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EFFICACY OF DRUG AND ENDOSCOPIC TREATMENT OF CROHN'S DISEASE STRICTURES: A SYSTEMATIC REVIEW

SHORT TITLE: DRUG AND ENDOSCOPIC TREATMENT OF CROHN'S DISEASE STRICTURES

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ABSTRACT

BACKGROUND & AIMS

Strictures are the commonest complication in Crohn's disease. Surgery and endoscopic dilation are the mainstays of treatment, while drug therapy has often been considered contra-indicated. The benefit of non-surgical treatments, particularly drug and endoscopic therapy, need to be defined.

METHODS

PubMed (MEDLINE), Embase, Emcare, EBSCO and the Cochrane Library (inception until August 30, 2019) were searched. Studies with ≥10 patients with Crohn's disease strictures, reporting on outcomes following medication or endoscopic treatment, were included.

RESULTS

Of 3480 records, 85 studies met inclusion criteria and formed the basis of this analysis. Twenty-five studies assessed drug therapy; none were randomized trials. Despite study heterogeneity anti-TNF therapy appeared effective, with 50% of patients avoiding surgery after 4 years follow up. No other drug therapy was of demonstrable benefit. Sixty studies assessed endoscopic therapy including 56 on endoscopic balloon dilation, two assessed needle knife stricturotomy, and two stent insertion. Dilation was equally effective for de-novo and anastomotic strictures ≤5cm in length, with most studies reporting a subsequent surgical rate of 30 to 50%. Repeat dilation was required in approximately half of all patients.

CONCLUSIONS

Anti-TNF drug therapy and endoscopic balloon dilation are effective strategies for avoiding surgery in patients with stricturing Crohn's disease. Additional endoscopic therapies require further evaluation. Early data suggest that combining these therapies may provide greater benefit than individual therapies. Optimisation of current drug and endoscopic therapy, and the incorporation of newer therapies, are needed for stricturing Crohn's disease.

Keywords:
Crohn's Disease, Stricture, Stenosis, anti-TNF therapy, Endoscopic Balloon Dilatation, Needle Knife Stricturotomy

INTRODUCTION

Strictures are the commonest complication of Crohn's disease.(1, 2) At diagnosis up to 28% of patients have stricturing disease and by five years more than one third will develop this complication.(1) The pathophysiology of stricturing disease is not well understood, although it is thought that chronic transmural gastrointestinal inflammation results in progressive narrowing of the bowel lumen and eventually partial or complete bowel obstruction.(3) Historically, surgery has been the treatment of choice for stricturing Crohn's disease.(4) However, the rate of post-operative recurrence is high, with up to 70% of patients requiring re-operation.(5) A treatment strategy involving drug and/or endoscopic therapy is needed.

Strictures comprise both inflammatory and non-inflammatory components including smooth muscle hyperplasia and fibrosis.(3, 6) Currently, all drug therapies for Crohn's disease target inflammation. There is emerging interest in therapies targeting fibrosis, although these agents are not yet part of routine care.(7) Anti-TNF therapy has been the mainstay of treatment for moderate-to-severe Crohn's disease over the past 15 years.(8-10) New biologic therapies targeting different immune pathways have been introduced over recent years.(11, 12) The efficacy of drug treatment for stricturing Crohn's disease, particularly in the biologic era, is not well understood. There is a paucity of high-quality studies on drug therapy for stricturing Crohn's disease.

More is known about endoscopic therapy in the treatment of strictures with several reviews published on this topic.(13), (14), (15), (16) However, new techniques have been adopted in the last two years, including needle knife stricturotomy.(17) Additionally, the combined effectiveness of drug and endoscopic therapy has not been reported.

The aims of this review are to evaluate the efficacy of drug therapy and endoscopic therapy for the treatment of Crohn's disease strictures. We also aimed to analyse patient, disease and stricture characteristics that influence the need for surgery and/or repeated endoscopic intervention. The safety of non-surgical treatment for Crohn's disease strictures has also been reviewed.

METHODS

This systematic review was carried out in accordance with the PRISMA Statement.(18) The protocol was registered with PROSPERO (Registration number CRD42018091221).

The interventions studied in this systematic review for stricturing Crohn's disease include treatment with any approved Crohn's disease medication as well as any endoscopic treatment for Crohn's disease including, but not limited to, endoscopic balloon dilatation.

Publications were identified through a systematic search of seven databases: Ovid Medline; Embase (Ovid); Ovid Emcare; PsycINFO (Ovid); CINAHL Plus with Full Text (EBSCOhost); Health Collection, Humanities & Social Sciences Collection (Informit) and the Cochrane Library.

Search strategies combined Crohn's disease AND strictures AND (drug OR endoscopic treatments), using a combination of text words and subject headings. Results were limited to English language and no date limits were applied. Animal studies were excluded. An initial strategy was developed for Medline (Figure 1) and adapted for other databases (Appendix 1). All searches were carried out on 4 September 2019.

Search results were exported to Endnote and duplicates removed. Records were screened by publication type and case reports, conference abstracts and papers, letters, notes and comments were excluded. All remaining records were loaded into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) and screened on title and abstract, and then full text, by two independent reviewers (JS and EW). Given the small number of studies in this area, we included a broad range of study designs using inclusion and exclusion criteria in Table 1. Disagreement by reviewers was resolved by discussion.

Data was extracted on 3 October 2019. Quality of evidence was assessed using the Newcastle Ottawa Scale risk of bias tool.(19) A quantitative analysis was not performed given the substantive heterogeneity in study design, method and modality of stricture diagnosis, therapeutic intervention and patient follow up. All included studies were presented in table(s) for overview together with a narrative synthesis.

RESULTS

Eligible Studies

Of 3480 records identified through database searching, 85 studies met our inclusion criteria (Figure 2). Twenty-five assessed outcomes of drug therapy and 60 of endoscopic therapy. These studies were heterogenous with regards to cohort selection, intervention, follow up and design. A summary of these studies is listed in table 2 (drug therapy studies) and table 3 (endoscopic therapy studies).

Nineteen of the 25 drug therapy studies were retrospective cohort studies and six were prospective cohort studies. There were no randomised controlled trials. Seventeen studies included patients with

both non-stricturing and stricturing phenotypes in their analysis. One prospective study by Bouhnik et al included a cohort solely of stricturing Crohn's disease patients treated with drug therapy for 24 weeks.(20)

Sixty studies involving endoscopic therapy for strictures met the predefined inclusion and exclusion criteria. Endoscopic balloon dilation (EBD) was by far the most common endoscopic treatment. Needle knife stricturotomy (4 studies), intralesional corticosteroid injection (15 studies) and the use of metal or biodegradable stents (3 studies) were also included.

All studies included in our systematic review were assessed using the Newcastle-Ottawa Scale(19) and were deemed of acceptable to high quality (Score ≥5).

Diagnosis and Definition of Stricturing Crohn's disease

Of the 25 drug therapy studies, there was no consensus amongst the studies on the method(s) used to diagnose Crohn's strictures with various modalities used including magnetic resonance enterography (MRE), computed tomography (CT), small bowel x-ray series and endoscopy. Seven of the 25 studies failed to cite the modality used to diagnose a stricture (Table 2). In studies that did report the modality of stricture diagnosis, the stricture definition was heterogenous, ranging from 'constant luminal narrowing' to the more specific bowel wall thickening >3mm and pre-stenotic bowel dilation >2.5cm which was reported in 3 studies.(21-23)

The degree of stricturing reported in the 60 endoscopic studies (Table 3) was also highly variable. In many studies this was not reported. These strictures were all confirmed endoscopically. A few studies defined strictures as 'mild resistance to the passage of the scope' whilst most defined a stricture endoscopically as non-passable with a standard adult colonoscope.(24)

Drug Therapies for Stricturing Crohn's Disease

Corticosteroid Therapy for Stricturing Crohn's Disease

Two studies primarily assessed corticosteroid therapy for patients with Crohn's disease strictures. Bemelman et al assessed drug treatment of stricturing Crohn's in the pre anti-TNF era (1985 to 1994) in 86 hospitalised patients.(25) Ten required upfront surgery. Seventy-six were treated with corticosteroids, with 47 (62%) progressing to surgery, and the remaining followed for a mean of eight years. A further 32% required re-operation for recurrent disease during the follow up period. In a 2006 study by Ho et al, 14 patients had stricturing disease out of a total of 60 Crohn's disease patients. All patients were followed following their first course of corticosteroids. The rate of surgery at 12 months was significantly higher for the stricturing cohort compared to those with non-stricturing, non-penetrating Crohn's disease (57% vs 31% respectively).(26)

Thiopurine Therapy for Stricturing Crohn's Disease

Two studies examined thiopurine use for stricturing disease. Yoshino et al retrospectively assessed the efficacy of thiopurines in 47 biologic naive patients in steroid-free clinical remission.(27) Seventeen patients had documented stricturing disease, with 7 (41%) relapsing during the 59 month follow up period, compared to 18% of those with purely inflammatory disease (P = 0.036).

Moran et al followed a Crohn's disease cohort for up to five years after initiation of a thiopurine. Of the of 261 patients, 19% had stricturing disease. Those with stricturing disease at the time of thiopurine prescription were significantly more likely to undergo surgery (adjusted HR, 4.63; 95% CI, 2.00–10.71) when compared to patients with non stricturing (Montreal B1 or B3) disease at five years follow up (34% B2 vs 12% B1 and 19% B3; P = 0.01).(28)

Anti-TNF Therapy for Stricturing Crohn's Disease

Twenty studies analysed (at least in part) the efficacy of anti-TNF therapy for the treatment of Crohn's disease in patients with strictures. Twelve studies included patients with and without Crohn's disease strictures and eight reported exclusively on patients with stricturing disease. Several studies directly compared treatment response rates in stricturing vs inflammatory luminal disease.(29)

Matsumoto et al in a total of 138 symptomatic Crohn's patients, showed an inferior response to infliximab in stricturing disease compared to purely inflammatory disease (OR 0.41; 95% CI 0.17-0.97). However, infliximab was shown to be effective at reducing symptoms and avoiding surgery in 53% of patients with stricturing disease.(30) Peters et al, reported in 197 adalimumab treated patients, a higher failure rate of induction treatment in patients with stricturing versus non-stricturing disease (OR 3.73; 95% CI 1.07 to 12.92).(31) On multivariable analysis there was a trend to better response for non-stricturing disease which was not statistically significant (OR 3.31; 95% CI 0.94-11.66). Gibson et al assessed 75 patients who underwent baseline MRE prior to commencing anti-TNF therapy for Crohn's disease.(32) Twelve of 18 patients with an MRE-identified stricture required surgery with a hazard ratio of 26.5 (95% CI 5.45–128.49) for surgery for B2 versus B1 disease. In a cohort of 322 patients commenced on anti-TNF therapy, Moran et al found that a stricturing phenotype at treatment onset was associated with an increased risk of surgery compared to non stricturing disease (OR 6.17; 95% CI 2.81–13.54).(28)

The 'Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture': CREOLE study has been the only study to date which has prospectively examined the effect of anti-TNF therapy on symptomatic Crohn's disease strictures.(20) In this study 97 patients with symptomatic Crohn's disease small bowel strictures were treated with standard maintenance dose adalimumab (40mg fortnightly). Sixty-two patients (64%) achieved 'treatment success', defined as the

avoidance of surgery or endoscopic dilatation, at week 24. These patients were then followed for a median of 3.8 years. Of the 35 patients who did not achieve 'treatment success', eight required intestinal resection and two endoscopic dilation. In longer term follow up, of the 62 patients who had 'treatment success' at week 24, 46% remained on adalimumab for a median of 4 years. In total, 47% of the cohort required an operation. Several factors were identified as being associated with treatment success or failure (see 'Predictors of Treatment Response' below).

Beppu et al showed the value of endoscopic healing in strictures.(33) In 54 patients with ileal or ileo-colonic ulceration treated with infliximab, 23 (43%) patients had concomitant severe endoscopic stenosis. Seventy percent of patients with stricturing disease responded well and avoided surgery with treatment, including 100% of stricture patients who achieved mucosal healing on follow up endoscopy. Pallotta et al performed pre-treatment and follow up ultrasound studies which showed that stricture regression on imaging does occur with infliximab treatment. In this small study, 8 of 15 stricture patients had an excellent response to infliximab treatment with stricture regression on imaging. No patients in this study required surgery.(22)

Whilst early treatment with anti-TNF biologic appears to prevent the development of stricturing complications of Crohn's disease, according to a large study by Frei et al comparing early versus late anti-TNF treatment (<24 months versus ≥24 months) in patients with established stricturing disease there did not appear to be a difference in treatment outcomes. (34)

No studies involving ustekinumab or vedolizumab, met our inclusion and exclusion criteria.

Other Drug Therapies for Stricturing Crohn's Disease

Two studies used exclusive enteral nutrition (EEN) for the treatment of stricturing Crohn's disease. In a study by Konno et al, 8 of 13 patients avoided surgery with a median follow up of 50 months.(35) In a prospective study with a much shorter follow up of only 12 weeks, Yang et al showed that 6 of 10 patients with stricturing disease responded well to EEN.(36)

Predictors of Drug Treatment Success in Patients with Crohn's Disease Strictures

Of all drug treatment studies, the predictors of treatment success are best characterised in the prospective study by Bouhnik et al.(20) The factors are listed in table 4. However, the treatment success was based on relatively short follow up of 24 weeks. Patients with two or less of these factors had only a 6% chance of treatment success with adalimumab therapy. Conversely, if four or more of these features were present then short-term treatment success was 89%.

In a retrospective study by Alloca et al, 51 patients with stricturing disease were treated with either adalimumab or infliximab. Pre-stenotic dilatation (per 1-mm increase, HR 1.08; 95% CI 1.01–1.15) and

the presence of any Crohn's related internal fistula (HR 9.8; 95% CI 3.0–31.9), were independent risk factors for surgery on multivariable analysis.(37)

Campos et al in 84 patients with stricturing disease found increased age to be associated with therapeutic failure, when a variety of drug therapies were used.(38) Patients on anti-TNF therapy were less likely to fail than those who received no anti-TNF therapy. Combination therapy was most strongly associated with a lower risk of treatment failure (HR 0.17; 95% CI 0.40–0.71). On imaging (CT or MRE), analysed in 55 of the 84 patients in the cohort, small stricture luminal diameter (HR 1.34; 95% CI 1.01–1.80), increased stricture wall thickness (HR 1.23; 95% CI 1.04–1.46) and fistula with abscess (HR 5.6 95% CI 1.6–19.4) were all predictors of treatment failure.

Endoscopic Therapy for Stricturing Crohn's Disease

Of the 60 included studies, study size ranged from 10 to 273 patients undergoing endoscopic therapy.[39, 40] Six hundred and one total procedures were performed in the largest study. Only two studies were randomized control trials, both assessing the use of corticosteroid injection into strictures as adjunctive treatment to EBD.(41, 42) Seven studies were prospective cohort studies, the largest included 55 patients.(43) The remaining studies were either retrospective cohort or case-control studies.

One study compared endoscopic dilation outcomes in strictures secondary to Crohn's disease versus non-Crohn's disease strictures. A similar reintervention rate (surgery or repeat dilation) was found in both groups.(44) However, the stricture locations were markedly different in these groups, with almost half the non-Crohn's patients having a colorectal anastomotic stricture versus none in the Crohn's disease cohort.

One study reported on patient satisfaction with endoscopic therapy with 83% of patients reporting satisfaction with the procedure.(45)

Outcomes of Endoscopic Balloon Dilation

Fifty seven of the 60 endoscopic studies involved EBD as the primary treatment modality. The main study outcomes are reported in Table 3.

In studies where patient symptoms were reported, at least 70% of the included patients across all studies were symptomatic, except in one study where only 14% were symptomatic.(46)

The percentage of patients requiring surgery post EBD was up to 59%,(47) although in 57 of the 60 studies surgery rates were below 50%. Repeat dilation was common and occurred in up to half the patients in most cohorts but reached as high as 83%. in the same study that had the highest surgical resection rate.(47)

Technical success was high (above 90%) in the majority of studies (table 2). Data on the maximum balloon size and associated success was highly variable with maximum balloon sizes varying from 15 to 25mm. Failure to achieve a maximum dilation of 14 mm or more increased the risk of surgery in a large and well conducted retrospective study (HR 2.9; 95% CI 1.1–7.5).(48) Overall, achieving dilatation with larger diameter balloons (ie. larger than 15mm) did not appear to have any impact on surgical or re-dilation outcomes.

Endoscopic Dilation of Anastomotic versus Non-anastomotic (De Novo) Strictures

Multiple studies have compared outcomes of EBD for anastomotic versus de novo strictures. In the majority of studies, there was no difference in therapeutic outcomes.[(49), (50, 51), (52), (53, 54)]

Endoscopic Dilation of Upper Gastrointestinal Strictures

Two studies reported exclusively on EBD outcomes for patients with upper gastrointestinal strictures. Singh et al analysed a cohort of 35 symptomatic patients of gastric and duodenal strictures.(55) Sixty-seven percent of the strictures were in the duodenum, 20% gastric and 11% both. Technical success was 93%. The overall surgical rate was 34%, with 57% requiring repeat dilation. This is comparable to lower GI strictures. The safety of dilation in these studies, despite the smaller numbers appeared comparable to colonoscopic dilation.

Endoscopic Therapy Combined with Drug Therapy

The impact of drug therapy in combination with endoscopic therapy was retrospectively described in 25% of the endoscopic studies. (Table 2) None of the prospective EBD studies incorporated a protocol for managing patients' drug therapy around the time of the EBD.

Thienpont et al in a cohort of 138 patients with mostly anastomotic strictures, found that a patient's baseline medical therapy did not influence the outcome of repeat dilation or need for surgery in patients undergoing EBD.(56) Sixteen percent were on biologics and 31% on immunomodulators.

Ding et al in a cohort of 55 patients showed that anti-TNF therapy, newly commenced post EBD, resulted in a reduced need for repeat EBD (HR 0.23; 95% CI 0.07–0.67).(57) Ono et al analysed a cohort of 185 patients treated with infliximab therapy of whom 33 had symptomatic stricture. Twenty-five patients underwent EBD and eight did not. Despite the small numbers, those having EBD had a

reduced risk of subsequent surgery (*P* = 0.038).(58) Honzawa et al, in a study of 25 patients, found that those treated with anti-inflammatory therapy including infliximab had a significantly reduced need for repeat EBD with a mean of 1.6 dilations compared to 4.8 in those without drug treatment (*P* = 0.04).(59)

Conversely, Reutemann et al showed that, whilst anti-TNF therapy at baseline did not pose an increased surgical risk, the initiation of anti-TNF therapy introduced post EBD was associated with an increased surgical risk (HR 2.4; 95% CI 1.1–5.3).(48) Andujar et al found similarly that not receiving anti-TNF at the time of dilation was associated with avoidance of surgery or repeat dilation (OR 1.7; 95% CI 1.1–2.6)

In two other studies the absence of thiopurine therapy increased the incidence of repeat intervention (EBD or surgery).[(46),] (51)

Other medications explored in combination with EBD included antibiotics which were found to be linked with an increased likelihood of re-intervention in one study(44) and concomitant corticosteroids which were associated with repeated intervention in two studies.(60, 61)

Endoscopic therapy versus upfront surgery

Two studies retrospectively compared EBD outcomes to surgical resection in patients with an ileo-colic anastomotic stricture.(62)[,] (63) Surgical stricture treatment was associated with a decreased risk of subsequent surgery compared to EBD (HR 0.49; 95% CI 0.32–0.76). A history of a single previous resection was also associated with better outcomes compared to those who had two or more previous resections in all patients (HR 0.41; 95% 0.26–0.66 for repeat surgery). Greener et al also reported a higher need for surgery/repeat surgery during follow-up in the endoscopically treated patients versus upfront surgery (OR 3.53; 95% CI, 1.01-12.29). Overall, 52% and 28% of the those undergoing EBD ultimately required stricture surgery in the studies by Lian et al and Greener respectively

One study compared EBD to primary ileo-colic resection in de-novo ileo-colic and terminal ileal strictures.(64) As with the anastomotic stricture studies, the cumulative probability of secondary surgery was higher in the EBD versus the upfront surgical cohort. (HR 4.7; 95% CI 2.4-9.1). Overall, 44% of patients in the 117 patients undergoing EBD required surgery in the study follow up period, similar to the findings for anastomotic strictures.

Endoscopic Balloon Dilation with Adjunctive Corticosteroid Injections

Two randomized controlled trials compared intralesional steroid versus placebo (saline) injection, in combination with EBD, with conflicting results. Both studies used 40mg triamcinolone. In the pilot study by East et al, published in 2007, worse outcomes were seen in the steroid treatment arm.(42)

One of 6 patients in the placebo group required redilatation, compared with 5 of 7 in the triamcinolone treatment arm (P = 0.06). In the per-protocol analysis the differences were more significant (log rank test; P = 0.03).

In contrast, Di Nardo et al in a randomized trial, included 29 paediatric patients (median age 14 years) with non-passable strictures. None of the 15 patients randomized to intralesional steroid in combination with EBD required surgery, whereas 4 of 14 patients in the placebo arm went on to surgical resection ($P = 0.02$).

The benefit of adjunctive intralesional steroid injection has not been reproduced in several larger cohort studies, showing no impact on surgery free survival.[65], [44], [52]

Needle Knife Stricturotomy for Treatment of Strictures

The use of an electrocautery needle knife as an adjunctive treatment for Crohn's disease strictures has been described from 1987 in case reports, (66) although the technique has been used for only a small number of patients.(52, 67)

Two retrospective studies in this review, have reported specifically on needle knife stricturotomy outcomes, both from the Cleveland Clinic, Ohio.

Lan et al published a retrospective study in 2018 which compared needle knife stricturotomy with EBD for anastomotic strictures.(68) Twenty-one patients were treated with needle knife stricturotomy and 164 treated with EBD. The median stricture length was short in both the stricturotomy cohort (1.5cm, IQR 1.0–2.4) and the EBD cohort (2.0cm, IQR 1.0-3.0). Technical success was 100% and 90% respectively. The rate of stricture surgery was 9.5% in the stricturotomy cohort versus 34% in the EBD cohort, although this was not significant given the shorter follow up in the stricturotomy cohort (10 months versus 4 years). Procedural complications differed, with no bowel perforations and a post procedural bleeding rate of 9% the stricturotomy group versus a 1% perforation and 0% bleeding rate in the EBD cohort (not statistically significantly).

A cohort of 35 who underwent needle knife stricturotomy (reported by the same group as above) were compared to a control cohort of 147 patients having ileo-colic anastomotic stricture resection.(69) Twenty-three percent of the needle knife stricturotomy cohort had previously undergone EBD without sustained success. There was no difference in the overall stricture-related secondary surgery rate (11% in the needle knife cohort versus 10% in the surgical cohort). However, the follow up was significantly shorter in those undergoing needle knife therapy compared with surgery (median 10 months versus 26 months).

Endoscopic Stent Insertion

Three studies incorporated the use of stents to treat Crohn's disease strictures in a largely treatment refractory cohort. In a large cohort of 187 patients who underwent EBD by Andujar et al, 11 patients had 'rescue' endoscopic stent placement after failure of EBD.(49) Of these 7 (64%) avoided surgery.

The largest series specifically focussing on temporary stent insertion was performed by Loras et al.(70) In this retrospective series of 17 patients, 41% came to surgical resection. Fourteen of the patients had previous EBD. Both partial and fully covered metal stents were used. On average stents were left insitu for 28 days. One patient had proximal stent migration requiring surgery.

Safety of Endoscopic Therapy

The most common complication arising from EBD is bowel perforation. The rate of EBD perforation varied from 0 to 10% with most in the 2-3% range (Table 3). The majority of these patients required surgery, though some were conservatively managed. Bleeding requiring transfusion was the second most common complication with a range of 0 to 5% following EBD. There were no factors that predicted complications.

Factors Associated with Endoscopic Treatment Success

Multiple predictors of treatment success were identified from the 60 endoscopic therapy studies. The most consistent predictor of treatment success was stricture length. [49, 60, 61, 71), (64] However, few studies included patients with strictures longer than 5cm. Winder et al, in a recent study of 64 patients, found that stricture length ≤4 cm was associated with avoidance of surgery on multivariable analysis (HR 0.31; 95% CI 0.10–0.99). Lan et al in a study of EBD for de novo (primary) strictures reported a hazard ratio of 2.0 for every 1-cm increment in stricture length (95% CI 1.3-3.3).(64) Andujar et al in another recent study found stricture length (≤ 2 cm) to be independently associated with therapeutic success on multivariate regression analysis (HR 2.43; 95% CI 1.1–5.3).(49)

Active endoscopic inflammation at the stricture was also associated with surgery. Breysem et al first reported this in a study of 16 patients undergoing EBD. Eight patients without active endoscopic inflammation all avoided stricture surgery, whilst in the 8 patients with endoscopic mucosal inflammation surgery was ultimately required in 50%.(72) Ding et al found in 55 patients with anastomotic strictures that increased stricture-associated endoscopic inflammation (Rutgeerts score >i3) was associated with surgery (HR 4.55, 95% CI 1.08–19.29).(57) Winder et al also found an inflamed stricture was associated with a decreased likelihood of treatment success (OR 0.19; 95% CI 0.06–0.57).(61) However, two studies found no impact of endoscopic inflammation on outcomes in anastomotic strictures.(56), (43)

Elevation of C-reactive protein (CRP) has been associated with an increased risk of surgery. Reutemann et al in a retrospective cohort of 135 patients found that an elevated CRP (>1.5 mg/dL), occurring in 33% of the entire cohort, was a risk factor (HR 2.64; 95% CI 1.28–5.44).(48) Bhalme et al, in a cohort of 79 patients undergoing EBD also reported an association between high CRP and reintervention (*P* = 0.008).(73) An elevated calprotectin level was associated with a need for repeated EBD in one study (HR 3.9; 95% CI 1.6-10.2).(46)

In the two of the largest prospective endoscopic therapy studies (55 and 37 patients), the only factors associated with treatment success was passage of the scope post dilation or technical success.(43), (74) This same finding was seen in many, but not all, of the larger retrospective cohorts.(49)

In the largest EBD study to date of 273 patients by Shivashankar et al, the only factor associated with subsequent surgery on regression analysis was younger age (HR 0.80; 95% CI 0.69–0.92).(40)

Disease duration did not appear to impact outcomes of endoscopic stricture treatment. Andujar et al found no difference between patients undergoing balloon dilation <10 years since Crohn's disease duration versus ≥10 years. (49) Similarly, in a large study by Atreja et al disease duration did not impact endoscopic treatment success or avoidance of surgery. (52)

Few endoscopic studies reported on radiologic findings. However, in a large cohort of patients with anastomotic strictures, pre-stenotic dilation seen on imaging was as a predictor of surgery on multivariable analysis (HR 2.3; 95% CI: 1.3-4.2). (65, 68)

Gustavsson et al, in a cohort of 83 patients (taken from a larger cohort of 178 patients) found that in up to five years of follow up, smokers had statistically significantly higher cumulative probability of repeat intervention compared to never smokers, 81% versus 52% (difference 29%; 95% CI 7-52%).(75)

Discussion

This systematic review has defined the current role of drug therapy, in particular anti-TNF therapy, for the treatment of Crohn's disease strictures. It has also confirmed the importance of endoscopic therapy in the management of selected patients with strictures.

Thiopurines do not appear to have a significant role in the medical management of patients with Crohn's disease strictures and corticosteroids do not alter long term outcomes. Exclusive enteral nutrition (EEN) is an attractive short-term treatment strategy as it involves a low residue diet, is not

immune suppressing and has an anti-inflammatory effect. Whilst helpful in the short term,(35, 36) EEN is not appropriate for longer-term treatment.

Preliminary data suggest that anti-TNF therapy may decrease inflammation at the site of the stricture, with subsequent prevention of stricture progression by decreasing bowel wall oedema, smooth muscle hyperplasia or hypertrophy, and fibrosis.(3) Ultimately, 47% of patients with symptomatic stricturing disease require surgical resection following standard dose anti-TNF after 4 years of follow up.(20)

For endoscopic stricture treatment, endoscopic balloon dilation (EBD) remains the mainstay of endoscopic therapy. Strictures less than 5cm in length are particularly amenable to EBD whereas its role in longer strictures in limited. Passage of the scope through the stricture post dilation and/or EBD technical success are the other factors consistently associated with prolonged surgery-free survival. The absence of stricture-associated inflammation (seen endoscopically or defined by CRP and/or faecal calprotectin) is also associated with improved EBD outcomes.(46, 48, 73) It is likely that adequate control of inflammation prior to, or in conjunction with EBD, will improve outcomes, but this has not been evaluated prospectively. To date, retrospective studies have been conflicting about the value of combining EBD with systemic anti-TNF therapy, with some showing benefit (58, 59, 76) and others showing worse outcomes.(48, 49)

Larger studies with longer term follow up are needed before needle knife stricturotomy and endoscopic stents can be recommended as primary treatments for Crohn's disease strictures, although small studies suggest that endoscopic stricturotomy is promising. Adjunctive corticosteroid injection cannot be recommended based on current evidence.

There are a number of limitations with respect to the studies included in this review. Most included studies were retrospective. The non-standardized and heterogenous definition of strictures also makes it difficult to make direct comparisons between studies. Despite recently updated European Crohn's Colitis Organization (ECCO) and American College of Gastroenterology (ACG) guidelines, the specific definition of what constitutes a Crohn's disease stricture remains imprecise.[77, 78] In addition, there is no standardised clinical assessment tool for characterizing symptoms in patients with Crohn's disease strictures. The Crohn's Disease Activity Index (CDAI) is unsuitable for characterising stricture related obstructive symptoms.(79) A promising clinical tool that requires validation is the Crohn's Disease Obstructive Score (CDOS).(20)

Even with best drug treatment, as illustrated in the CREOLE study,(20) or successful EBD, a significant number of patients with Crohn's strictures will come to surgery. To improve outcomes, a more sophisticated approach to stricture treatment is required. This would incorporate clinical, biochemical,

endoscopic and radiological information to inform decisions regarding best drug, endoscopic and surgical treatment.

Ultimately, effective anti-inflammatory drug therapy combined with optimal endoscopic therapy for suitable strictures may synergistically provide the most effective non-surgical treatment of strictures. However, this needs to be tested in high quality prospective trials. Endpoints following drug treatment should focus on endoscopic mucosal healing[(80),] (33) and/or transmural healing,(22) as these outcomes have most clearly demonstrated an association with improved patient symptoms and the avoidance of stricture surgery.

In conclusion, whilst historically most patients with Crohn's disease strictures have undergone surgical treatment, this review has highlighted that in symptomatic patients, drug treatments targeting inflammation (anti-TNF therapy) have the highest chance of prolonged treatment success.

For endoscopic treatment to be successful it appears that a shorter stricture length and control of mucosal inflammation are pre-requisites. Furthermore, improved overall patient and stricture characterization with respect to clinical, biochemical, endoscopic and radiologic features will help guide personalised care and allow us to optimise treatment outcomes. The development of novel treatment targets for rapid and potent control of inflammation as well as those targeting smooth muscle remodelling and fibrosis are also needed.

Finally, for treatment outcomes to improve, we require high quality prospective randomized studies with precise stricture definition and characterization in order to change the natural history of this complication.

References

1. Henriksen M, Jahnsen J, Lygren I, Aadland E, Schulz T, Vatn MH, et al. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). Scand J Gastroenterol. 2007;42(5):602-10.
2. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. The American journal of gastroenterology. 2010;105(2):289-97.
3. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. Gut. 2013;62(7):1072-84.
4. Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. Journal of Crohn's & colitis. 2017;11(2):135-49.
5. De Cruz P, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal Crohn's disease: a systematic review. Inflamm Bowel Dis. 2012;18(4):758-77.
6. Chen W, Lu C, Hirota C, Iacucci M, Ghosh S, Gui X. Smooth Muscle Hyperplasia/Hypertrophy is the Most Prominent Histological Change in Crohn's Fibrostenosing Bowel Strictures: A Semiquantitative Analysis by Using a Novel Histological Grading Scheme. Journal of Crohn's & colitis. 2017;11(1):92-104.
7. Danese S, Bonovas S, Lopez A, Fiorino G, Sandborn WJ, Rubin DT, et al. Identification of Endpoints for Development of Antifibrosis Drugs for Treatment of Crohn's Disease. Gastroenterology. 2018;155(1):76-87.
8. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. The Lancet. 2002;359(9317):1541-9.
9. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.
10. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232-9.
11. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel J-F, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. New England Journal of Medicine. 2013;369(8):711-21.
12. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn’s Disease. New England Journal of Medicine. 2016;375(20):1946-60.
13. Hassan C, Zullo A, De Francesco V, Ierardi E, Giustini M, Pitidis A, et al. Systematic review: Endoscopic dilatation in Crohn's disease. Aliment Pharmacol Ther. 2007;26(11-12):1457-64.
14. Navaneethan U, Lourdusamy V, Njei B, Shen B. Endoscopic balloon dilation in the management of strictures in Crohn's disease: a systematic review and meta-analysis of non-randomized trials. Surg Endosc. 2016;30(12):5434-43.
15. Bettenworth D, Gustavsson A, Atreja A, Lopez R, Tysk C, van Assche G, et al. A Pooled Analysis of Efficacy, Safety, and Long-term Outcome of Endoscopic Balloon Dilation Therapy for Patients with Stricturing Crohn's Disease. Inflamm Bowel Dis. 2017;23(1):133-42.
16. Morar PS, Faiz O, Warusavitarne J, Brown S, Cohen R, Hind D, et al. Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures. Aliment Pharmacol Ther. 2015;42(10):1137-48.
17. Lan N, Shen B. Endoscopic Stricturotomy with Needle Knife in the Treatment of Strictures from Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(4):502-13.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

19. Wells GS, B.; O'Connell, D.; Robertson, J.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [cited 2020 Apr 02].
20. Bouhnik Y, Carbonnel F, Laharie D, Stefanescu C, Hebuterne X, Abitbol V, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. Gut. 2018;67(1):53-60.
21. Aloi M, Viola F, D'Arcangelo G, Di Nardo G, Civitelli F, Casciani E, et al. Disease course and efficacy of medical therapy in stricturing paediatric Crohn's disease. Digestive & Liver Disease. 2013;45(6):464-8.
22. Pallotta N, Barberani F, Hassan NA, Guagnozzi D, Vincoli G, Corazziari E. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. World Journal of Gastroenterology. 2008;14(12):1885-90.
23. Amitai MM, Klang E, Levartovsky A, Rozendorn N, Soffer S, Taha GA, et al. Diffusion-weighted magnetic resonance enterography for prediction of response to tumor necrosis factor inhibitors in stricturing Crohn's disease. Abdominal Radiology. 2018;43(12):3207-12.
24. Chen M, Shen B. Ileoscopic balloon dilation of Crohn's disease strictures via stoma. Gastrointestinal Endoscopy. 2014;79(4):688-93.
25. Bemelman WA, Ivenski M, van Hogezand RA, Hermans J, Veenendaal RA, Griffioen G. How effective is extensive nonsurgical treatment of patients with clinically active Crohn's disease of the terminal ileum in preventing surgery? Digestive Surgery. 2001;18(1):56-60.
26. Ho GT, Chiam P, Drummond H, Loane J, Arnott ID, Satsangi J. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Alimentary Pharmacology & Therapeutics. 2006;24(2):319-30.
27. Yoshino T, Matsuura M, Minami N, Yamada S, Honzawa Y, Kimura M, et al. Efficacy of Thiopurines in Biologic-Naive Japanese Patients With Crohn's Disease: A Single-Center Experience. Intestinal Research. 2015;13(3):266-73.
28. Moran GW, Dubeau MF, Kaplan GG, Yang H, Seow CH, Fedorak RN, et al. Phenotypic features of Crohn's disease associated with failure of medical treatment. Clinical Gastroenterology & Hepatology. 2014;12(3):434-42.e1.
29. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749.
30. Matsumoto T, Iida M, Motoya S, Haruma K, Suzuki Y, Kobayashi K, et al. Therapeutic efficacy of infliximab on patients with short duration of Crohn's disease: a Japanese multicenter survey. Diseases of the Colon & Rectum. 2008;51(6):916-23.
31. Peters CP, Eshuis EJ, Toxopeus FM, Hellemons ME, Jansen JM, D'Haens GR, et al. Adalimumab for Crohn's disease: long-term sustained benefit in a population-based cohort of 438 patients. Journal of Crohn's & colitis. 2014;8(8):866-75.
32. Gibson DJ, Murphy DJ, Smyth AE, McEvoy SH, Keegan D, Byrne K, et al. Magnetic resonance enterography findings as predictors of clinical outcome following antitumor necrosis factor treatment in small bowel Crohn's disease. European Journal of Gastroenterology & Hepatology. 2015;27(8):956-62.
33. Beppu T, Ono Y, Matsui T, Hirai F, Yano Y, Takatsu N, et al. Mucosal healing of ileal lesions is associated with long-term clinical remission after infliximab maintenance treatment in patients with Crohn's disease. Digestive Endoscopy. 2015;27(1):73-81.
34. Frei R, Fournier N, Zeitz J, Scharl M, Morell B, Greuter T, et al. Early Initiation of Anti-Tnf is Associated with Favourable Long-Term Outcome in Crohn's Disease: 10-Year-Follow-Up Data from the Swiss IBD Cohort Study. Journal of Crohn's & colitis. 2019;07:07.
35. Konno M, Takahashi M, Toita N, Fujiwara S, Nojima M. Long-term therapeutic effectiveness of maintenance enteral nutrition for Crohn's disease. Pediatrics International. 2015;57(2):276-80.
36. Yang Q, Gao X, Chen H, Li M, Wu X, Zhi M, et al. Efficacy of exclusive enteral nutrition in complicated Crohn's disease. Scandinavian Journal of Gastroenterology. 2017;52(9):995-1001.

37. Allocca M, Bonifacio C, Fiorino G, Spinelli A, Furfaro F, Balzarini L, et al. Efficacy of tumour necrosis factor antagonists in stricturing Crohn's disease: A tertiary center real-life experience. Digestive & Liver Disease. 2017;49(8):872-7.
38. Campos C, Perrey A, Lambert C, Pereira B, Goutte M, Dubois A, et al. Medical Therapies for Stricturing Crohn's Disease: Efficacy and Cross-Sectional Imaging Predictors of Therapeutic Failure. Digestive Diseases & Sciences. 2017;62(6):1628-36.
39. Lavy A. Triamcinolone improves outcome in Crohn's disease strictures. Diseases of the Colon & Rectum. 1997;40(2):184-6.
40. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W, Faubion WA, Wong Kee Song LM, Bruining DH, et al. Outcomes of Endoscopic Therapy for Luminal Strictures in Crohn's Disease. Inflamm Bowel Dis. 2018.
41. Di Nardo G, Oliva S, Passariello M, Pallotta N, Civitelli F, Frediani S, et al. Intralesional steroid injection after endoscopic balloon dilation in pediatric Crohn's disease with stricture: a prospective, randomized, double-blind, controlled trial. Gastrointestinal Endoscopy. 2010;72(6):1201-8.
42. East JE, Brooker JC, Rutter MD, Saunders BP. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. Clinical Gastroenterology & Hepatology. 2007;5(9):1065-9.
43. Couckuyt H, Gevers AM, Coremans G, Hiele M, Rutgeerts P. Efficacy and safety of hydrostatic balloon dilatation of ileocolonic Crohn's strictures: a prospective longterm analysis. Gut. 1995;36(4):577-80.
44. Chen M, Shen B. Comparable short- and long-term outcomes of colonoscopic balloon dilation of Crohn's Disease and benign non-Crohn's Disease strictures. Inflammatory Bowel Diseases. 2014;20(10):1739-46.
45. Rueda Guzman A, Wehkamp J, Kirschniak A, Naumann A, Malek NP, Goetz M. Endoscopic balloon dilatation of Crohn's-associated intestinal strictures: High patient satisfaction and long-term efficacy. United European Gastroenterology Journal. 2016;4(6):794-9.
46. Lopes S, Rodrigues-Pinto E, Andrade P, Afonso J, Baron TH, Magro F, et al. Endoscopic balloon dilation of Crohn's disease strictures-safety, efficacy and clinical impact. World Journal of Gastroenterology. 2017;23(41):7397-406.
47. Thomas-Gibson S, Brooker JC, Hayward CM, Shah SG, Williams CB, Saunders BP. Colonoscopic balloon dilation of Crohn's strictures: a review of long-term outcomes. European Journal of Gastroenterology & Hepatology. 2003;15(5):485-8.
48. Reutemann BA, Turkeltaub JA, Al-Hawary M, Waljee AK, Higgins PDR, Stidham RW. Endoscopic Balloon Dilation Size and Avoidance of Surgery in Stricturing Crohn's Disease. Inflammatory Bowel Diseases. 2017;23(10):1803-9.
49. Andujar X, Loras C, Gonzalez B, Socarras M, Sanchiz V, Bosca M, et al. Efficacy and safety of endoscopic balloon dilation in inflammatory bowel disease: results of the large multicenter study of the ENEIDA registry. Surgical Endoscopy. 2019;29:29.
50. Hagel AF, Hahn A, Dauth W, Matzel K, Konturek PC, Neurath MF, et al. Outcome and complications of endoscopic balloon dilatations in various types of ileocaecal and colonic stenosis in patients with Crohn's disease. Surgical Endoscopy. 2014;28(10):2966-72.
51. Gustavsson A, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn's disease. Alimentary Pharmacology & Therapeutics. 2012;36(2):151-8.
52. Atreja A, Aggarwal A, Dwivedi S, Rieder F, Lopez R, Lashner BA, et al. Safety and efficacy of endoscopic dilation for primary and anastomotic Crohn's disease strictures. Journal of Crohn's & colitis. 2014;8(5):392-400.
53. Ferlitsch A, Reinisch W, Puspok A, Dejaco C, Schillinger M, Schofl R, et al. Safety and efficacy of endoscopic balloon dilation for treatment of Crohn's disease strictures. Endoscopy. 2006;38(5):483-7.
54. Matsui T, Ikeda K, Tsuda S, Yao K, Sou S, Satoh S, et al. Long-term outcome of endoscopic balloon dilation in obstructive gastrointestinal Crohn's disease: a prospective long-term study. Diagnostic & Therapeutic Endoscopy. 2000;6(2):67-75.

55. Singh A, Agrawal N, Kurada S, Lopez R, Kessler H, Philpott J, et al. Efficacy, Safety, and Long-term Outcome of Serial Endoscopic Balloon Dilation for Upper Gastrointestinal Crohn's Disease-associated Strictures-A Cohort Study. Journal of Crohn's & colitis. 2017;11(9):1044-51.
56. Thienpont C, D'Hoore A, Vermeire S, Demedts I, Bisschops R, Coremans G, et al. Long-term outcome of endoscopic dilatation in patients with Crohn's disease is not affected by disease activity or medical therapy. Gut. 2010;59(3):320-4.
57. Ding NS, Yip WM, Choi CH, Saunders B, Thomas-Gibson S, Arebi N, et al. Endoscopic Dilatation of Crohn's Anastomotic Strictures is Effective in the Long Term, and Escalation of Medical Therapy Improves Outcomes in the Biologic Era. Journal of Crohn's & colitis. 2016;10(10):1172-8.
58. Ono Y, Hirai F, Matsui T, Beppu T, Yano Y, Takatsu N, et al. Value of concomitant endoscopic balloon dilation for intestinal stricture during long-term infliximab therapy in patients with Crohn's disease. Digestive Endoscopy. 2012;24(6):432-8.
59. Honzawa Y, Nakase H, Matsuura M, Higuchi H, Toyonaga T, Matsumura K, et al. Prior use of immunomodulatory drugs improves the clinical outcome of endoscopic balloon dilation for intestinal stricture in patients with Crohn's disease. Digestive Endoscopy. 2013;25(5):535-43.
60. Asairinachan A, An V, Daniel ES, Johnston MJ, Woods RJ. Endoscopic balloon dilatation of Crohn's strictures: a safe method to defer surgery in selective cases. ANZ Journal of Surgery. 2017;87(12):E240-E4.
61. Winder O, Fliss-Isakov N, Winder G, Scapa E, Yanai H, Barnes S, et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. Medicine. 2019;98(35):e16864.
62. Lian L, Stocchi L, Remzi FH, Shen B. Comparison of Endoscopic Dilation vs Surgery for Anastomotic Stricture in Patients With Crohn's Disease Following Ileocolonic Resection. Clinical Gastroenterology & Hepatology. 2017;15(8):1226-31.
63. Greener T, Shapiro R, Klang E, Rozendorn N, Eliakim R, Ben-Horin S, et al. Clinical Outcomes of Surgery Versus Endoscopic Balloon Dilation for Stricturing Crohn's Disease. Diseases of the Colon & Rectum. 2015;58(12):1151-7.
64. Lan N, Stocchi L, Ashburn JH, Hull TL, Steele SR, Delaney CP, et al. Outcomes of Endoscopic Balloon Dilation vs Surgical Resection for Primary Ileocolic Strictures in Patients With Crohn's Disease. Clinical Gastroenterology & Hepatology. 2018;16(8):1260-7.
65. Lian L, Stocchi L, Shen B, Liu X, Ma J, Zhang B, et al. Prediction of need for surgery after endoscopic balloon dilation of ileocolic anastomotic stricture in patients with Crohn's disease. Diseases of the Colon & Rectum. 2015;58(4):423-30.
66. Neufeld DM, Shemesh EI, Kodner IJ, Shatz BA. Endoscopic management of anastomotic colon strictures with electrocautery and balloon dilation. Gastrointestinal Endoscopy. 1987;33(1):24-6.
67. Blomberg B, Rolny P, Jarnerot G. Endoscopic treatment of anastomotic strictures in Crohn's disease. Endoscopy. 1991;23(4):195-8.
68. Lan N, Shen B. Endoscopic Stricturotomy Versus Balloon Dilation in the Treatment of Anastomotic Strictures in Crohn's Disease. Inflammatory Bowel Diseases. 2018;24(4):897-907.
69. Lan N, Stocchi L, Delaney CP, Hull TL, Shen B. Endoscopic stricturotomy versus ileocolonic resection in the treatment of ileocolonic anastomotic strictures in Crohn's disease. Gastrointestinal Endoscopy. 2019;90(2):259-68.
70. Loras C, Perez-Roldan F, Gornals JB, Barrio J, Igea F, Gonzalez-Huix F, et al. Endoscopic treatment with self-expanding metal stents for Crohn's disease strictures. Alimentary Pharmacology & Therapeutics. 2012;36(9):833-9.
71. Maehata Y, Nagata Y, Moriyama T, Matsuno Y, Hirano A, Umeno J, et al. Risk of surgery in patients with stricturing type of Crohn's disease at the initial diagnosis: a single center experience. Intestinal Research. 2019;17(3):357-64.
72. Breysem Y, Janssens JF, Coremans G, Vantrappen G, Hendrickx G, Rutgeerts P. Endoscopic balloon dilation of colonic and ileo-colonic Crohn's strictures: long-term results. Gastrointestinal Endoscopy. 1992;38(2):142-7.

73. Bhalme M, Sarkar S, Lal S, Bodger K, Baker R, Willert RP. Endoscopic balloon dilatation of Crohn's disease strictures: results from a large United kingdom series. Inflammatory Bowel Diseases. 2014;20(2):265-70.
74. Scimeca D, Mocciaro F, Cottone M, Montalbano LM, D'Amico G, Olivo M, et al. Efficacy and safety of endoscopic balloon dilation of symptomatic intestinal Crohn's disease strictures. Digestive & Liver Disease. 2011;43(2):121-5.
75. Gustavsson A, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Smoking is a risk factor for recurrence of intestinal stricture after endoscopic dilation in Crohn's disease. Alimentary Pharmacology & Therapeutics. 2013;37(4):430-7.
76. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. Aliment Pharmacol Ther. 2016;43(1):30-51.
77. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. Journal of Crohn's & colitis. 2019;13(2):144-64.
78. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. The American journal of gastroenterology. 2018;113(4):481-517.
79. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-44.
80. Echarri A, Ollero V, Barreiro-de Acosta M, Fernandez-Villaverde A, Hernandez V, Lorenzo A, et al. Clinical, biological, and endoscopic responses to adalimumab in antitumor necrosis factor-naive Crohn's disease: predictors of efficacy in clinical practice. European Journal of Gastroenterology & Hepatology. 2015;27(4):430-5.
81. Olivera P, Thiriet L, Luc A, Baumann C, Danese S, Peyrin-Biroulet L. Treatment Persistence for Infliximab Versus Adalimumab in Crohn's Disease: A 14-Year Single-Center Experience. Inflammatory Bowel Diseases. 2017;23(6):976-85.
82. Naganuma M, Okuda S, Hisamatsu T, Matsuoka K, Mori K, Hosoe N, et al. Findings of ulceration and severe stricture on MRE can predict prognosis of Crohn's disease in patients treated with anti-TNF treatment. Abdominal Radiology. 2017;42(1):141-51.
83. Yu L, Yang X, Xia L, Zhong J, Ge W, Wu J, et al. Infliximab preferentially induces clinical remission and mucosal healing in short course Crohn's disease with luminal lesions through balancing abnormal immune response in gut mucosa. Mediators of Inflammation. 2015;2015:793764.
84. Eder P, Michalak M, Katulska K, Lykowska-Szuber L, Krela-Kazmierczak I, Stawczyk-Eder K, et al. Magnetic resonance enterographic predictors of one-year outcome in ileal and ileocolonic Crohn's disease treated with anti-tumor necrosis factor antibodies. Scientific Reports. 2015;5:10223.
85. Mao R, Chen BL, He Y, Cui Y, Zeng ZR, Chen MH. Factors associated with progression to surgery in Crohn's disease patients with endoscopic stricture. Endoscopy. 2014;46(11):956-62.
86. Pelletier AL, Kalisazan B, Wienckiewicz J, Bouarioua N, Soule JC. Infliximab treatment for symptomatic Crohn's disease strictures. Alimentary Pharmacology & Therapeutics. 2009;29(3):279-85.
87. Taida T, Nakagawa T, Ohta Y, Hamanaka S, Okimoto K, Saito K, et al. Long-Term Outcome of Endoscopic Balloon Dilatation for Strictures in Patients with Crohn's Disease. Digestion. 2018;98(1):26-32.
88. Lee HW, Park SJ, Jeon SR, Ye BD, Park JJ, Cheon JH, et al. Long-Term Outcomes of Endoscopic Balloon Dilation for Benign Strictures in Patients with Inflammatory Bowel Disease. Gut & Liver. 2018;12(5):530-6.
89. Kanamori A, Sugaya T, Tominaga K, Takahashi F, Takenaka K, Hoshino A, et al. Endoscopic balloon dilation for stenotic lesions in Crohn's disease. Turkish Journal of Gastroenterology. 2017;28(2):117-24.

90. Guo F, Huang Y, Zhu W, Wang Z, Cao L, Chen A, et al. Efficacy and Safety of Endoscopic Balloon Dilation for Upper Gastrointestinal Strictures of Crohn's Disease. Digestive Diseases & Sciences. 2016;61(10):2977-85.
91. Romanko I, Bortlik M, muricova D, Lukas, Machkova N, Hruba V, et al. Biologic therapy does not affect results of endoscopic balloon dilations in Crohn's disease patients. Gastroenterologie a Hepatologie. 2015;69(1):40-4.
92. Krauss E, Agaimy A, Gottfried A, Maiss J, Weidinger T, Albrecht H, et al. Long term follow up of through-the-scope balloon dilation as compared to strictureplasty and bowel resection of intestinal strictures in crohn's disease. International Journal of Clinical & Experimental Pathology. 2014;7(11):7419-31.
93. Nanda K, Courtney W, Keegan D, Byrne K, Nolan B, O'Donoghue D, et al. Prolonged avoidance of repeat surgery with endoscopic balloon dilatation of anastomotic strictures in Crohn's disease. Journal of Crohn's & colitis. 2013;7(6):474-80.
94. Endo K, Takahashi S, Shiga H, Kakuta Y, Kinouchi Y, Shimosegawa T. Short and long-term outcomes of endoscopic balloon dilatation for Crohn's disease strictures. World Journal of Gastroenterology. 2013;19(1):86-91.
95. de'Angelis N, Carra MC, Borrelli O, Bizzarri B, Vincenzi F, Fornaroli F, et al. Short- and long-term efficacy of endoscopic balloon dilation in Crohn's disease strictures. World Journal of Gastroenterology. 2013;19(17):2660-7.
96. Karstensen JG, Hendel J, Vilmann P. Endoscopic balloon dilatation for Crohn's strictures of the gastrointestinal tract is feasible. Danish Medical Journal. 2012;59(7):A4471.
97. Attar A, Maunoury V, Vahedi K, Vernier-Massouille G, Vida S, Bulois P, et al. Safety and efficacy of extractible self-expandable metal stents in the treatment of Crohn's disease intestinal strictures: a prospective pilot study. Inflammatory Bowel Diseases. 2012;18(10):1849-54.
98. Rejchrt S, Kopacova M, Brozik J, Bures J. Biodegradable stents for the treatment of benign stenoses of the small and large intestines. Endoscopy. 2011;43(10):911-7.
99. Mueller T, Rieder B, Bechtner G, Pfeiffer A. The response of Crohn's strictures to endoscopic balloon dilation. Alimentary Pharmacology & Therapeutics. 2010;31(6):634-9.
100. Stienecker K, Gleichmann D, Neumayer U, Glaser HJ, Tonus C. Long-term results of endoscopic balloon dilatation of lower gastrointestinal tract strictures in Crohn's disease: a prospective study. World Journal of Gastroenterology. 2009;15(21):2623-7.
101. Hoffmann JC, Heller F, Faiss S, von Lampe B, Kroesen AJ, Wahnschaffe U, et al. Through the endoscope balloon dilation of ileocolonic strictures: prognostic factors, complications, and effectiveness. International Journal of Colorectal Disease. 2008;23(7):689-96.
102. Foster EN, Quiros JA, Prindiville TP. Long-term follow-up of the endoscopic treatment of strictures in pediatric and adult patients with inflammatory bowel disease. Journal of clinical gastroenterology. 2008;42(8):880-5.
103. Ajlouni Y, Iser JH, Gibson PR. Endoscopic balloon dilatation of intestinal strictures in Crohn's disease: safe alternative to surgery. Journal of Gastroenterology & Hepatology. 2007;22(4):486-90.
104. Nomura E, Takagi S, Kikuchi T, Negoro K, Takahashi S, Kinouchi Y, et al. Efficacy and safety of endoscopic balloon dilation for Crohn's strictures. Diseases of the Colon & Rectum. 2006;49(10 Suppl):S59-67.
105. Singh VV, Draganov P, Valentine J. Efficacy and safety of endoscopic balloon dilation of symptomatic upper and lower gastrointestinal Crohn's disease strictures. Journal of clinical gastroenterology. 2005;39(4):284-90.
106. Sabate JM, Villarejo J, Bouhnik Y, Allez M, Gornet JM, Vahedi K, et al. Hydrostatic balloon dilatation of Crohn's strictures. Alimentary Pharmacology & Therapeutics. 2003;18(4):409-13.
107. Morini S, Hassan C, Lorenzetti R, Zullo A, Cerro P, Winn S, et al. Long-term outcome of endoscopic pneumatic dilatation in Crohn's disease. Digestive & Liver Disease. 2003;35(12):893-7.
108. Brooker JC, Beckett CG, Saunders BP, Benson MJ. Long-acting steroid injection after endoscopic dilation of anastomotic Crohn's strictures may improve the outcome: a retrospective case series. Endoscopy. 2003;35(4):333-7.

109. Dear KL, Hunter JO. Colonoscopic hydrostatic balloon dilatation of Crohn's strictures. Journal of clinical gastroenterology. 2001;33(4):315-8.
110. Ramboer C, Verhamme M, Dhondt E, Huys S, Van Eygen K, Vermeire L. Endoscopic treatment of stenosis in recurrent Crohn's disease with balloon dilation combined with local corticosteroid injection. Gastrointestinal Endoscopy. 1995;42(3):252-5.

Figure 1 - Search Strategy developed for Medline

Figure 2 - PRISMA flow diagram describing the identification, screening, eligibility and included studies in this systematic review

Table 1. Inclusion and exclusion criteria

Inclusion Criteria.
• Adult and paediatric patients with a confirmed diagnosis of Crohn's disease and current stricturing disease (B2 disease according to the Montreal Classification)(29) • Full papers (not abstracts) which describe patient outcomes following drug and/or endoscopic therapy for Crohn's disease associated strictures. • Anastomotic (secondary) and de novo (primary) strictures.
Exclusion criteria
• Single case reports • Practice guidelines • Expert opinions • Conference abstracts, conference papers, comments, letters and notes • Animal studies • Cohorts with <10 patients with stricturing disease • Non-English language articles • Anal strictures • Ileal pouch-anal anastomosis associated strictures • Malignant bowel strictures • Endoscopic studies only involving double balloon enteroscopy for stricture treatment

Table 2. Drug therapy for stricturing Crohn's disease

Author	Year	Cohort Type	Drug therapy used	Comparison - in Stricturing cohort	n Total	% with Stricture	Exclusive stricture cohort	Modality of stricture diagnosis	Follow up (months)	Response to treatment n (%)	Response/ Surgery?
Frei *et al* (34)	2019	Prospective	Anti-TNF	Early vs late initiation anti-TNF treatment	1592	32%	No	Clinical symptoms, imaging and endoscopy	<120	-	
Maehata *et al* (71)	2019	Retrospective	various drug therapy	Clinical and radiological factors associated with stricture surgery	53	100%	Yes	Double contrast small bowel x-ray	60	25/53 (47%)	28 of 53 required surgery
Amitai *et al* (23)	2018	Retrospective	Infliximab or adalimumab	Factors associated with treatment failure	21	100%	Yes	MRE	12	12/21 (57%)	5 of 21 required surgery
Bouhnik *et al* (20)	2018	Prospective	Adalimumab	Factors associated with treatment success	97	100%	Yes	MRE	45	62/97 (64%) after 24 weeks and 29/97 (30%) after long term follow up	48 of 97 required surgery
Olivera *et al* (81)	2017	Retrospective	Anti-TNF (Mainly infliximab)	Persistence rates of infliximab vs Adalimumab	487	29%	No	-	63	-	
Yang *et al* (36)	2017	Prospective	EEN	EEN treatment outcomes	41	24%	No	-	3	6/10 (60%)	
Naganuma *et al* (82)	2017	Prospective	Infliximab or adalimumab	MRE findings that predict clinical recurrence.	50	32%	No	MRE	18	8/16 (50%)	50% with severe stricture required surgery
Campos *et al* (38)	2017	Retrospective	Steroids, immunomodulators, Anti-TNF therapy and others	Drug therapy associated with therapeutic success	84	100%	Yes	MRE, CT and endoscopy	<60	28/84 (33%)	26 pf 84 required surgery
Allocca *et al* (37)	2017	Retrospective	Infliximab or adalimumab	Factors associated with avoidance of surgery	51	100%	Yes	MRE, Endoscopy	16	31/51 (61%)	20 of 51 required surgery - median 37 months
Konno *et al* (35)	2015	Retrospective	EEN	EEN and aminosalicylate treatment outcomes	58	22%	No	Endoscopy	50	8/13 (63%)	
Echarri *et al* (80)	2015	Prospective	Adalimumab	Factors associated with treatment response	68	41%	No	-	24	8/28 (29%)	
Yoshino *et al* (27)	2015	Retrospective	Thiopurines	Stable patients treated with monotherapy thiopurine	47	36%	No	-	39	10/17 (58%)	7 relapses, 3 of these patients underwent surgery

Author	Year	Cohort Type	Drug therapy used	Comparison - in Stricturing cohort	n Total	% with Stricture	Exclusive stricture cohort	Modality of stricture diagnosis	Follow up (months)	Response to treatment n (%)	Response/ Surgery?
Yu *et al* (83)	2015	Retrospective	Infliximab	Efficacy of induction treatment	106	27%	No	-	2.5	21/29 (72%)	Response defined by CDAI
Beppu *et al* (33)	2015	Retrospective	Infliximab	Mucosal healing on infliximab	54	43%	No	Endoscopy	45	16/23 (70%)	All patients with mucosal healing avoided surgery
Eder *et al* (84)	2015	Retrospective	Infliximab or adalimumab	MRE features predictive of remission in patients treated with anti-TNF	61	16%	No	MRE	12	6/10 (60%)	
Gibson *et al* (32)	2015	Retrospective	Anti-TNF. Infliximab and Adalimumab	MRE findings for predicting outcome	75	24%	No	MRE	17	6/18 (33%)	
Peters *et al* (31)	2014	Retrospective	Adalimumab	Factors associated with response	197	-	No	Imaging	3	-	
Moran *et al* (28)	2014	Retrospective	Thiopurines and/or Anti-TNF	Drug treatment factors associated with surgery	425	20-25% of total	No	-	138	66 to 68% avoided surgery	
Mao *et al* (85)	2014	Retrospective	Infliximab use (9 patients), New steroid use (26)	Risk factors predictive of surgery	86	100%	yes	Endoscopy	36	33/86 (38%)	33 of 86 required surgery
Aloi *et al* (21)	2013	Retrospective	various drug therapy	Factors associated with successful drug therapy	36	100%	Yes	MRE	24	20/36 (56%)	4 patients underwent 'early' surgery. 16 in total had surgery.
Pelletier *et al* (86)	2009	Retrospective	Infliximab	Factors associated with clinical response	18	100%	Yes	Barium contrast x-ray	18	7/18 (39%)	4 of 18 underwent surgery
Matsumoto *et al* (30)	2008	Retrospective	Infliximab	Early vs Late treatment with Infliximab	138	38%	No	Imaging, endoscopy	<12	28/53 (53%)	
Pallotta *et al* (22)	2008	Prospective	Infliximab	Regression of stenosis on imaging	20	75%	No	Small intestinal contrast ultrasound, MRI, endoscopy	38	8/15 (53%)	3 of 15 patients required surgery
Ho *et al* (26)	2006	Retrospective	Corticosteroids	Factors associated with treatment response	60	23%	No	-	12	6/14 (43%)	
Bemelman *et al* (25)	2001	Retrospective	Steroids, enteral feeding, 5-ASA therapy, thiopurines, methotrexate, antibiotics	Non-surgical management of hospitalised patients	76	89%	No	Small bowel series	96	19/68 (28%)	10 patients required upfront surgery

Table 3. Endoscopic therapy for stricturing Crohn's Disease

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Lan *et al (69)*	2019	Case-Control study	Needle knife stricturotomy vs surgical resection	35	2	49	-	100%	-	51%	11%	37%	2 % perforation, 7% bleeding	10
Winder *et al (61)*	2019	Retrospective cohort		64	1.5	138	85%	50%	- (Most)	22%	33%	47%	4% perforations, 0.7% bleeding	40
Andujar *et al (49)*	2019	Retrospective cohort	Stent in 11 patients	187	2.8	400	80%	41%	100%	39%	22%	62%	1% perforation	40
Shivashankar *et al (40)*	2018	Retrospective cohort	15% steroid injection	273	2	601	91%	48%	95%	50%	30%	42%	1% perforation, 0.4% bleeding	31
Taida *et al (87)*	2018	Retrospective cohort		26	-	65	100%	15%	100%	77%	8%	42%	0%	30
Lee *et al (88)*	2018	Retrospective cohort		30	1	55	87%	19%	100%	33%	3%	27%	4% perforation	135
Lan *et al (64)*	2018	Case-Control study		375 Total. 117 treated with primary EBD, 258 with primary surgical resection	1.5	-	86%	0%	85% In EBD group	34%	44%	34%	1% perforation	96
Lan *et al (64)*	2018	Case-Control study	EBD vs needle knife stricturotomy	185	1.5 (Endoscopic stricturotomy), 2.0 (EBD)	-	100% in ES group and 90% in EBD group	100%	71% ES group 82% EBD group	43% ES, 25% EBD	9.5% ES 34% EBD (P=0.03)	57% repeat ES, 60% repeat EBD	0% perforation, 9% bleeding ES. 1% perforation, 0% bleeding EBD	10 (ES group), 48 (EBD group)

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Lopes *et al (46)*	2017	Retrospective cohort		58	-	69	92%	100%	14%	-	3%	27%	0%	34
Singh *et al (55)*	2017	Retrospective cohort	Steroid injection 3%, needle knife 1%	35	-	96	93%	0%	100%	52%	34%	57%	3% perforation	22
Reutemann *et al (48)*	2017	Retrospective cohort		135	-	292	-	39%	-	61%	28%	29%	1% perforation	42
Lopes *et al (46)*	2017	Retrospective cohort	Comparison anastomotic vs non-anastomotic EBD	80	-	Median 2 per patient	98%	54%	31%	45%	4%	53%	0%	53
Lian *et al (62)*	2017	Retrospective cohort		289* 176 had EBD and 131 surgery	-	447	90%	100%	100%	21%	52%	Median 2 dilations per patient	1% Perforation	35
Kanamori *et al (89)*	2017	Retrospective cohort		30	2	-	90%	27%	100%	73%	23%	47%	0%	13
Asairinachan *et al (60)*	2017	Retrospective cohort		47	-	161	88%	67%	78%	51%	38%	65%	2% perforation	37
Rueda et al (45)	2016	Retrospective cohort		46	-	118	90%	38%	-	7%	44%	40%	2% perforation	58
Guo *et al (90)*	2016	Retrospective cohort		24	-	67	93%		100%	0%	38%	79%	3% perforation	23
Ding *et al (57)*	2016	Retrospective cohort		55	2	151	89%	100%	100%	6% at baseline (30% post-dilation)	18%	69%	2% perforation	70
Lian *et al (65)*	2015	Retrospective cohort		185	-	465	91%	100%	80%	17%	36%	59%	1% perforations	47
Greener *et al (63)*	2015	Retrospective cohort		79	5.8	72	82%	19%	100%	42%	28%	36%	0% perforation, 3% bleeding	37

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Romanko *et al (91)*	2015	Retrospective cohort		109	-	220	77%	85%	53%	19%	32%	-	0.5% perforation 1% bleeding	-
Chen *et al (24)*	2014	Retrospective cohort	4 patient needle knife (16%) and 7 corticosteroid injection (28%). All patients had a stoma.	25	1.1			0%	72%		8%	64%	3% perforation	22
Krauss *et al (92)*	2014	Case-Control study	EBD vs surgery. 30% steroid injection & EBD	88 (51 had EBD)	3	160	-	25%	-	1%	-	82%	14% perforation	52
Hagel *et al (50)*	2014	Retrospective cohort		77	2	237	55% (following 1st dilation)	57%	Not stated	-	35%	54%	2% perforation, Bleeding 2%	24
Bhalme *et al (73)*	2014	Retrospective cohort		79	-	191	95%	61%	-	29%	23%	57%	0%	27
Chen *et al (44)*	2014	Retrospective cohort	CD compared to non-Crohn's strictures. 25% Corticosteroid injections	90	1.5	151 (CD patients)	94%	73%	100%	25%	33%	48%	5% perforation	50
Atreja *et al (52)*	2014	Retrospective cohort		128	2.7	430	83%	48%	-	23%	33%	59%	1% perforation, 0.2% bleeding	22
Nanda *et al (93)*	2013	Retrospective cohort		31	-	55	100%	100%	100%	8%	55%	48%	0%	46
Endo *et al (94)*	2013	Retrospective cohort		30		47	94%	36%	100%	13%	36%	32%	4% perforation	26
de'Angelis *et al (95)*	2013	Prospective cohort		26	4.6	46	100%	56%	100%	23%	7%	50%	0%	41
Honzawa *et al (59)*	2013	Retrospective cohort		25	4	83	88%	21%	100%	5%	24%	60%	4% perforation	46

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Ono *et al (58)*	2012	Retrospective cohort		32	-	-	-	15%	100%	100%	15%	-	-	24
Karstensen *et al (96)*	2012	Retrospective cohort		19	-	54	-	42%	100%	4%	26%	74%	2% perforation	21
Gustavsson *et al (51)*	2012	Retrospective cohort	Steroid inj. in 9 pts and needle knife in 7	178	-	776	89%	80%	81%	0%	36%	Not stated. (52% required 1 or 2 dilations only)	1% perforation, 1% Bleeding	60
Loras *et al (70)*	2012	Retrospective cohort	25 stents inserted in total	17	3	23	92%	59%	100%	59%	41%	6%	0% perforation. spontaneous migration common - 1 day to >2weeks	14
Attar *et al (97)*	2012	Prospective cohort	metal stent inserted in all patients	11	4	11	91%	82%	100%	45%	18%	-	0%	49
Scimeca *et al (74)*	2011	Prospective cohort		37	-	72	84%	90%	100%	5%	11%	49%	0%	26
Rejchrt *et al (98)*	2011	Prospective cohort		11	-	11	91%	64%	-	55%	-	0%	3 stent migration (30%)	17
Thienpont *et al (56)*	2010	Retrospective cohort		138	-	237	97%	84%	100%	16%	24%	46%	3% perforation	70
Mueller *et al (99)*	2010	Retrospective cohort		55	3	93	95%	31%	100%	0%	24%	31%	1% perforation	44
Di_Nardo *et al (41)*	2010	Prospective randomized controlled pilot study	Steroid inj. in 15 patients (52%)	29	1.4	35	93%	41%	100%	24%	29% in placebo arm and 0 in steroid injection arm	7% steroid arm and 36% placebo arm	0%	12
Stienecker *et al (100)*	2009	Prospective cohort		25	1-10	33	97%	52%	100%	-	16%	46%	3% perforation	81

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Hoffmann *et al (101)*	2008	Retrospective cohort		25	-	51	90%	57%	100%	0%	24%	-	2% perforation	17
Foster *et al (102)*	2008	Retrospective cohort	65% steroid injection	24	-	71	92%	38%	100%	83%	8%	54%	3% perforation	32
Ajlouni *et al (103)*	2007	Retrospective cohort		37	-	54	90%	37%	95%	-	8%	22%	0% perforation	20
East *et al (42)*	2007	Prospective randomized controlled pilot study	7 received steroid injections	13	2	19	92%	100%	100%	0%	17%	46%	0%	12
Nomura *et al (104)*	2006	Retrospective cohort		16	2.2	20	94%	44%	100%	6%	44%	25%	10% perforation, 5% bleeding	39
Ferlitsch *et al (53)*	2006	Retrospective cohort	6 patients had steroid injected (15%)	39	2	73	95%	59%	100%	0%	28%	62%	3% perforation, 1% bleeding	21
Singh *et al (105)*	2005	Retrospective cohort	10 patients had steroid inj.	17	2	29	97%	35%	100%	0%	24%	24%	10% perforation	19
Thomas-Gibson *et al (47)*	2003	Retrospective cohort		59	3	124	81%	90%	100%	0%	59%	83%	2% perforation	29
Sabate *et al (106)*	2003	Retrospective cohort		38	2.1	53	84%	74%	100%	0%	39%	38%	2% perforation	23
Morini *et al (107)*	2003	Retrospective cohort		43	2.4	Mean of 3 procedures per patient	79%	72%	100%	0%	47%	65%	0%	64
Brooker *et al (108)*	2003	Retrospective cohort	Steroid injection in 20 of 26 cases	14	-	26	86%	79%	100%	0%	21%	29%	0%	16
Dear *et al (109)*	2001	Retrospective cohort		22	-	71	100%	95%	100%	0%	27%	45%	0	45
Matsui *et al (54)*	2000	Retrospective cohort		55	2	115	85%	43%	82%	0%	23%	55%	1% perforation	37
Lavy *et al (39)*	1997	Retrospective cohort	Steroid inj. In all 10 patients	10	1	14	100%	50%	not stated	0%	0%	20%	0%	24

Author	Year	Study Design	Additional therapy or comparison	n Total	Average Stricture length (cm)	Total no. of Endoscopic Procedures	Technical success %	Anast. Stricture %	Symptomatic patients	% on biologic therapy	Surgical Intervent. Rate	Redilation rate	% perforation / bleeding*	Follow up (months)
Ramboer *et al (110)*	1995	Prospective cohort	Corticosteroid injection	13	-	53	-	69%	-	0%	0%	77%	0%	47
Couckuyt *et al (43)*	1995	Retrospective cohort		55	4	78	90%	64%	100%	0%	38%	33%	8% perforation rate	34
Breysem *et al (72)*	1992	Retrospective cohort		18	-	26	89%	72%	100%	0%	33%	28%	0%	17
Blomberg *et al (67)*	1991	Retrospective cohort	4 patients needle knife incision	27	-	137	-	100%	100%		33%	-	1% perforation, 1% bleeding	15

*bleeding requiring blood transfusion

Table 4. Crohn's disease stricture imaging and clinical factors associated with anti-TNF treatment success(20)

Combination immunosuppressive treatment
Crohn's disease obstructive score (CDOS) >4*
Duration obstructive symptoms <5 weeks
Length of stricture <12 cm
Maximal small bowel diameter proximal to stricture on MRE of 18–29mm
Marked enhancement on delayed MRE T1-weighted sequence
Absence of internal fistula

*See Supplementary material for CDOS scoring