-like" clinical presentation, while ASCA antibody (anti-*Saccharomyces cerevisiae* antibody), OmpC (*Escherichia coli* outer membrane porin C), *Pseudomonas fluorescens*-associated sequence I2 (bacterial sequence I2) and Cbir1 (flagellin) correlate with more complicated CD.¹³

Nucleotide-binding oligomerization domain 2(NOD2)/caspase recruitment domain-containing 15 (CARD15) remains the most established genetic predictor of complicated CD, though it is not currently able to predict which patients should be targeted for more aggressive early intervention.¹⁴ The three major polymorphisms reported with CD are Arg702Trp (SNP8), Gly908Arg (SNP12), and Leu1007insC (SNP13), and they have been associated with ileal disease, stenosis, and need for surgery.^{4,14} Apart from NOD2, other genetic markers for CD confirmed in multiple populations include ATG16L1 (autophagy-related 16-like1 gene) and IL-23R (IL-23 receptor gene).⁴

Diagnostic techniques: the role of radiologists and endoscopists

Symptomatic CD patients often undergo diagnostic imaging studies for assessment of disease activity or complications including bowel strictures and obstructions.¹⁵ It is vital to differentiate between inflammatory versus fibrous-predominant strictures, as the optimal therapy will consequently differ.¹⁶

Intestinal ultrasound

Intestinal ultrasound (US) represents a useful option to evaluate aspects including wall thickness, transmural complications, color Doppler grade, quantitative analysis of the contrast enhancement, and the presence and severity of strictures. Ripollés et al investigated the accuracy of several US parameters for evaluation of mural inflammation in CD,

referring to the related histopathology findings.¹⁶ They report a good correlation between the sonographic and pathology scores, for both inflammatory and fibrostenosing strictures. According to this study, US can be a useful tool for distinguishing inflammatory from fibrostenotic lesions in CD.¹⁶

Magnetic resonance enterography and computed tomography

Computed tomography (CT) and magnetic resonance enterography (MRE) are now widely used in patients with CD, both for diagnosis and monitoring.¹⁷ These techniques have almost completely replaced traditional barium small bowel follow-through studies.⁷ MRE provides information regarding disease activity, chronicity, and stricture formation without using ionizing radiation.¹⁵ A retrospective study by Ha et al (Table 1) showed that MRE provides an effective alternative to CT for evaluating and directing care in CD patients, particularly those presenting with obstructive symptoms.¹⁵ Positive findings of CD including active inflammation, stricturing, and penetrating disease were more frequent in patients with obstructive symptoms, in respect to other indications ($P=0.001$).¹⁵

Other supporting data are provided in a retrospective study by Patel et al (Table 1), who sought to assess the use of MRE for management of IBD in a single medical center.¹⁷ The authors validated the potential of enterography in revealing active disease and its complications, which are not evident on endoscopy (including strictures, perianal fistulas, and abscesses). They concluded that MRE should be considered in the initial diagnosis, assessment of disease activity, and monitoring of therapy in patients with IBD.¹⁷

Small bowel endoscopy

The role of small bowel endoscopy (SBE) for diagnosis and assessment in pediatric patients with suspected or established CD was investigated in a prospective cohort study conducted by Di Nardo et al.¹⁸ On the basis of the success rate and of the absence of complications, the authors concluded that SBE is a useful and safe endoscopic procedure for evaluating the small bowel in pediatric patients with CD. In fact, not only does it have the potential to provide a definite diagnosis of CD when this is uncertain, but it is also an effective option in the management of small-bowel strictures, thus allowing clinicians to avoid surgery.¹⁸

Table 1 Diagnostic techniques for stenosing Crohn's disease. Synopsis of main papers cited in this review

Authors	Study type	Number of patients	Main findings	Conclusions
Ha et al ¹⁵	Retrospective cohort study	119 Crohn's disease pts; 133 MRE scans	Positive findings of Crohn's disease (eg, active inflammation, stricturing, and penetrating disease); more frequent in pts with obstructive symptoms (87.5%) vs other indications (58.1%) ($P=0.001$) In the subgroup of pts with obstructive symptoms, MRE findings assisted in directing a change of clinical management toward escalation of medical therapy in 55% and surgery in 32.5% pts, respectively Review of surgical resection specimens confirmed MRE findings of disease activity and fibrosis in 92% of cases	MRE provides an effective alternative to CT for evaluating and directing care in Crohn's disease pts, particularly those presenting with obstructive symptoms
Ripollés et al ¹⁶	Prospective cohort study	25 Crohn's disease pts	Good correlation between the US and pathology scores, for both inflammatory and fibrostenosing strictures Significantly negative association between the color Doppler grade and the pathologic fibrostenotic score	US and CEUS: useful tools for distinguishing inflammatory from fibrostenotic lesions in Crohn's disease US yields useful information for the management of Crohn's disease
Patel et al ¹⁷	Retrospective cohort review	270 IBD pts; 258 Crohn's disease pts; 311 enterography studies (291 MRE and 20 CT enterographies)	Active SB disease noted in 73/311 (23.5%) of studies Complications (eg, strictures, perianal fistulas, abscesses, and SB fistulas) noted in 108/311 (34.7%) of studies Endoscopic and enterography defined active disease had an agreement of $\kappa=0.36$ in the ileum ($n=179$) 142/311 (45.7%) enterographies were associated with recommended medication changes within 90 days Surgery or EBD of stricture recommended following 41/311 (13.2%) enterographies	Enterography reveals active disease and complications not evident on endoscopy Enterography should be considered in the initial diagnosis, assessment of disease activity, and monitoring of therapy in pts with IBD

Abbreviations: CT, computed tomography; EBD, endoscopic balloon dilatation; MRE, magnetic resonance enterography; pts, patients; SB, small bowel; vs, versus; US, ultrasound; IBD, inflammatory bowel disease; CEUS, contrast-enhanced ultrasound.

Medical availabilities: the role of gastroenterologists and pediatricians

While potent anti-inflammatory medications have reduced the symptoms of CD, more than 60% of patients eventually require surgery due to the development of fibrosis.¹⁹ Even after the introduction of biologics, the population-based rate of surgery for CD has not decreased. This might be due to late initiation of these therapies, after the fibrosis cascade is unstoppable. To date, no specific intestinal antifibrotic therapy exists.⁷ Despite the lack of data in literature, azathioprine has been shown to reverse the inflammatory changes at the anastomotic site and to maintain remission in patients with CD.²⁰

The role of biological therapy in case of CD strictures remains controversial.^{21–24} Because of reports of complete obstruction after treatment with infliximab in patients with or without initial stricture, its use was contraindicated in stenotic forms of CD by some authors.^{21–24} Theoretically, the rapid tissue healing induced by infliximab administration may result in marked architectural changes in the intestinal wall, which can lead to wall stricturing.²⁵ However, strictures do not occur without inflammation, and chronic inflammation per se may lead to strictures. In fact, a long-term inflammatory process sustained by increased cytokine production results in an excess of fibrotic response. On the other hand, substantial thickening of the mesenchymal layers is observed during mucosal repair. According to the latest evidence, the control of chronic inflammation to prevent fibrosis and stenosis seems more important than the risk of fibrosis induced by treatment, thus justifying infliximab infusions.^{23,24,26}

Govani et al reviewed the evidence that suggests early aggressive therapy is beneficial, especially in patients diagnosed before the age of 40 years, and with ileal or perianal disease. Patients with symptomatic strictures may benefit from early surgery (before penetrating complications) followed by initiation of biologics. With increased early use of biologics and better control of inflammation, a global reduction in intestinal fibrosis and related complications arising from CD should be expected.¹⁹

The role of surgeons

CD is usually managed medically, without surgery, while surgery is mostly indicated for complications that do not respond to other medical management. Within 13 years of the disease onset, an estimated 74% of cases require surgery. Also, in the subsequent 10-year follow-up period, the rate of relapse is about 30%–50%.²⁷ Chronic fibrosis and scarring

that do not respond to conservative management necessitate surgery, and 25% of patients with CD undergo surgery for intestinal obstruction.²⁷ CD patients with ileocolonic disease do worse with medical therapy ($P=0.026$) and may require surgery sooner than patients with ileal disease ($P=0.023$).²⁸ A removal/resection is required in case a longer segment of intestine is involved or when multiple strictures that preclude a simple strictureplasty are present.²⁷ As an alternative to intestinal resection, fibrotic strictures can be treated with strictureplasty.²⁹ Although the latter has the advantage of preserving bowel length, it is still associated with a significant operative recurrence rate of 34% during a median follow-up period of 7.5 years.¹⁰

There are 15 distinct strictureplasty methods described, though the two most commonly employed for CD are the Heineke–Mikulicz and the Finney methods. In particular, jejuno–ileal disease offers the widest choice for types of strictureplasty, and generally a Heineke–Mikulicz procedure is used for a shorter disease extent (<5 – 10 cm), whereas the Finney or Jaboulay procedures are used for longer segment strictures. Modified procedures include Judd, Moskel, Walske, Neumayer, and isoperistaltic strictureplasties.^{30,31} According to a 2007 meta-analysis that analyzed 1,112 patients with a total of 3,259 strictureplasties, this approach has a complication rate of 4% (including leak, fistula, and abscess) and a recurrence rate of 28% by 5 years (Table 2).³²

A colectomy can be required when significant or large segments of the colon are involved. An anastomosis between the ileum and the rectum can be performed when the rectum is free of disease.²⁷ A segmental colectomy represents a possible option when a short segment is involved, and the patient has not presented with a significant number of complications or recurrences.³³ A proctocolectomy is needed when the rectum is involved, and an ileostomy is usually performed in conjunction.²⁷ Ileo-anal pouch anastomosis is a surgical procedure done between the ileum and anus after proctocolectomy. This procedure is usually not an option for CD, as the terminal ileum, which is used to form the pouch, is likely to relapse.²⁷

The surgical management of CD has advanced considerably over the past two decades. Surgeons are more specialized, and minimally invasive techniques have been introduced from which young patients with CD benefit in particular. Moreover, thanks to improved indications to surgery, such options still represent, at present, a valuable alternative to long-term medical treatments in selected patients. A number of studies have compared short-term outcomes associated with laparoscopic and with open approaches for ileocolic resections in patients

with non-penetrating primary CD, though only two of these studies are randomized controlled trials (RCT).^{19,20} These findings clearly favored the laparoscopic approach over its open counterpart in terms of postoperative morbidity and length of hospital stay, despite the higher costs for the longer operative time. No increase in morbidity or mortality rates was observed.^{34,35}

Although surgical treatment is effective for CD strictures, there is invariably a high risk of recurrence of CD. Medications used in the treatment of CD, such as immunosuppressants, render the patients more prone to complications and post-surgical procedures.²⁷ Symptomatic recurrence is usually seen in approximately 30% of patients at 3 years, with considerably increasing incidence in 10 years. In 20 years, surgery for recurrence is estimated at 70%. Anastomosis sites are the most common locations of recurrence. In the immediate postoperative period, thickening of the loops may be reactive. Obstruction of the bowel due to disease recurrence or the presence of extensive adhesions requires surgical correction.²⁷ Repeated surgery can result in complications related to short bowel syndrome, requirement for total parenteral nutrition, and related complications. Younger patients tend to run an aggressive course with a shorter duration to reoperation.²

The role of operative endoscopy

The advent of endoscopy in the management of complicated CD strictures has changed the approach to the management of anastomotic and small bowel strictures in these patients. Balloon enteroscopy now allows the assessment of areas not deemed possible in the past for dilations.³⁶ Endoscopic balloon dilation (EBD) is a minimally invasive technique that can reduce or delay the need for surgery in patients with CD-related strictures.^{6,37}

There have been several studies aimed at reporting the clinical efficacy, technical feasibility and short and long term results of EBD.^{6,36,37} Almost all studies have used resolution of symptoms and/or surgery-free period as outcomes. Most studies included had less than 60 patients.^{36,37}

According to current knowledge, EBD in CD strictures appears to be a safe technique (technical success rate of 70%–95%, defined as achieving an endoscopically passable residual stricture) with a low complication rate (0%–10%). Usually, more than one dilatation session is required for every stricture. Complications such as hemorrhages are rare, while perforations are reported mostly in studies in which 25 mm balloons are used. Up to 47% of CD patients show a long-term global benefit, ie, a surgery-free period at 3-year follow-up.^{38,39}

Moreover, with the new generation of double or single endoscopic balloon enteroscopy, this procedure can be performed at almost any level of the gastrointestinal tract, which allows for conserving the bowel length.^{37,40} The only factor that was proved to significantly affect dilatation efficacy and surgery-free follow-up was the stricture length. In contrast, naïve vs post-surgical, steroid injection, and active vs inactive CD were all deemed to be non-significant.³⁶

Up to now, EBD has been shown to be equally effective in adult and pediatric CD patients. The endoscopic management of CD strictures is of particular importance in children, considering the long life expectancy of these patients together with the major consequences of developing a short bowel syndrome, if repeated surgical resections are performed. Moreover, many clinical concerns are related to malnutrition and subsequent failure to thrive in children with obstructive condition or post-large bowel resections.^{6,41} EBD could also be taken into consideration as an adjunct to surgery, given that it has been shown to add at least 50% efficacy to the initial surgery by prolonging the surgery-free period.³⁶

It is difficult, at present, to define the relapse risk after EBD, as the published studies are based on very different follow-up periods. According to a prospective long-term study by Stienecker et al, stricture relapses were observed in 46% of patients after a mean of 32 months. Endoscopic re-dilatation was successful in 64% of the patients with relapsing strictures, and the long-term success rate was 80%. On the basis of these long-term results, the authors concluded that EBD, repeated if necessary, is comparable to surgical treatment, whereas the relapse rate after a single balloon dilatation is probably higher than after surgical intervention (Table 2).³⁷

De Angelis et al evaluated short- and long-term efficacy of EBD in a cohort of consecutive patients with symptomatic CD-related strictures (Table 2).⁶ Both naïve and post-operative strictures of any length or diameter, with or without associated fistula, were included. During the follow-up time, the technical success of EBD was 100%, there were no procedure-related complications, and surgery was avoided in 92.6% of the patients. Two patients, both presenting with ileocecal strictures associated with fistula, failed to respond to treatment and underwent surgical stricture resection. No difference was observed between the EBD success rate for naïve and postoperative CD related strictures ($P>0.05$). The authors of that study concluded that EBD appears to be a safe and effective procedure in the therapeutic management of CD-related strictures of any origin and dimension in order to prevent surgery.⁶

Table 2 Surgical treatments for stenosing Crohn's disease. Synopsis of the main papers cited in this review

Authors	Study type	Number of patients	Main findings	Conclusions
Futami et al ³⁰	Retrospective pt review	103 pts with obstructive Crohn's disease 293 strictureplasties (235 Heineke–Mikulicz, 22 Finney, 35 Jaboulay, and one side-to-side isoperistaltic strictureplasty)	No operative mortality Septic complications related to strictureplasty in four pts, reoperation in two pts (1.9%) 5- and 10-year reoperation rates were 45% and 61.9%, respectively, for all pts Further operation for recurrence required in 45 pts (43.7%); 21 pts (20.4%) with recurrence at the site of strictureplasty; 14 pts with re-stricture; seven pts with perforating disease Perforating disease for recurrence: more frequent at the site treated by the Finney or Jaboulay procedure compared with Heineke–Mikulicz Median operative time: 248 (190–292) minutes 15 (16%) conversions: not associated with increased length of stay or with postoperative complications Overall postoperative length of stay: 5 (range, 4–7) days Short-term complications in 34% (reoperation in five pts; obstruction in three, anastomotic leak in two pts) No 30-day mortality Median length of the incision: 5 cm in the laparoscopic group vs 12 cm in the conventional group Overall recovery of 80% of FEV (1 second) and FVC: median of 2.5 days for laparoscopic vs 3.5 days for conventional ($P=0.03$) Flatus and first bowel movement returned a median of 3 and 4 days after laparoscopic vs 3.3 and 4 days after conventional surgery, respectively ($P=0.21$) Median length of stay: 5 days (range, 4–30 days) for laparoscopic, and 6 days (range, 4–18 days) for conventional surgery Major complications in one pt in each group. Minor complications in four laparoscopic and eight conventional pts ($P<0.05$) No mortality Two laparoscopic pts converted to conventional as a result of adhesions or inflammation All pts recovered well, with no clinical recurrences in the follow-up period (median, 20; range, 12–45 months) Conversion rate: three pts (10%) Median operating time longer in laparoscopic compared with open surgery (115 vs 90 minutes; $P<0.003$) Hospital stay shorter in the laparoscopic group (5 vs 7 days; $P=0.008$) The number of pts with postoperative morbidity within the first 30 days differed between the laparoscopic and open group (10% vs 33%; $P=0.028$) No statistically significant difference in QoL between the groups during follow-up Median overall costs during the 3 months' follow-up were significantly different (higher for open surgery; $P=0.042$)	In the long term, strictureplasty is safe and useful for preserving the intestine in the surgical treatment of Crohn's disease if strictures are carefully selected Minimally invasive colectomy in pts with Crohn's disease colitis can be safely accomplished with reasonable operative times, conversion rates, and excellent postoperative outcomes Within a single centre experience, laparoscopic techniques offered a faster recovery of pulmonary function, fewer complications, and shorter length of stay compared with conventional surgery for selected pts undergoing ileocolic resection for Crohn's disease
Holubar et al ³³	Retrospective pt review (Single center; time period: 1997–2008)	92 Crohn's disease pts who underwent minimal invasive colectomy		
Milsom et al ³⁴	Prospective, randomized trial in one surgical department (comparing laparoscopic vs conventional techniques)	60 Crohn's disease pts		
Maartense et al ³⁵	Prospective, randomized controlled trial	60 Crohn's disease pts (randomized for laparoscopic-assisted or open surgery)		Although QoL measured by SF-36 and GIQLI questionnaires was not different for laparoscopic-assisted compared with the open ileocolic resection, morbidity, hospital stay, and costs were significantly lower

Abbreviations: CT, computed tomography; FEV, forced expiratory volume; FVC, forced vital capacity; MRE, magnetic resonance enterography; pts, patients; QoL, Quality of Life; vs, versus; SF-36, Short Form (36) Health Survey; GIQLI, Gastrointestinal Quality of Life Index.

A study performed by Chen and Shen showed that the efficacy and safety of EBD in the treatment of strictures is comparable for CD and non-CD related strictures (Table 3).⁴² Three larger studies have recently been performed to assess the efficacy of EBD for Crohn's strictures.^{4,38,43,44} All the studies used a Boston Scientific through the scope balloon, 12–25 mm in diameter, and conscious sedation. Mueller et al (Table 3) investigated 55 patients, mostly with de novo strictures (69%) and reported an initial success rate of 95%.⁴³ Moreover, 76% of patients never required repeat treatment during the follow-up period. They also reported a statistically significant correlation between the need for surgery and stricture length ($P=0.006$), with average stricture requiring surgery being 7.5 cm vs 2.5 cm for the strictures amenable to endoscopic therapy. One patient was perforated.⁴³

Scimeca et al (Table 3) followed 37 CD patients prospectively (39 strictures, 72 dilations) at a single centre. The strictures were mostly post-surgical (97%), with 77% being at ileocolonic anastomosis sites. The success rate post-first dilation was 51%, and the overall success rate (after subsequent dilations) was 89%. No complications were reported.³⁸ The Gustavsson et al retrospective study (Table 3) included a total of 178 patients, most of whom had either ileal or ileocolonic disease, and approximately 40% had stricturing disease at presentation (anastomotic or de novo). At 5 years, 52% of patients had at most one additional dilation, and 36% had a surgical resection.⁴⁴

Recently, a combined medical and endoscopic therapy has been shown to be effective in the treatment of CD-related strictures. EBD should therefore be considered, together with the medical therapy, as an option to bridge the patient to surgery in better performance conditions (eg, nutrition, inflammatory status), shifting from emergency to elective surgery.⁶ In cases of multiple strictures, based on their clinical experience, Stienecker et al suggested that only one stricture should be dilated in each session. Strictures of more than 5 cm in length should instead be treated surgically. Fistulas originating from the stricture were considered contraindications for EBD (Table 3).³⁷

The use of intralesional injection of medications in stricturing CD

Given the high rate of stricture recurrence after dilatation, intralesional injection of medications has also been studied.^{45–47} Nowadays, it is still unknown whether additional medical treatment can influence the recurrence rate.³⁶ Raedler et al treated 30 patients after successful dilatation of ileocecal strictures with azathioprine and budenoside or

with placebo. After both 6 and 12 months, the patients in the placebo group presented with a statistically significant greater number of symptoms due to strictures, and needed surgical interventions more frequently.⁴⁶ A pediatric study of 29 patients also reported a significant trend in patients, who did not receive intralesional steroids, toward re-dilatation and surgery.⁴⁷

However, another study that investigated single treatment of intrastricture triamcinolone injection did not prove any reduction in the time to re-dilatation after EBD of CD ileocolonic anastomotic strictures (Table 3).⁴⁵ Moreover, Thienpont et al observed no significant effect of active disease at the time of dilation or systemic medical therapy afterwards, on re-dilatation or surgery (Table 3).⁴⁸ The effect of intralesional injection of infliximab has been studied in a small number of patients and consensus is lacking. Thus, there is no clear evidence at this time to support the role of intralesional injection of medications following dilation.

The use of extractible metallic stents in stricturing CD

The use of extractible metallic stents has also been considered as a possible alternative to EBD, in order to lower the number of recurrences. Levine et al (Table 3) undertook a retrospective review of all patients undergoing endoluminal stenting for CD strictures.⁴⁹ Five patients underwent this procedure with a 100% rate of technical and an 80% rate of clinical success. There was one complication involving re-obstruction, which required surgical intervention; there were no mortalities. The authors concluded that stenting of CD strictures is a safe and effective alternative to surgery, which can provide lasting benefit in selected patients.⁴⁹

A prospective pilot study conducted by Attar et al (Table 3) aimed at investigating the feasibility and clinical effectiveness of the use of extractible stents in the treatment of CD intestinal strictures.⁵⁰ Eleven patients were prospectively included and were treated with transitory stent placement, which was technically successful in ten patients. Obstructive symptoms were relieved in six out of ten patients. Two patients needed surgery related to the procedure, and six downstream migrations were observed.⁵⁰ The authors concluded that although stenting appears an effective technique in treating symptomatic CD intestinal strictures, the procedure is associated with a prohibitively high rate of spontaneous migrations and complications.⁵⁰ Other recent studies that have used self-expanding metallic and biodegradable stents, and report a high incidence of migration.^{2,49,50} Nevertheless, clinical success has ranged from 45%–80%. The majority

Table 3 Endoscopic techniques for diagnosis and treatment of stricturing Crohn's disease, and synopsis of the main studies cited in this review

Authors	Study type	Number of patients	Main findings	Conclusions
De Angelis et al ⁶	Prospective cohort study	26 Crohn's disease pts (27 symptomatic strictures)	46 EBDs performed: technical success of 100% No procedure-related complications EBD success rate after first dilation: 81.5% Surgery avoided in 92.6% of the pts during the entire follow-up Surgical stricture resection required in two pts with no response to treatment (both with ileocecal strictures and fistula) No difference observed between the EBD success rate for naïve and postoperative Crohn's disease-related strictures ($P>0.05$) WCE: diagnostic of Crohn's disease in three pts, and suggestive of Crohn's disease in seven SBE allowed successful dilation of SB strictures in two pts with suspected Crohn's disease and in three with long-lasting Crohn's disease No complications occurred	EBD: safe and effective procedure in the therapeutic management of Crohn's disease-related strictures of any origin and dimension, in order to prevent surgery
Di Nardo et al ¹⁸	Prospective cohort study	30 total, 16 with suspected Crohn's disease and unspecific upper and lower GI endoscopies; 14 with longstanding Crohn's disease and previous surgery	Stricture relapses in eleven pts (46%) after a mean of 32 months 13 pts: successfully dilated, remained free of symptoms and stricture relapse over the complete follow-up period of >6.5 years Endoscopic re-dilatation successful in 64% of the pts with relapsing strictures Long-term success rate: 80%	SBE is a useful and safe endoscopic procedure for evaluating the SB in pediatric pts with suspected or established Crohn's disease SBE: effective in the management of SB strictures SBE can be helpful in redirecting therapy in selected Crohn's disease pts
Stienecker et al ³⁷	Prospective cohort study	25		EBD, repeated if necessary, is comparable to surgical treatment Relapse rate after a single balloon dilatation: higher after EBD than after surgical intervention In cases of multiple strictures, only one stricture should be dilated in each session Strictures of more than 5 cm in length should be treated surgically Fistulas originating from the stricture: contraindications for EBD
Chen et al ⁴²	Retrospective cohort study	90, including 30 (33.3%) with non-Crohn's disease strictures and 60 (66.7%) with Crohn's disease strictures	Pts with Crohn's disease strictures were younger than those with non-Crohn's disease strictures at the time of disease diagnosis ($P<0.001$) and at the time of the first dilation ($P<0.001$) No significant differences in characteristics of strictures and their endoscopic treatments between the Crohn's disease and non-Crohn's disease groups, except for the percentage of pts who were treated with intralesional corticosteroid injection (25.0% versus 6.7%, respectively, $P=0.046$) Pts in the two groups had similar technical success rates (94.0% versus 93.9%, respectively, $P=1.00$) Fewer pts in Crohn's disease stricture group required emergency room visits due to obstructive symptoms from recurrence of disease (1.7% versus 16.7%, respectively, $P=0.02$) No procedure-related complications in either of the two groups Success rate post first dilation: 51% No complications	The efficacy and safety of EBD in the treatment of Crohn's disease and non-Crohn's disease strictures seems to be comparable
Scimeca et al ³⁸	Prospective cohort study	37 Crohn's disease pts (39 strictures, 72 dilations) (Strictures: 97% post-surgical; 77% at ileocolonic anastomosis sites)		Overall success rate of EBD (after subsequent dilations): 89%

Mueller et al ⁴³	Retrospective pt review (study time period: 1999–2008)	55 Crohn's disease pts 93 EBDs for 74 symptomatic strictures	Endoscopic treatment: successful in 76% of the pts; ~ 24% of the pts required surgery All pts who underwent surgery had de novo strictures in the TI (significantly longer compared to the ileal strictures that responded to endoscopic treatment) Failure of endoscopic treatment was observed only in long-segment strictures in the TI Cumulative proportions of pts undergoing surgery at 1, 3, and 5 yrs: 13%, 28%, and 36%, respectively Complication rate per procedure for all 178 pts: 41/176 (5.3%); bowel perforation (n=1, 1.4%); major bleeding requiring blood transfusion (n=8, 1.0%); minor bleeding (n=10, 1.3%); abdominal pain or fever (n=12, 1.5%) Ten pts underwent surgery due to complications (perforation, n=8, bleeding n=2) No procedure-related mortality	The long-term success of EBD depends on the type of the strictures, their location, and their length Statistically significant correlation between the need for surgery and stricture length ($P=0.006$), with average stricture requiring surgery being 7.5 cm vs 2.5 cm for the strictures amenable to endoscopic therapy EBD: efficacious and safe alternative to surgical resection of intestinal strictures in Crohn's disease At 5-year follow-up, 52% of pts required no further or one additional dilation only; 36% had undergone surgical resection Low complication frequency
Gustavsson et al ⁴⁴	Retrospective cohort study	178 Crohn's disease pts (776 dilations, of which 621 [80%] were on anastomotic strictures)	Re-dilatation in one of six pts in the placebo group and in five of seven pts in the steroid group ($P=0.06$)	A single treatment of intrastricture triamcinolone injection did not reduce the time to re-dilatation after EBD of Crohn's disease ileocolonic anastomotic strictures, and there was a trend toward a worse outcome
East et al ⁴⁵	Prospective cohort study (pilot study comparing local quadrantic injection of triamcinolone [40 mg total dose] after EBD of Crohn's disease ileocolonic anastomotic strictures vs saline placebo)	13 Crohn's disease pts (seven treated with steroids, six with placebo)	Re-dilatation required in one of the 15 pts receiving CS vs five of the 14 placebo pts Surgery needed in four of the placebo pts, but in none of those receiving CS The two groups statistically differed in the time free of re-dilatation ($P=0.04$), as well as for time free of surgery after EBD ($P=0.02$), which were worse in the placebo group compared to the CS group Immediate success of a first dilatation: 97% Complication rate: 5% Recurrent obstructive symptoms led to new dilatation in 46% or surgery in 24% after a median follow-up of 5.8 yrs 100% rate of technical and 80% rate of clinical success Mean follow-up: 28 months Mean long-term luminal patency: 34.8 months One complication involving re-obstruction, required surgical intervention No mortality	In stricturing pediatric Crohn's disease, intraleisional CS injection after EBD is an effective strategy for reducing the need both for re-dilatation and surgery Long term efficacy of EBD of Crohn's disease outweighs the complication risk
Di Nardo et al ⁴⁷	Prospective, randomized, double-blind, controlled trial	29 pediatric pts with stricturing Crohn's disease (randomized to receive intrastricture injection of CS [n=15] or placebo [n=14] after EBD) 138 237 dilations	Stent placement: technically successful in ten pts Obstructive symptoms: relieved in six out of ten pts Two pts needed surgery related to the procedure Six downstream migrations Only one pt could have the stent extracted as scheduled on day 28 and remained symptom-free after 73 months of follow-up	Endoluminal stenting of Crohn's disease strictures is a safe and effective alternative to surgery which can provide lasting benefit in selected pts
Thienpont et al ⁴⁸	Retrospective cohort study	Five	Stent placement: technically successful in ten pts Obstructive symptoms: relieved in six out of ten pts Two pts needed surgery related to the procedure Six downstream migrations Only one pt could have the stent extracted as scheduled on day 28 and remained symptom-free after 73 months of follow-up	Though stenting appears an effective technique in treating symptomatic Crohn's disease intestinal strictures, the procedure is associated with a prohibitively high rate of spontaneous migrations and complications
Levine et al ⁴⁹	Retrospective review (all pts undergoing endoluminal stenting for Crohn's disease strictures from 2001–2010)	Eleven (quiescent Crohn's disease pts except for obstructive symptoms associated with intestinal stenosis of less than 50 mm length on enterography)		
Attar et al ⁵⁰	Prospective cohort study			

Abbreviations: CS, corticosteroids; CT, computed tomography; EBD, endoscopic balloon dilatation; GI, gastrointestinal; MRE, magnetic resonance enterography; pts, patients; SB, small bowel; TI, terminal ileum; vs, versus; WCE, wireless capsule endoscopy; yrs, years; SBE, single balloon enteroscopy.

of stents in these studies were placed in postsurgical strictures.² Overall, metal stents have been reported as an effective alternative to surgery for the palliation of patients with colorectal neoplastic obstruction.² However, at present, the role of endoluminal stenting in benign obstruction, especially for CD, is still controversial, with limited data and widely disparate outcomes.^{49,50}

Practical guidelines for the management of strictures in CD

The European Panel on the Appropriateness of CD Therapy (EPACT II)⁵¹ have developed appropriateness criteria for the management of CD strictures. Moreover, a flow chart on this topic is also outlined in a recent review by Rieder et al.⁷ In summary, when clinical symptoms of intestinal obstruction appear in patients with CD, a radiologic assessment of bowel obstruction and an evaluation for active intestinal inflammation are prompted. When intestinal strictures are documented, anti-inflammatory treatments are recommended if signs of active disease are present; if this is not the case, a fibrotic stricture should be presumed, and its location, number, angulation, and diameter of the narrowed tract ($>$ or $<$ 4 cm) need to be assessed. Once the diagnostic assessment is completed, options including surgical resection, strictureplasty, or endoscopic dilatation have to be evaluated.^{7,51}

Indications for strictureplasty include: presence of multiple strictures over extensive length of bowel, previous significant small bowel resection ($>$ 100 cm), short bowel syndrome, strictures without phlegmon or septic fistula, duodenal strictures, and anastomotic strictures. Contraindications include: associated abscess or phlegmon, perforation with diffuse peritonitis, suspicion of carcinoma in the stricture, or poor nutritional status. Strictureplasty can be performed safely in active disease.^{7,51}

Oncological strictures

Patients with IBD and dysplasia have pathologic characteristics and risks that differ from those of patients with sporadic carcinomas. Therefore, surgical interventions need to be more aggressive in this group of patients than in sporadic cases.⁵² Only 1%–2% of all general colorectal cancer (CRC) cases per year are diagnosed as CRC arising in IBD. However, as 15% of all IBD deaths are associated with CRC, cancer screening is particularly required in this group. It has to be considered that cancers in patients with UC and CD often present not as mass lesions, but as dysplasia, strictures, or diffuse dysplasia. The risk for CRC development is lower before 8–10 years after symptom onset (3%). The rates of

CRC in CD (associated with a 5- to 20-fold increase in risk, in comparison with the general population) seem to mirror those of UC.^{53,54}

Cancer in CD is more likely to be right-sided and associated with ileal and right-sided colonic location.^{52,54} Colonic strictures are more common in CD (5%–17% of patients) than in UC (5% of patients). Thanks to the medical treatments currently available, which allow more patients to achieve remission, the rate of stricture occurrence seems to be improving nowadays.^{52,54} Colonic strictures should be considered malignant until proven otherwise.⁵² A study by Gumaste et al found that 29% of strictures in UC patients were malignant, whereas this malignancy rate was encountered in only 6.8% of CD colorectal strictures.⁵⁵

Strictureplasty is not indicated as primary management of colonic strictures in IBD. Strictures found at prior anastomotic sites in CD may be carefully dilated to allow endoscopic evaluation of recurrence or surgical complications from the original resection.^{52,56} Dysplasia and carcinoma at colonic strictures cannot always be detected preoperatively. Ideally, a stricture should be traversed, adequately examined, and biopsied. Nevertheless, a risk of sampling error can still occur.^{52,56} Oncology resection is indicated any time malignancy cannot be excluded.^{52,56}

While in UC proctocolectomy represents the only option to get to a definitive diagnosis or to rule out a carcinoma and to treat possible multifocal malignancy, in CD colorectal stricture, a segmental oncologic resection may be appropriate in a patient with limited segmental disease.⁵²

In summary, identification and treatment of dysplasia and CRC in IBD is a challenging task for clinicians.⁵² As sporadic adenomas and inflammatory-related dysplasia in patients with IBD are associated with a different type of risk for the patient, the treatment strategy should therefore be modulated accordingly. Surgical interventions should be based on disease location, finding of dysplasia, and patient morbidities. Although the gold standard for oncologic resection remains total proctocolectomy, many appropriate options exist that are aimed at intestinal continuity.⁵²

Perianal strictures

Perianal CD (PCD) comprises fistulizing lesions (fistulas and abscesses) and non-fistulizing lesions (fissures, ulcers, and strictures). While fistulizing PCD has been thoroughly described and analyzed by guidelines and literature, respectively, data on non-fistulizing PCD remain scarce. Anorectal strictures in CD are either associated with fistulizing

PCD or are a long-term consequence of the inflammatory process.⁵⁷

According to the Cardiff-Hughes classification, strictures are graded on a scale ranging from 0–2 (0= not present, 1= reversible stricture, and 2= irreversible stricture), and location-wise, they are distinguished as anal or lower rectum strictures. Although strictures S1 are mainly inflammatory, and strictures S2 tend to be fibrotic, in most cases both inflammatory and fibrotic compounds occur in association.⁵⁸

In order to assess the natural history and long-term outcomes of anorectal strictures, Brochard et al⁵⁷ reviewed all outcomes of patients with non-fistulizing PCD followed in a single unit, as well as subsequent therapeutic management. Out of a total of 102 CD patients, 59% achieved anorectal stricture healing after a median follow-up period of 2.8 years. An unfavorable course (defined as persistent stricture S2, or persistent stoma, or proctectomy at the end of follow-up) was seen in 32% of patients at the end of follow-up, and two patients developed anal adenocarcinoma. A multiple regression analysis showed that female gender, disease duration of CD of less than 10 years, and anal fistula at stricture diagnosis were significantly associated with anorectal stricture healing. Moreover, gender and introduction or optimization of tumor necrosis factor alpha (TNF α) antagonist treatment were associated with a decreased risk of unfavorable course. Conversely, the luminal B2 phenotype at CD diagnosis was the only factor associated with unfavorable course. The authors concluded that anorectal strictures related to severe perianal CD should not be considered as a non-reversible and complicated condition. In fact, in the era of biologics, this study shows a healing rate of anorectal stricture for more than 50% of patients after a 3-year follow-up period. Nevertheless, the need for stoma or proctectomy was required in approximately 25% of patients, which suggests that the presence of anorectal stricture still remains a marker of disease severity.⁵⁷

Dietary management: the role of dietitians

Given that CD is a debilitating chronic inflammatory condition of the bowel, it is of fundamental importance to promote an appropriate use of diet and nutritional therapy as part of the disease management. The British Dietetic Association has developed evidence-based guidelines on the dietary management of CD in adults, aimed at reducing variation in clinical practice. These guidelines include dietary management of stricturing disease.⁵⁹ The guidelines state that after a course of enteral nutrition for induction of remission, food re-introduction diets may be useful to help maintain disease

remission. Dietary fiber is contraindicated in the presence of strictures because of the risk of mechanical obstruction.⁵⁹

Conclusion

Stricture formation is a common complication of CD, occurring in approximately one-third of all patients with this condition. CD fibrotic strictures generally show poor response to medical therapies, and surgical bowel resection or surgical strictureplasty are often required.

Endoscopic dilatation represents a valuable treatment of small and large bowel strictures, with an acceptable rate of complications. EBD and surgery should not be seen as mutually exclusive alternatives for treating CD strictures; rather, EBD may be a complementary low-risk procedure that should be considered in both adult and pediatric patients in order to reach a symptom-free condition.

At present, given the complexity in reaching such a condition, the management of patients with stricturing CD requires a multidisciplinary approach. Gastroenterologists, pediatricians, radiologists, surgeons, specialist nurses, and dietitians are among the health care providers involved in supporting these patients throughout diagnosis, prevention of complications, and treatment.

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