

## Endoscopic management of inflammatory bowel disease strictures

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### Abstract

Stricture formation is a common complication of Crohn's disease, occurring in approximately one third of all patients with this condition. While the traditional management of such strictures has been largely surgical, there have been case series going back three decades highlighting the potential role of endoscopic balloon dilation in this clinical setting. This review article summarizes the stricture pathogenesis, focusing on known clinical and genetic risk factors. It then highlights the endoscopic balloon dilation research to date, with particular emphasis on three large recent case series. It concludes by describing the literature consensus regarding specific methodology and presenting avenues for future investigations.

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### INTRODUCTION

Crohn's disease is a chronic autoimmune disorder of the gastrointestinal tract, characterized by periods of disease activity and quiescence. The treatment is focused on prolonging the periods of inactivity, and minimizing the amount of inflammation when a flare does occur. However, 10%-15% of patients will have a continuous, unremitting course and at present, the disease is incurable<sup>[1]</sup>.

### DEMOGRAPHIC INFORMATION

The highest incidence of Crohn's disease has been reported in northern Europe (4-10.7/10<sup>5</sup>) the United Kingdom (0.7-6.7/10<sup>5</sup>) and North America (5.8-7.9/10<sup>5</sup>). The prevalence of Crohn's disease in North America is 44-201/10<sup>5</sup>; in Europe, the range is more variable, between 8-214/10<sup>5</sup>[2]. The number of patients affected is rising in the rest of the world as well. In South Korea, comparing the interval 1986-1990 to 2001-2005, the incidence of Crohn's disease increased significantly from 0.05/10<sup>5</sup> to 1.3/10<sup>5</sup>[3]. In China, the incidence of Crohn's disease incidence was found to be 1 × 10<sup>5</sup> and tripled in a decade of follow-up<sup>[3]</sup>.

### NATURAL HISTORY

The natural disease progression begins with aphthous ulcers, which progress to fistulae or strictures, more often in patients with ileal rather than colonic disease<sup>[4]</sup> The digestive segment affected tends to be stable over time<sup>[5]</sup> Approximately 40% patients will need surgery after 10

years of disease<sup>[6,7]</sup> and about 10% will have a permanent stoma<sup>[8]</sup>. Crohn's disease patients have a 1.52 greater mortality than the general population<sup>[9]</sup>.

Strictures, which occur in approximately 1/3 of patients after 10 years of disease<sup>[5]</sup>, are thought of as either inflammatory or fibrotic. Strictures and fistulae are often found in proximity of one another, either both being caused by the inflammation or the fistula developing to decompress the lumen from the increased wall tension caused by the stricture (Figure 1)<sup>[10]</sup>. Luminal dilation proximal to the stricture site is considered an indication that the wall has lost its elasticity and the stricture is permanent. Strictures also frequently occur at anastomotic sites, where generally the disease is likely to recur first<sup>[4]</sup>.

While there are medical options for addressing inflammatory strictures, the management of fibrotic ones has traditionally been thought of as largely surgical<sup>[11-13]</sup>. The role of endoscopy in the management of fibrotic strictures has not been well-defined, but several recent studies have shed significant light on this topic. Advantages of using endoscopic dilation over the more established surgical methods (strictureplasty or resection with primary anastomosis) include decreased invasiveness and adhesion formation, as well as preservation of intestinal length. Disadvantages include the need for repeat dilation.

This review article will describe the known risk factors for stricture formation, summarize the historical literature regarding endoscopic dilation of these strictures, and subsequently focus on three recent large studies on this subject, describing their findings and limitations.

## PREDISPOSING FACTORS FOR STRICTURE FORMATION

Known factors predisposing to stricture formation can be broadly categorized into clinical presentation parameters, serologic markers and genetic susceptibility.

An analysis of a database of 600 European patients, followed for 15 years, and published this year in *Gut*, reveals that parameters that have been proven to correlate with poorer disease outcome are smoking, lower educational level, younger age at diagnosis and shorter disease duration prior to inclusion in the database<sup>[14]</sup>. Similar data can be found in other demographic groups. An Israeli population of over 200 Crohn's disease patients with an average follow-up interval of 12 years demonstrated that smoking and male gender are correlated with increased risk of complications<sup>[15]</sup>. A New Zealand patient database of over 700 patients revealed that younger age at diagnosis, complicated disease and ileal disease all correlate with increased risk of perirectal disease<sup>[16]</sup>. The clinical factors demonstrated to correlate specifically with stricture formation, according to the TREAT registry, are severity of disease at the time of stricture formation, with a hazard ratio (HR) of 2.35, (95%CI 1.35-4.09), duration of Crohn's disease, HR 1.02, (95%CI 1-1.04), and new corticosteroid use, HR 2.85, (95% CI 1.23-6.57)<sup>[17]</sup>.

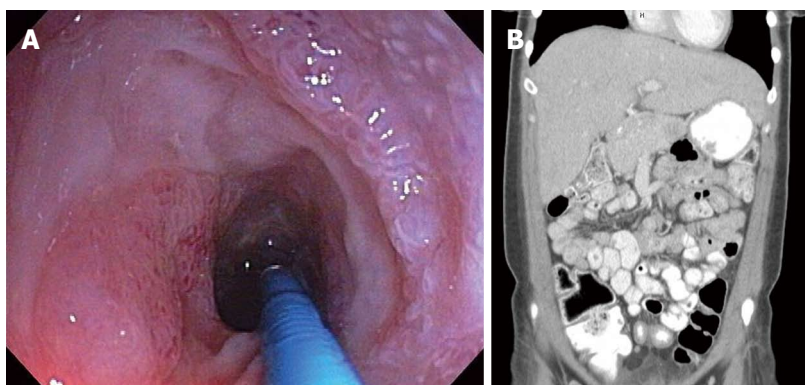
The role of serologic markers in predicting disease

course is at this point not well defined, though generally pANCA positivity is thought to correlate with a more benign, ulcerative colitis-like clinical presentation, while antibodies to oligomannan (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 Crohn's disease<sup>[18-22]</sup>.

*NOD2/CADR15* remains the most established genetic predictor of complicated Crohn's disease, though it is not currently able to predict which patients should be targeted for more aggressive early intervention. Located on chromosome 16q12, *NOD2* is a disease susceptibility gene, which when mutated increases the risk of developing Crohn's. It is expressed intracellularly and is considered part of the innate bacterial sensing mechanism. In a recent meta-analysis of 36 studies studying the role of the *NOD2* genotype on Crohn's disease<sup>[23]</sup> the relative risk of stricturing disease with any (one or more) mutant *NOD2* allele was 1.17 (95%CI 1.10-1.24,  $P < 0.001$ ). The 3 major polymorphisms reported with Crohn's are *Arg702Trp* (SNP8), *Gly908Arg* (SNP12), *Leu1007insC* (SNP13). These polymorphisms have been associated with ileal disease, stenosis, and need for surgery<sup>[24]</sup>. In the 10 studies that were able to analyze this further, the most likely mutation associated with stricturing disease was *Gly908Arg*, with a risk ratio of complicated disease of 1.33, sensitivity of 0.11 (95%CI 0.07-0.13) and a specificity of 0.93 (95%CI 0.88-0.96). Overall, the mutation most likely to correlate with an aggressive course was a homozygous mutation of *Leu1007insC*, with a AuROC of 0.98 but the confidence intervals of both the positive 2.6 (95% CI 0.4-16.6) and the negative 0.98 (95%CI 0.94-1.03) likelihood ratios cross 1. A recent analysis of banked blood from 593 patients with Crohn's disease also revealed that *Leu1007insC* (SNP13) was the most high risk allele of *NOD2*, with a  $P < 0.001$  for complication risk versus patients without *NOD2* mutations<sup>[25]</sup> and an odds ratio (OR) of 13.61 (95%CI 2.62-250.70). Apart from *NOD2*, other genetic markers for Crohn's confirmed in multiple populations include ATG16L1 (autophagy-related 16-like 1 gene) and IL23R (interleukin 23 receptor gene), the latter in a protective role<sup>[26]</sup>.

## ENDOSCOPIC BALLOON DILATION-HISTORICAL BACKGROUND

While the predisposing factors leading to stricture formation have not been fully elucidated, the generally accepted treatment paradigm has traditionally been surgical. This view has been challenged by novel endoscopic techniques. A review article<sup>[27]</sup> evaluated both surgical stricturoplasties and endoscopic balloon dilation studies performed between 1980 and 2009. 574 patients were studied in the endoscopic balloon dilation group, on whom a total of 1003 procedures were performed. There was a median technical success rate of 90%, a median intention-to-treat surgical recurrence rate of 27.6% (after



**Figure 1** Endoscopic and computed tomography imaging of a terminal ileum stricture in a patient with Crohn's disease. A: Endoscopic imaging of a terminal ileum stricture in a patient with Crohn's disease; B: Computed tomography imaging of a terminal ileum stricture in a patient with Crohn's disease.

a mean follow-up period of 21 mo) and a major complications rate of 3%. There was no uniform approach in terms of the technique used (including balloon size, time of insufflation, or use of intralesional steroid injections) and very few of the 23 papers included reported the site-specific recurrence rate. The surgical data from the same review article, which analyzed 1958 patients, revealed an equivalent median surgical recurrence rate of 24% after a median follow-up of 46 mo. Of note, the surgical complication rate was higher than the endoscopic one, 5% *vs* 3%.

A smaller, earlier and more detailed review<sup>[28]</sup> focused only on endoscopic dilation demonstrates similar results. The observation interval was 1990-2007. The total number of Crohn's patients included in this review was 347, with 353 strictures and 695 dilation sessions. The technical success rate was 86%, long-term clinical success rate was 58% and the rate of major complications 2%. The vast majority of these complications were perforations. The majority of the patients in these studies (66%) had dilation at the site of a prior surgery. In contrast to the former review article, the percent of patients requiring surgery after dilation (after successful dilation) was higher at 42%, perhaps partially explained by the longer follow-up period of 33 mo. The mean interval between dilation and surgery was 15 mo, and more than 2/3 of the patients in whom the procedure was performed successfully were able to avoid surgery during the entire follow-up period. The average patient age was 54 years old, the average time between diagnosis and dilation was 13 years. 29% patients had been on immunosuppressive therapy at the time of the dilation. The mean stricture length was 2.7 cm, and < 5 cm in 84% patients. Most studies did not use intra-lesional steroid injections, and the maximum balloon caliber was 18-25 mm. There was no consensus on insufflation technique, with both incremental increase and initial largest possible diameter being used. The time spent dilating was also highly variable, from 2 min to 1 h. The mean number of dilations per patient was 2.2. 14% patients were considered endoscopic failures, with angulated stenosis being the most common reason for this. The endoscopists in these studies applied the same technique to all the patients in their respective studies, with no alteration of procedure based on stricture characteristics or general disease state. An interesting finding of this

review was that a stricture of  $\leq 4$  cm in length had an OR of 4.01 for a surgery-free outcome.

## ENDOSCOPIC BALLOON DILATION-RECENT DATA

The data on this topic is limited by very small numbers. The studies included in the above two reviews are all less than 60 patients, retrospective and without a control group. However, three recent larger studies have been performed to help determine the utility of endoscopic dilation of Crohn's strictures. These studies are larger, single center cohort studies. Two are prospective, and the largest and most recent one is a retrospective chart review. The patients included were generally middle-aged (40-50 s). A stricture was defined as inability to traverse a segment of colon with the scope or a radiographically determined area of luminal narrowing with corresponding obstructive symptoms. Therapeutic success was defined as the ability to pass the scope through the stricture post-dilation. All three studies averaged about 2 dilations per patient. All the studies used a Boston Scientific through the scope balloon, 12-25 mm in diameter, and conscious sedation (Table 1). Strictures were generally anastomotic with the exception of the Mueller *et al* study, in which 69% had *de novo* strictures. Only the Scimeca *et al*<sup>[29]</sup> study recorded the number of smokers in the group (43%), and this proved to be insignificant as an outcome variable in that study.

The Gustavsson *et al*<sup>[30]</sup> study was the largest one to date, including a total of 178 patients, and the one with the longest follow-up period (median 12 years). It is a retrospective case series. Most patients had either ileal or ileocolonic disease, and approximately 40% had stricturing disease at presentation. The management was homogeneous, which is a weakness of the study, in that patients enrolled earlier in the study were dilated whenever they were scoped (19%), whereas patients enrolled later were only dilated based on symptoms. 80% of the dilations were performed on anastomotic strictures. 1% of the cases were done with general anesthesia. Another study weakness is that the length of the strictures was not recorded. 1.4% of the cases were complicated by bowel perforation. The largest balloon diameter (25 mm) had an overall 9.3% complication rate, as compared to 3.5%

**Table 1 Summary of significant endoscopic stricture dilation studies**

Ref.	Study design	n	dilations	Stricture length (cm)	Stricture diameter (mm)	Maximum insufflation dia. (mm)	Insufflation interval (s)	Initial success rate (%)	Follow-up interval	Long-term success rate (%)	Major complication rate(%)
Scimeca <i>et al</i> <sup>[29]</sup>	Prospective, single center cohort	37	72	3.4 (2-6)	6 (3-8)	10-20	60-90	51	26.3 mo (2-61)	89	0
Gustavsson <i>et al</i> <sup>[30]</sup>	Retrospective single center cohort	178	776	NA	> 5 mm	12-25	60-180	89	12 yr	52	5.3
Mueller <i>et al</i> <sup>[31]</sup>	Prospective, single center cohort	55	93	3 (1-25)	NA	15-18	60	95	44 mo (1-103)	76	2

NA: Not available.

**Table 2 Major complications related to endoscopic balloon dilation of strictures**

Ref.	Complication
Gustavsson <i>et al</i> <sup>[29]</sup>	1.4% bowel perforation 1% major bleeding 1.3% minor bleeding 1.2% abdominal pain or fever
Scimeca <i>et al</i> <sup>[30]</sup>	None
Mueller <i>et al</i> <sup>[31]</sup>	2% bowel perforation

for the other sizes ( $P < 0.01$ ). Patients fared equally well whether their strictures were anastomotic or *de novo*. At 5 years, 52% patients had at most one additional dilation, and 36% had a surgical resection. A strength of the study is that several different endoscopists of various skill level performed the dilations, which therefore makes this data more applicable to centers where there is at present no established expertise in this technique.

The Scimeca *et al*<sup>[29]</sup> study followed prospectively 37 Crohn's patients (39 strictures) during 72 dilations, at a single center in Italy. Almost all the strictures (97%) were post-surgical, with 77% being at ileo-colonic anastomosis sites. Patients included in the study had at least 2 episodes of clinical and radiologic obstruction in the 6 mo preceding the study, and at best an incomplete response to medical therapy. A maximum of four attempts at dilation were made per endoscopic session. There was a 51% rate of success after the first dilation, but an 89% rate of success after subsequent dilations. This group had no complications at all (Table 2), which perhaps is also related to the lower initial success rate compared to the other 2 studies cited (51% *vs* 89%-95% for the other 2). A weakness of the study is that patients were rescoped in 4-6 wk when the endoscopist judged the initial dilation to be incomplete, as this is a subjective assessment that is hard to replicate in other centers. 11% patients required surgery. An strength of the study is that there was no loss to follow-up, but this study has the shortest mean follow-up period of the three presented, namely about 2 years.

The Mueller *et al*<sup>[31]</sup> study is a German prospective single center study of 55 patients, with 74 symptomatic strictures, which resulted in 93 dilations. As opposed to the other studies cited here, the majority of patients in this study (69%) had *de novo* strictures. The inclusion criteria were clinical obstructive symptoms and sonographic

or radiologic evidence of stricture. The default approach was direct visualization, but fluoroscopic guidance was employed when visualization was not possible (unclear how often this was necessary). There was no stricture diameter or length parameter used to determine eligibility, and some of the strictures dilated were as long as 25 cm. There was a 95% initial success rate, and 76% patients never required repeat treatment over the period of follow-up. 24% patients did eventually receive surgery over the follow-up period, on average within the first 6 wk (0-20 mo). There was a statistically significant correlation between the need for surgery and stricture length ( $P = 0.006$ ) with the average stricture requiring surgery being 7.5 cm *vs* 2.5 cm for the strictures amenable to endoscopic therapy. One patient was perforated and 2 patients could not be dilated due to stricture anatomy.

## RECOMMENDED ENDOSCOPIC APPROACH

In summary, these studies demonstrate an experience with endoscopic balloon dilation of Crohn's disease strictures dating back almost 2 decades. These procedures can be done with conscious sedation, on an outpatient basis. The perforation rate of up to 2% is considered acceptable, since the alternative as well as the perforation management is surgical. Boston Scientific balloons in the range of 10-20 mm are recommended, since larger 25 mm balloons do seem to increase the perforation risk. The response to dilation is similar whether the stricture is *de novo* or anastomotic. No consensus has been reached on the optimal length of stricture amenable to endoscopic manipulation, though based on the average length in the studies included 5 cm would be a reasonable cut-off. This would also make inherent sense considering the Boston Scientific balloon is 5.5 cm in length. The exact methodology by which the strictures should be dilated (i.e., how many minutes should the inflated balloon be held in position, or how many sequential insufflations should be attempted per procedure) has not been standardized yet, though dilating each balloon through the 3 diameters it can accommodate and holding the insufflated balloon at the stricture site for 30-60 s would be a reasonable starting point. Patients should be told that generally endoscopic balloon dilation requires two procedures to

achieve patency over a period of 5 years, and has long-term efficacy in at least half the patients it has been attempted in. These recommendations are concordant with expert opinions on this topic<sup>[32]</sup>, though other sources still consider strictureplasty the first line approach<sup>[12]</sup>.

It is difficult to compare the endoscopic results with the surgical literature. The data for segmental resection and anastomosis is homogeneous, as this surgery is not exclusively employed for stricture management. In addition, there are 15 distinct strictureplasty methods described<sup>[33]</sup>, though the two most commonly employed for Crohn's are Heineke-Mikulicz and Finney. According to a 2007 metanalysis which analyzed 1112 patients with a total of 3259 strictureplasties, this approach has a complication rate of 4% (leak, fistula, abscess) and a recurrence rate of 28% by 5 years<sup>[34]</sup>. Though the average number of procedures per patient were > 2 in this period of time, the authors point out that only 3% of the repeat procedures involved re-instrumenting a site that had been operated on prior (the vast majority of the recurrences occurred at new sites of stricture). The majority of the strictures analyzed in the metanalysis were small bowel, which would not be amenable to dilation by traditional endoscopic techniques. In terms of laparoscopic resection, a large case series of over 300 patients from Mount Sinai Hospital in New York reported a postoperative complication rate of 13% (primarily obstruction and leak), which makes the endoscopic option more attractive, at least in the short term<sup>[35]</sup>.

## FUTURE RESEARCH AVENUES

It would be important to understand, in terms of the natural history of Crohn's disease, at which point intervening on a stricture would yield the maximum benefit. Perhaps it is not when the area has become fibrotic, but rather soon after a flare has resolved, that the initial dilation should be performed. It is unclear which of the medical treatment options available for the treatment of Crohn's would be most efficacious in preventing stricture formation. It would be useful to understand if injecting (with steroids or infliximab) or stenting the stricture would decrease the recurrence rate, as the current literature on this topic is scarce and lacking consensus<sup>[36-38]</sup>. It would also be important to determine the minimum number of dilations required to achieve operator proficiency, the optimal characteristics of a stricture that would make it amenable to endoscopic intervention, and the desirable diameter to which a stricture should be dilated such as to avoid both perforations and future obstructive symptoms.

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