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Ecco Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment

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Abstract

This article is the second in a series of two publications on the European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on the management of Crohn's disease. The first article covers medical management; the present article addresses surgical management, including preoperative aspects and drug management before surgery. It also provides technical advice for a variety of common clinical situations. Both articles together represent the evidence-based recommendations of the ECCO for Crohn's disease and an update of prior ECCO Guidelines.

Keywords: Crohn's disease; surgery; inflammatory bowel disease [IBD]

1. Introduction

The incidence and prevalence of Crohn's disease [CD] is on the rise globally, with increases in incidence ranging from 4% to 15% yearly over the past three decades.[1] CD is a lifelong disease and optimal management is multidisciplinary and interprofessional, and has become increasingly complex. Surgery is a major therapeutic avenue in this context. Indeed, half of patients with CD undergo one or more operations during their lifetime. Patients with CD often suffer from malnutrition and psychological comorbidities, and may have to accept and live with a stoma.[2–5] Many different medications and combinations thereof are reshaping clinical practice, and refined surgical techniques, tailored approaches, and a wider acceptance of a surgical alternative benefit patients. Hence, the best possible outcomes are currently achieved within dedicated expert centres providing personalised medicine.[6–10] The European Crohn's and Colitis Organisation [ECCO] provides an interdisciplinary framework with these evidence-based Guidelines to inform and guide practice and clinicians caring for patients with CD. The present Guidelines focus on surgery for CD, including pre- and perioperative aspects, and provides technical advice for a variety of common clinical presentations. Further, ECCO Guidelines offer guidance on most aspects of interdisciplinary and interprofessional care for CD in separate publications.[11–16]

2. Methods

A detailed description of the methodology used is presented in the Supplementary materials. This article is the second in a series of two publications on the ECCO evidence-based consensus on the management of CD. The first article covered medical management[17]; the present article is focused on surgical management while covering both medical and surgical management of perianal CD. These two articles together represent the evidence-based recommendations of the ECCO for CD, and update prior Guidelines published in 2020.[18,19] The present Guidelines follow the GRADE methodology in terms of framing clinically relevant questions to draw evidence-based statements and recommendations. However, due to the peculiarities of the surgical literature, appraisal of the systematically researched literature was conducted according to the Oxford Centre for Evidence-Based Medicine, which grades from evidence level [EL]1: systematic review of randomised controlled trials, to EL5: expert opinion.[20] This allowed us to formulate statements and practice recommendations that can effectively inform and guide clinical management.

3. Perianal Crohn's disease

3.1. Medical approaches

Statement 3.1: ECCO CD Treatment GL - SURGICAL [2024] We do not recommend use of antibiotics as monotherapy for treatment of complex perianal fistulae in patients with CD [EL4]

Although antibiotics are widely used in the treatment of perianal CD, most available studies are uncontrolled.[21] To our knowledge, only one randomised controlled trial [RCT] compared placebo with antibiotics in perianal fistulae [Supplementary Table 1]. Remission at Week 10 was observed in 1/8 [12.5%] versus 3/17 [17.6%] patients treated with placebo or antibiotics, respectively (relative risk [RR]: 1.41; 95%

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confidence interval [CI]: 0.17–11.54). Complete healing was observed in 3/10 [30%] patients treated with ciprofloxacin and 0/8 patients treated with metronidazole.[22] Uncontrolled data and data from studies on combination therapy with anti-tumour necrosis factor [TNF] suggest that ciprofloxacin can improve the efficacy of anti-TNF in the short term, with good safety but with no impact on longer-term healing rates.[23,24] Importantly, despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics are indicated and recommended to treat and control perianal sepsis.

Statement 3.2: ECCO CD Treatment GL - SURGICAL [2024]
We suggest against using thiopurines as monotherapy [azathioprine, mercaptopurine] for treatment of complex perianal fistulae in patients with CD [EL3]

The effect of azathioprine [AZA] on fistula healing in perianal CD has been numerically reported in RCTs in 18 patients only.[25–28] A meta-analysis on this limited group of patients demonstrated that AZA is not superior to placebo for fistula healing [RR: 2.00; 95% CI: 0.67–5.93].[29] Another study reported complete fistula closure in 9/29 [31%] fistulae during mercaptopurine therapy, in contrast to 1/17 [6%] with placebo-treated fistulae[30] [Supplementary Table 2]. Nevertheless, these data could not be incorporated in the pooled analysis, as they were reported as number of fistulae closing rather than number of patients who had complete fistulae closing. With the availability of effective anti-TNF agents, it seems inappropriate to recommend any further randomised, placebo-controlled trial studying the efficacy of AZA in complex perianal fistulae.

Statement 3.3: ECCO CD Treatment GL - SURGICAL [2024]
We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in CD [EL2]

Infliximab was the first agent shown to be effective in a RCT for inducing closure of perianal fistulae and for maintaining this response over 1 year. Complete response [defined as the absence of any draining fistulae at two consecutive visits at least 4 weeks apart] was observed in 4/31 [12.9%] placebo-treated patients versus 29/63 [46%] infliximab-treated patients [RR: 3.57; 95% CI: 1.38–9.25].[31] Subsequently, the ACCENT II trial evaluated the efficacy of infliximab [5 mg/kg every 8 weeks] in a maintenance trial in 195 patients who had a response [defined as a reduction of 50% of draining fistulae in two visits at least 4 weeks apart] at Week 14 after open-label induction treatment with infliximab. A complete response was maintained until Week 54 in 19/99 [19.2%] placebo-treated patients versus 33/96 [34.4%] infliximab-treated patients [RR: 1.79; 95% CI: 1.10–2.92].[32] A recent meta-analysis of the existing data revealed that infliximab was effective in inducing [RR: 3.57; 95% CI:1.38–9.25] and maintaining clinical fistula healing [RR: 1.79; 95% CI:1.10–2.92][33] with no significant risk of serious adverse events [AEs] as compared with placebo [RR: 1.31; 95% CI: 0.11–15.25, Supplementary Figure 1]. A combined evaluation of both RCTs for safety revealed a risk of serious AEs of 18.9% [33/175 patients] in the placebo groups versus 11.9% [24/201 patients] in the infliximab groups. Overall, the most recent meta-analysis [2023] provided low certainty on clinical outcomes. Some retrospective data suggest that fistula healing is more likely in patients with higher infliximab trough levels, suggesting the need for personalised dosing in this setting.[34–38]

Statement 3.4: ECCO CD Treatment GL - SURGICAL [2024]
We suggest use of adalimumab for induction and maintenance of remission in complex perianal fistulae in CD [EL3]

Fistula healing in the subgroup of patients with enterocutaneous or perianal fistulae [or both] at baseline [$n = 117$] was a secondary endpoint of the CHARM double-blind, placebo-controlled, randomised trial.[39] A subsequent post hoc analysis, that focused specifically on the efficacy of adalimumab over time in this subgroup, confirmed the superiority of adalimumab over placebo [RR: 2.57; 95% CI: 1.13–5.84] for fistula healing after 56 weeks[39] [Supplementary Table 3]. Data from CHARM, combined with data from the open-label extension study ADHERE, revealed that there was no significant increase in serious AEs for patients treated with adalimumab [RR: 1.21; 95% CI: 0.43–3.38].[40–43] Data were insufficient to ascertain maintenance of fistula healing beyond 56 weeks, resolution of perianal sepsis, stoma-free survival, and quality of life. In a retrospective multicentre analysis evaluating 46 patients [83% with complex fistula] naïve to anti-TNF therapy, 72% of patients responded to adalimumab [54% remission, 18% partial response] at 6 months and 49% of patients maintained response at 12 months [41% remission, 8% partial response].[44] Additional data suggested that adalimumab may have a role in patients who failed infliximab because of immunogenicity [either primary non-responders or secondary loss-of-response]. The open-label CHOICE trial indeed demonstrated that complete fistula healing [mainly perianal fistula] could be achieved in 39% [34/88] of patients who initiated adalimumab after infliximab failure.[42] This finding has also been reported in a limited case series.[41] Some retrospective data suggest that fistula healing is more likely in patients with higher adalimumab trough levels, suggesting the need for personalised dosing in this setting.[35,37,40,45]

Statement 3.5: ECCO CD Treatment GL - SURGICAL [2024]
There is insufficient evidence to recommend use of certolizumab pegol as a treatment for complex perianal fistulae in patients with CD [EL4]

Certolizumab pegol [CZP], a pegylated humanised Fab' fragment that targets TNF-α, was evaluated for treatment of CD in two RCTs [PRECISE 1 and PRECISE 2]. The PRECISE 1 study included 662 patients with moderate-to-severe CD, who were randomly assigned to receive either CZP 400 mg or placebo subcutaneously at Weeks 0, 2, and 4, followed by administration every 4 weeks up to Week 26.[46] Fistula closure was a secondary endpoint; 30% [14/46] of patients in the CZP group achieved closure versus 31% [19/61] in the placebo group. According to this study, CZP did not show a significant benefit for fistula closure.

The PRECISE 2 trial included 668 adults with moderate-to-severe CD[47] and used the same induction therapy as in PRECISE 1. Patients with clinical response [reduction of ≥ 100 from baseline score on the Crohn's

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disease activity index] were randomly assigned to receive CZP 400 mg or placebo every 4 weeks through Week 26. Among patients responding to induction therapy with CZP, 28 of those randomised to CZP and 30 of those randomised to placebo had draining fistulae at baseline. The primary endpoint of the fistula subanalysis was fistula closure, defined as ≥ 50% closure at two consecutive post-baseline visits ≥ 3 weeks apart. At Week 26, 54% [15/28] of CZP-treated patients achieved fistula closure [per protocol] compared with 43% [13/30] of placebo-treated patients; the difference was not statistically significant [$p = 0.069$]. At Week 26, 36% of patients in the CZP group achieved complete fistula closure compared with 17% in the placebo group [$p = 0.038$]. Among patients who achieved the predefined criteria for fistula closure, there was a higher numerical proportion of patients who received continuous treatment with CZP compared with those who initially underwent induction therapy followed by placebo. However, these differences were not statistically significant for the small sample size analysed. Patients randomised to CZP in the maintenance phase maintained a 50% fistula closure rate at Week 26 (11/15 [73%] patients vs 39% [5/15] patients; $p = 0.069$) and achieved 100% closure at Week 26 (10/15 [67%] patients vs 4/13 [31%] patients; $p = 0.064$). The results from these post hoc analyses suggest a possible effect of CZP in complex perianal fistulae in CD. However, possibly due to limited sample size, the benefit of CZP over placebo was not demonstrated.

Statement 3.6: ECCO CD Treatment GL - SURGICAL [2024] There is insufficient evidence to recommend use of vedolizumab for the treatment of complex perianal fistulae in CD [EL4]

Vedolizumab [VDZ], a gut-selective α4β7 integrin antibody, was assessed for the treatment of complex perianal fistulae in an exploratory analysis of data from the GEMINI 2 study.[48] GEMINI 2 was a phase 3, randomised, double-blind, placebo-controlled trial that consisted of separate induction and maintenance phases. Following a 6-week induction period with VDZ, responders were randomly assigned to receive either placebo [VDZ/placebo group] or VDZ [VDZ/VDZ group] and entered a maintenance phase. Fistula closure was defined as the absence of clinically draining fistulae at Weeks 14 and 52. A total of 57 patients with draining fistulae at the start of the maintenance period were included in the analysis; half of them previously failed anti-TNF therapy. By Week 14, 28% [11/39] of patients in the VDZ/VDZ group and 11% [2/18] of patients in the VDZ/placebo group achieved fistula closure. However in a meta-analysis, maintenance with VDZ did not reach statistical significance [RR: 2.54; 95% CI: 0.63–10.29; $p = 0.19$].[49] At Week 52, 31% in the VDZ/VDZ group and 11% in VDZ/placebo group had fistula closure. Despite the numerically greater proportion of fistula healing observed in patients treated with VDZ, no statistically significant differences were observed. This post hoc analysis has several limitations, including a small sample size and inadequate statistical power. It is also biased by the induction phase with VDZ, and lacks a design specifically evaluating VDZ for fistula closure.

A small clinical trial compared the efficacy of standard VDZ dosing versus standard dosing plus an additional dose at Week 10 in patients with one or more draining perianal fistula at baseline.[50] Fistula closure was observed at Week 30 in 12 [42.9%] patients [seven patients in the standard and five patients in the additional VDZ dose group].

In summary, the available evidence is of low quality and insufficient to recommend VDZ for complex perianal fistulae in patients with CD. However, VDZ could be considered in patients refractory or intolerant to anti-TNF therapy. Further studies with appropriate design are warranted to determine the benefit of VDZ in the treatment of complex perianal fistulae.

Statement 3.7: ECCO CD Treatment GL - SURGICAL [2024] There is insufficient evidence to recommend use of ustekinumab as a treatment for complex perianal fistulae in CD [EL4]

The sole study comparing ustekinumab with placebo in treating complex perianal fistulae was a post hoc pooled analysis of data from the phase 2 CERTIFI and from the phase 3 UNITI-1 and UNITI-2 trials. This analysis provided information on the induction of fistula response and remission rates.[51] A total of 150 patients was treated with ustekinumab and 71 were treated with placebo. Due to the limited sample size, data from the final induction visit at Week 8 were aggregated across the three studies for evaluation. The analysis revealed a higher proportion of fistula closure after 8 weeks of treatment in the ustekinumab group [24.7%] compared with the placebo group [14.1%], although the observed difference did not reach statistical significance [$p = 0.073$]. This finding was confirmed in a meta-analysis [RR: 1.77; 95% CI: 0.93–3.37].[49]

In the maintenance phase, fistula response to treatment was assessed at Weeks 22 and 44. However, all patients included in the maintenance phase were either responders or non-responders to induction with ustekinumab, who were re-randomised to receive ustekinumab or placebo, which may bias the results. Among patients in the maintenance phase, fistula response at Week 22 occurred in 9/19 [47%] patients in the ustekinumab group and in 6/20 [30%] patients in the placebo group of the CERTIFI study, and in 12/15 [80%] and 5/11 [45.5%] patients, respectively, at Week 44 in the IM-UNITI study. Despite the numerically higher proportion of fistula healing in patients treated with ustekinumab, no significant differences were found. Moreover, being a post hoc analysis, fistula response or remission was a secondary outcome, making it an exploratory study with insufficient statistical power and a small sample size. In a recent meta-analysis that included 25 studies [most of which were observational studies and 20% of them being abstracts], 24.7% of patients achieved clinical remission of complex perianal fistulae at Weeks 8–12 and 41.9% at 12 months.[52] Overall, there is insufficient evidence to recommend ustekinumab for treatment of complex perianal fistulae in patients with CD. However, ustekinumab could be considered in patients with perianal fistulae who are refractory or intolerant to anti-TNF agents. Further studies with appropriate design are warranted to determine the benefit of ustekinumab in the treatment of complex perianal fistulae.

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Statement 3.8: ECCO CD Treatment GL - SURGICAL [2024]
There is insufficient evidence to recommend use of upadacitinib for the treatment of complex perianal fistulae in CD [EL4]

Upadacitinib [UPA] is currently the only JAK inhibitor approved for CD. Patients with moderate-to-severe CD were randomised to UPA 45 mg once daily or placebo for 12 weeks in two phase 3 induction trials. Patients who achieved clinical response after 12 weeks of UPA therapy were randomly assigned to receive UPA 30 mg or 15 mg or placebo once daily for 52 weeks. Among 1021 enrolled patients, 143 patients had fistulae at baseline [124 patients had perianal fistulae, 19 had enterocutaneous fistulae]. Post hoc analyses published as an abstract reported that in patients with draining fistulae at baseline, the proportion of patients with ≥ 50% reduction in draining fistulae at Week 12 was significantly higher with UPA 45 mg compared with placebo (22/44 [50%] patients vs 3/22 [13.6%] patients; $p = 0.004$).

Furthermore, complete resolution of draining fistulae at Week 12 was also significantly higher with UPA 45 mg than with placebo (21/44 [47.7%] patients vs 2/22 [9.1%] patients; $p = 0.002$). Numerically, a similar resolution pattern was seen in patients treated with either UPA 30 mg or 15 mg (1/11 [9.1%] and 3/17 [17.6%] patients, respectively vs 0/8 [0%] placebo-treated patients). Closure of the external fistula opening at Week 52 was higher with either UPA 30 mg or 15 mg (4/19 [21.1%] and 6/35 [17.1%] patients, respectively vs 0/25 [0%] placebo-treated patients).[53] Nevertheless, this post hoc analysis has several limitations, including small sample size and inadequate statistical power.

In summary, the available evidence is of low quality and insufficient to recommend UPA as treatment for complex perianal fistulae in patients with CD. Further studies with appropriate design are warranted to determine the benefit of UPA in the treatment of complex perianal fistulae.

Statement 3.9: ECCO CD Treatment GL - SURGICAL [2024]
There is lack of evidence to recommend use of risankizumab for the treatment of complex perianal fistulae in CD [EL5]

3.2. Surgical techniques

Statement 3.10: ECCO CD Treatment GL - SURGICAL [2024]
We recommend fistulotomy in carefully selected CD patients with a simple fistula in the absence of proctitis [EL4]

Studies on fistulotomy in CD are largely retrospective, single-centre studies with specific eligibility criteria, including Parks classification: superficial, intersphincteric, or low transsphincteric fistula[54–60]; absence of proctitis[57,58]; quiescent abdominal disease[61]; and a low number of daily bowel motions.[57] Few studies have compared the outcomes of fistulotomy in these select patients with alternative surgical procedures, which were mostly performed in patients with more complex or high anal fistulae. Due to this selection bias, these studies demonstrated improved healing and reduced recurrence rates in patients undergoing fistulotomy when compared with sphincter-preserving procedures, seton removal, and treatment with mesenchymal stem cells [MSC].[55,58,60] In the largest studies, recurrence rates of 3–13% up to 1 year post-fistulotomy[55,57,58,60] were reported. However, few studies provide robust data on continence and wound healing. Other reports present data from heterogeneous populations, including non-CD fistulae[54,59] or those undergoing multiple procedures prior to fistulotomy,[62] highlighting the difficulty in drawing recommendations from such data. Therefore, fistulotomy can only be recommended in simple, superficial, or low anal fistulae with absence of proctitis and stable intestinal disease.

Statement 3.11: ECCO CD Treatment GL - SURGICAL [2024]
We suggest advancement flap as a treatment option for selected patients with CD and complex perianal fistulae in the absence of proctitis [EL4]

Fistula closure can be achieved by raising a flap of mucosal tissue within the anus and lower part of the rectum. The advancement flap [AF] is then used to cover the internal opening of the fistula. CD patients with a single internal fistula opening and without proctitis or an anal stenosis are eligible. A systematic review identified 11 retrospective studies that reported data from 135 patients with CD perianal fistulae treated with an AF.[63] The pooled success rate was 66%. However, results were heterogeneous, probably due to varying definitions of success and length of follow-up. In a more recent meta-analysis, Stellingwerf *et al*. observed a weighted overall success rate of 61% in CD patients.[64] Results were not significantly different when compared with the success rate of ligation of the intersphincteric fistula tract [LIFT] procedure.

Additional prospective and retrospective series not included in the meta-analyses showed comparable clinical healing rates with AF, ranging from 47% to 90%[65–68] and recurrence rates of ~15–20%. Two studies showed a higher clinical healing rate when AF was performed in patients treated with anti-TNF/immunomodulators [75.0% vs 37.5%] and after seton drainage.[68] One study also showed a 100% success rate in diverted patients.[66]

The disadvantage of AF is risk of impaired continence. The systematic review showed an acceptable postoperative incontinence rate, which was higher in AF when compared with the LIFT procedure [7.8% vs 1.6%].[64] However, most prospective series revealed a postoperative higher incontinence rate of up to 20% following AF. Conversely, one retrospective study reported a postoperative improvement in faecal continence.[68]

Statement 3.12: ECCO CD Treatment GL - SURGICAL [2024]
We recommend ligation of the intersphincteric fistula tract as a treatment option for selected patients with CD and complex perianal fistulae [EL3]

LIFT aims to achieve fistula closure by ligation of the fistula tract in the intersphincteric plane, close to the internal opening. A theoretical advantage of LIFT over AF in CD patients is that it does not involve surgery of the [diseased] mucosa. Patients with a single, non-branching fistula and a well-epithelialised tract are preferably eligible.

Two systematic reviews and meta-analyses, both including approximately 1300 patients, demonstrated a high clinical

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success rate of 77% and 69% [range 47–95%], respectively, after a median follow-up of over 1 year.[64,69] However, there was only a minority of patients with CD in these studies, and these patients had a lower success rate of 53%. Included studies were heterogeneous, with a wide range of outcomes and follow-up times, which makes it difficult to draw firm conclusions. The described recurrence rates were low [1.6%] and compared favourably to AF [7.8%].

Two retrospective and one prospective study published after the aforementioned meta-analyses reported results on an additional 95 patients with CD.[68,70,71] Clinical closure rates were comparable to the results previously published. However, data on recurrence were only reported in one series, with a rate of 21%.[70] Overall, this suggests a possible underreporting in the systematic reviews and meta-analyses. Another retrospective study demonstrated that in patients with a [predominantly] fibrotic tract after LIFT at magnetic resonance imaging [MRI], no reinterventions or recurrences were seen during long-term follow-up, which also emphasises the requirement of radiological healing to consider a patient healed.[68]

The only prospective series included 46 patients with a mean follow-up of 33 months and demonstrated fistula healing in 65% of patients.[71] Smoking at time of surgery was significantly associated with failure (hazard ratio [HR] 3.2), and a trend was seen towards increased failure in patients with active proctitis [HR 2.0]. No other factors [use of biologics, prior seton drainage, type of fistula, previous repair attempts] appeared to influence LIFT healing.

Postoperative complications after LIFT were seen in up to 14% of patients and were predominantly wound dehiscence. Incontinence rates appeared to be lower when compared with AF. However, continence should be interpreted with caution, as there is a risk of underreporting in the literature. The only retrospective series specifically examining postoperative incontinence, in 37 patients demonstrated increased incontinence in 16% of patients after LIFT, whereas 53% of patients operated with LIFT and 43% with AF reported a postoperative improvement in faecal continence.[68]

Statement 3.13: ECCO CD Treatment GL - SURGICAL [2024]
We recommend against the use of fibrin glue in the treatment of patients with complex perianal CD fistulae [EL4]

Fibrin glue for treatment of perianal CD fistulae was assessed in an open-label RCT, with 71 patients randomised to instillation of fibrin glue into the fistula tract or no further treatment after seton removal.[72] This RCT demonstrated a significant difference in overall clinical remission rate [38% for fibrin glue and 16% in the observation group; $p = 0.04$]. However, the length of follow-up in this RCT was only 8 weeks and was insufficient for a definitive judgement on the true success rate. The only retrospective series with adequate follow-up time [5 years] suggested an acceptable healing rate of 45% at 1 year,[73] but the single predictor for complete clinical remission was combination with medical therapy. This series also demonstrated a worrisome cumulative incidence of iterative anal surgery of 54% within 5 years, suggesting a high recurrence rate after fibrin glue. Despite the limited efficacy of fibrin glue in daily clinical practice, a uniform characteristic of all studies is the relatively good safety profile of this technique with no reported injury to the sphincter muscles.

Statement 3.14: ECCO CD Treatment GL - SURGICAL [2024]
We recommend against anal fistula plug in the treatment of patients with complex perianal CD fistulae [EL4]

Use of a collagen anal fistula plug [AFP] in patients with perianal CD fistulae was assessed in a single RCT including 106 patients, which compared AFP after seton removal with seton removal only.[74] The fistula closure rate after 12 weeks in the AFP group was 33.3% in patients with complex fistulae and 30.7% in patients with simple fistulae, as compared with 15.4% and 25.6% with seton removal alone, respectively. These differences were not statistically significant. In addition, there was a trend towards more AEs in the AFP group [17% vs 8%; $p = 0.07$], although cumulative AE rates at 12 months follow-up were similar.

A systematic review of 12 observational studies, including 84 patients with CD, demonstrated an overall AFP success rate of 58%, with 14% recurrence after median follow-up of 9 [3–24] months.[75] However, there was no uniform definition for fistula closure or follow-up regimen. The quality of evidence for this systematic review was low due to risk of bias and imprecision. Use of an AFP in patients with CD appears to be relatively safe and may not affect continence [limited data on continence reported].[76] However, in studies using AFP for cryptoglandular fistulae, the abscess formation/sepsis rate ranged from 4% to 29% and the plug extrusion rate from 4% to 41%.[77]

Statement 3.15: ECCO CD Treatment GL - SURGICAL [2024]
There is insufficient evidence to recommend use of video-assisted anal fistula treatment, fistula-tract laser closure, or over-the-scope clip for achieving healing in complex perianal fistulae in CD [EL5]

The role of video-assisted anal fistula treatment [VAAFT] in the treatment of anal fistulae in CD has been investigated only in small cohort studies. A first retrospective study, including a mixed population of 84 patients with cryptoglandular and CD fistulae [$n = 11$] with a limited median follow-up of 8 months, revealed a 27% healing rate in patients with CD.[78] Data on postoperative complications and risk of postoperative incontinence were lacking. A second retrospective study reported an overall healing rate of 82% at 9 months follow-up.[79] However, these results are difficult to interpret due to the very limited sample size of 11 patients and by the fact that internal opening closure was achieved by fashioning a rectal advancement mucosal flap. Furthermore, in ~40% of patients, faecal diversion [FD] was present at time of surgery. No patients experienced postoperative morbidity or postoperative faecal incontinence. VAAFT was further evaluated in a retrospective analysis of prospectively collected data of 25 patients with anal fistulae refractory to multiple previous surgeries and adequate medical treatment with biologics.[80] Of 25 patients, 21 [84%] had a statistically significant improvement in a quality-of-life questionnaire before and 6 weeks after surgery, in particular in both pain and discharge scores; 81% agreed that the procedure was the right decision and no patient regretted undergoing the procedure. Reoperation was necessary in one patient [4%].

Fistula-tract laser closure [FiLaC] is a relatively new sphincter-preserving technique initially reported in 2011.

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A systematic review published in 2022 identified six retrospective studies investigating FiLAC as a treatment option for perianal CD on a total of 50 patients.[81] There was heterogeneity in length of follow-up, fistula characteristics, and outcomes reported. The techniques used were only partially described, particularly how to address internal opening[s] of the fistula, and included technical variations. The pooled rate of primary healing among the studies was 68% [95% CI: 53.0–84.0%]. No postoperative complications or faecal incontinence was observed, although not all studies reported these outcomes.

The role of over-the-scope clip [OTSC] in the treatment of anal fistulae in CD has only been investigated in several small observational case series, often with mixed populations; the majority were cryptoglandular cases and fewer were CD-related fistulae. Mennigen *et al.* reported a case series of 10 patients including data on six patients with CD.[81] A total of 4/6 [66.7%] patients were on biologic therapy at the time of OTSC and all these patients achieved fistula closure; only one patient not receiving biologics healed. Although no postoperative morbidity or faecal incontinence was observed, the OTSC may be spontaneously passed [2/6, 33%] or need to be subsequently removed due to discomfort [1/6, 16.7%]. A study by Prosst and Joos reported OTSC in 100 patients (11 had inflammatory bowel disease [IBD]) with a closure rate of 45% in IBD.[82] Overall, the OTSC was spontaneously passed in 18 patients and appeared to be associated with a lower fistula closure rate of 33% [6/18 patients]. The OTSC needed to be removed or operatively explanted in 14 patients. No significant postoperative morbidity or faecal incontinence was reported. Although OTSC appears to be safe and may result in fistula closure in some patients, widespread adoption of this technique is currently limited by a paucity of data in CD.

Statement 3.16: ECCO CD Treatment GL - SURGICAL [2024] We recommend against use of chronic seton treatment as the sole treatment for perianal CD fistulae other than as palliation [EL3]. We recommend against a cutting seton due to the risk of incontinence [EL5]

There are no RCTs or studies comparing seton drainage with no treatment for perianal CD fistulae. Two systematic reviews, including 10 studies [$n = 305$ patients] on patients treated solely with seton drainage, reported varying results.[83,84] Complete closure rates ranged from 13.6% to 100% and recurrence rates from 0% to 83.3%. Timing of seton removal differed among studies [range 3 weeks to 40 months]. Included studies were prospective and retrospective cohort studies and case series, and mostly of questionable quality.

Additionally, the PISA trial published in 2020 compared the following three treatment strategies: long-term seton drainage alone, anti-TNF treatment, and surgical closure [the latter two with prior seton drainage].[85] The study was stopped by the data safety monitoring board because of futility. Seton treatment was associated with the highest reintervention rate [10/15 seton vs 6/15 anti-TNF vs 3/14 surgical closure patients; $p = 0.02$]. No substantial difference in perianal disease activity and quality of life was observed between the groups. Interestingly, in the accompanying PISA prospective registry, inferiority of chronic seton treatment was not observed for any of these outcome measures. This study suggested that chronic seton treatment should not be recommended as the sole treatment for perianal CD fistulae.

The cutting seton, in which a non-absorbable thread is inserted into the fistula tract and exteriorised through the anorectal canal with subsequent tightening, causing gradual cutting through the anal sphincter, should not be used as many studies have shown associated complications, including prolonged perianal pain and incontinence rates up to 58%.[84]

3.3. Combined approaches

Statement 3.17: ECCO CD Treatment GL - SURGICAL [2024] We recommend seton drainage preceding medical or surgical therapy for complex perianal CD fistulae [EL3]. Combined anti-TNF therapy and seton removal could result in improved healing rates, faster time to healing, longer time to relapse, and a reduced need for surgery than either therapy alone [EL3]

There were no RCTs comparing medical or surgical therapy with or without preceding seton drainage. Five systematic reviews were included.[83,84,86–88] Most studies focused on anti-TNF therapy. One of the largest systematic reviews [42 studies] included studies assessing anti-TNF agents for perianal fistulae. In most studies, anti-TNF was combined with preceding seton placement, and it was suggested that combining seton drainage with an anti-TNF agent was superior. These results are consistent with another, large, systematic review that revealed that a combination of surgical treatment [including seton drainage] with medical therapy [anti-TNF agents and immunomodulators] may have additional benefit on healing of perianal CD fistulae compared with surgery or medical therapy alone.[88] One study showed that 75% of patients treated with anti-TNF therapy after prior seton placement healed, compared with 63% of patients without initial seton.[89] Another study revealed that patients with seton placement prior to anti-TNF therapy had a better initial response [100% vs 82.6%; $p = 0.014$], lower recurrence rate [44% vs 79%; $p = 0.001$], and longer time to recurrence [13.5 vs 3.6 months; $p = 0.0001$] compared with patients receiving infliximab alone.[90] Additionally, patients with seton placement prior to anti-TNF therapy were less likely to require hospitalisation and had reduced health care costs.[87] Studies have also shown shorter mean time to healing,[91,92] longer time to relapse,[92] and reduced need for repeat surgery[93] than with either therapy alone.

Timing of seton removal is largely variable and inconsistent between studies, ranging from 4 to 27 weeks post-insertion.[93,94] However, the heterogeneity and low quality of the mainly retrospective studies included should be considered.

In most studies, seton drainage was performed prior to surgical closure in patients with perianal CD fistulae. However, several small retrospective studies showed no association between fistula healing rate after a LIFT procedure and prior seton placement or duration of seton drainage prior to surgery.[71,95]

A recent retrospective study analysed medical and surgical therapies to identify the optimal care strategy in 200 patients. Seton drainage prior to anti-TNF therapy alone did not significantly increase the fistula closure [HR: 1.15; 95% CI 0.61–2.32; $p = 0.66$]. The combination of seton placement and anti-TNF therapy followed by fistula closure surgery

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within 52 weeks was the best management strategy for fistula healing in multivariate analysis [$p = 0.02$]. Cumulative probabilities of fistula closure following the latter combined approach were 43.8%, 82.2%, and 93.7% at 1, 3, and 5 years, respectively. Patients concomitantly treated with a combination of anti-TNF therapy and immunosuppression at surgery had the highest long-term closure rate.[96]

Importantly, particularly in case of perianal sepsis, adequate seton drainage seems to be of key importance to create optimal circumstances prior to starting medication or proceeding to surgical closure.

Statement 3.18: ECCO CD Treatment GL - SURGICAL [2024]
We recommend the combination of medical therapy with surgical fistula closure in amenable patients with complex perianal fistulae, as surgical closure results in improved long-term outcomes [EL3]

Two RCTs and one retrospective study investigated surgical closure of the fistula tract in combination with medical therapy. A first multicentre RCT compared seton removal and surgeon's choice of closure with seton removal alone in patients treated with adalimumab. There was no difference in clinical closure at 12 months [surgery 56.3% vs control 65.4%; $p = 0.48$] or in secondary outcomes measuring quality of life, continence, and AEs. Patients with surgical closure experienced longer disease duration and were more likely to have been previously treated with infliximab, suggesting more aggressive disease. Most patients [79%] were treated with fibrin glue with limited efficacy in perianal CD. In addition, the study was underpowered and robust conclusions could not be drawn from these data.[97]

In the patient preference PISA II trial,[9] 94patients were enrolled [38 patients with surgical closure and 56 with anti-TNF therapy].[8] At 18 months, radiological healing was significantly more common after surgical closure (12/38 [32%] patients) than after anti-TNF therapy (5/56 [9%] patients; $p = 0.005$). Clinical closure was not significantly different between the two treatments [68% vs 52%, respectively; $p = 0.076$]. Fewer patients required a reintervention and the perianal disease activity index was significantly lower after surgical closure. Long-term results after a median follow-up of 5.7 years showed no recurrences in patients with radiological healing; recurrence was observed in 41% of patients with clinical closure without radiological healing.[98]

A retrospective study of 226 patients found no difference in healing when patients underwent a variety of surgeries alone compared with those undergoing surgery with concurrent infliximab [60% vs 59%, respectively]. Surgical procedures included seton drainage [50%], fistulotomy [41%], fibrin glue [6%], advancement flap [2%], and collagen plug [1%]. However, time to healing was 6.5 months after combination therapy [surgery and infliximab] and 12.1 months after surgery alone [$p < 0.0001$].[91]

Statement 3.19: ECCO CD Treatment GL - SURGICAL [2024]
There are conflicting data on allogenic adipose-derived stem cell therapy for the induction and maintenance of remission in complex perianal fistulae in CD [EL5]

The efficacy of MSC in treatment of perianal fistulae CD is mediated by anti-inflammatory properties and by the capacity to engraft and transdifferentiate into healthy tissue.[99] Allogeneic MSC from adipose tissue [Cx601-darvadstrocel; Alofisel] was assessed in a phase 3 RCT that included 212 patients with refractory, fistulising perianal CD.[100] At Week 52, a significantly higher proportion of patients treated with darvadstrocel achieved combined remission when compared with controls [56.3% vs 38.6%; 95% CI 4.2–31.2; $p = 0.010$]. Combined remission was defined as closure of all treated external openings at clinical examination and absence of collections > 2 cm at MRI. A study extension including 40 patients was prospectively conducted through Week 104.[101] Clinical remission was reported in 14/25 [56%] patients in the darvadstrocel group and 6/15 [40%] patients in the control group, which was not statistically significant [95% CI: -15.5 to 47.5]. No serious AEs were reported at Week 52 or Week 104. Due to the high cost of darvadstrocel, the costs and potential benefits should be considered on a case-by-case basis of the clinical situation.

A meta-analysis published in 2018 that included three studies suggested that MSC of different origin significantly improved healing of perianal fistulae when compared with control at 6 to 24 weeks (odds ratio [OR]: 3.06; 95% CI: 1.05–8.90; $p = 0.04$) and numerically at 24 to 52 weeks [OR: 2.37; 95% CI: 0.90–6.25; $p = 0.08$].[102] No significant increases in AEs [OR: 1.07; 95% CI: 0.61–1.89; $p = 0.81$] were observed in treated patients. Limitations of the available studies on MSC in perianal CD include heterogeneity in protocols [allogeneic or autologous MSC, bone marrow- or adipose tissue-derived MSC], low number of patients, varying definitions of fistula healing, and lack of consensus on definition of perianal fistula healing in MRI. Further studies based on robust, well-defined, radiological targets are needed to evaluate the role of MSC on the natural history of perianal fistulising CD. Results from the phase 3, RCT, ADMIRE-CD II will provide additional information.[103] Although the results of the ADMIRE-CD II were not yet published at the time of writing the present Guidelines, the sponsor announced in a press release dated 17 October 2023 that the primary endpoint of combined remission at 24 weeks in complex perianal CD fistulae treated with darvadstrocel was not met. These inconclusive results were also presented at ECCO 2024 on 23 February 2024. The safety profile for darvadstrocel was consistent with prior studies, and no new safety signals were identified. The final results of ADMIRE-CD II will help position this treatment in the management of complex perianal fistulae in CD.

Statement 3.20: ECCO CD Treatment GL - SURGICAL [2024]
We suggest autologous adipose-derived stem cells may be used as a treatment option in complex perianal CD [EL4]. There is insufficient evidence to recommend use of platelet-derived factors or stromal vascular fraction in complex perianal CD [EL5]

Autologous stem cells [ASC] have the advantage of originating from the patient undergoing treatment, as opposed to donor-based therapy, thus making ASC readily available and less costly. ASC may be injected in a similar manner as allogeneic MSC, mixed with fibrin glue, or loaded onto a fistula plug.

The most recent systematic review summarising results of four RCTs demonstrated increased clinical healing rates of ASCs when compared with control patients treated with

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fibrin glue alone [OR: 3.19; 95% CI: 1.05–9.65; $p = 0.04$].[104] Unfortunately, it is difficult to draw firm conclusion for patients with CD, as only 20 patients with CD were included in these studies and most patients had a short follow-up of only 8 weeks. There are no studies that directly compared autologous with allogeneic stem cells for perianal CD fistulae.

The best evidence on the use of ASCs for perianal CD fistulae comes from various prospective case series, including a total of 110 patients.[105–110] Although treatment protocols varied substantially, most involved curettage of the fistula tract, suturing of the internal opening [with or without an advancement flap], and filling of the fistula tract with ASCs. Most studies allowed a second injection of ASCs in patients with incomplete closure. Clinical healing rates, defined as no suppuration from the external orifices, ranged from 33% to 91%. However, most of these series lacked an adequate follow-up [range 2–12 months], with recurrence rates rarely described. The largest study included 30 patients and showed a closure rate of 83.3% with a recurrence rate of 33%.[109]

Despite the additional requirement of harvesting cells via liposuction to obtain ASC, the procedure appeared safe. The most common AEs were postoperative pain, abscess, or bleeding.[104] There were no significant differences in AEs when compared with the control group [OR: 1.06; 95% CI: 0.71–1.59; $p = 0.77$].

There are also some studies that investigated the effects of injecting freshly collected, microfragmented, autologous adipose tissue, platelet-derived growth factors, or stromal vascular fraction into perianal CD fistulae.[108,110,111] Feasibility was demonstrated in most patients and results appeared comparable to ASCs, with clinical healing ranging from 38% to 67%. Harvesting, preparation, and administration of these tissues are described as easy, inexpensive procedures with minimal AEs. Again, these series suffer from small patient numbers and brief follow-up and lack description of recurrence rates. Further studies are required to define the true potential of these approaches.

Statement 3.21: ECCO CD Treatment GL - SURGICAL [2024] We suggest medical treatment in anogenital and rectogenital CD fistulae, and counselling for surgical closure in selected patients with CD [EL5]

Anogenital and rectogenital fistula are complex and disabling conditions that are better managed by an experienced multidisciplinary team. No RCTs or prospective studies were found that compared anti-TNF agents alone versus anti-TNF agents and surgery combined to treat these fistulae.

A post hoc analysis of the ACCENT II study identified 25 women with ano- or rectovaginal fistulae.[112] This study demonstrated that infliximab is more effective than placebo in prolonged closure [defined as non-draining fistula at Week 14]; 13/29 [44.8%] fistulae responded to induction regimen with infliximab and were closed. From Weeks 14 to 46, among responders in the infliximab maintenance group, the proportion of rectovaginal fistulae that closed ranged from 54.5% to 90.0% compared with 28.6% to 42.9% in the placebo group.

A French, retrospective, multicentric, observational study, including 131 consecutive patients treated with anti-TNF agents for 1 year, found that 37% of patients had complete clinical fistula closure, 22% had partial response, and 41% had no response.[113] Complementary surgery was allowed, including advancement flap [rectal, vaginal, or Martius flap], fibrin glue, collagen plug, or gracilis muscle interposition and performed during the first year in 10 patients [8%], translating into a higher closure rate in multivariate analysis [adjusted RR: 2.02; 95% CI 1.25–3.26; $p = 0.004$]. A retrospective study of 166 patients who underwent operations for anogenital fistulae revealed an overall fistula healing rate of 71.7% [$n = 119$] with a median follow-up of 5.5 [1.2–9.8] years.[114] Nearly one-third of patients [33.1%] achieved complete healing after first surgery, 51.8% [$n = 86$] after the second, and 62.1% [$n = 103$] after the third operation.

A recent systematic review found nine studies that reported healing, success, or closure [range 14–81%] across multiple surgical procedures; seven studies reported success rates ranging from 50% to 75%.[115] However, those studies were of low quality and had limited sample sizes, various concomitant medical therapies, heterogeneous fistula and patient characteristics, outcomes considered, and definition of outcomes.

Statement 3.22: ECCO CD Treatment GL - SURGICAL [2024] We suggest faecal diversion with a defunctioning ileostomy or colostomy for treatment of refractory, complex perianal CD [EL4]

Patients with treatment-refractory perianal CD may benefit from faecal diversion [FD] with a diverting ileostomy or colostomy. Indeed, FD is associated with a high early clinical response rate and an improved quality of life, although FD often becomes permanent. A systematic review of 16 retrospective studies with 556 patients with perianal CD found that FD is associated with early clinical response in 63.8% [95% CI: 54.1–72.5%].[116] However, stomas were often permanent and only 16.6% [95% CI: 11.8–22.2%] of patients ultimately had successful ostomy reversal. The rate of proctectomy after failure of temporary diversion was 41.6% [95% CI: 32.6–51.2%]. Proctitis was associated with increased risk of permanent diversion.

One study compared FD plus local procedures for perianal CD [$n = 13$] with local procedure without FD [$n = 26$].[117] Complete resolution of perianal CD was observed in 11 [85%] patients with FD versus five [19%] patients without FD. Of the FD patients, six [46%] had stoma reversal, of whom three [50%] remained disease free, one [17%] required successful additional local procedures, and two [33%, 15% overall] required re-diversion. Thus only 4/13 [31%] of FD patients ultimately had stoma reversal. Another study, of 21 patients, showed that although some patients may achieve complete healing, many do not; initial improvement was followed by plateau in seven [33%], temporary improvement in six [29%], no effect in four [19%], and healing in four [19%] patients.[118] In this study, 11 [52%] patients subsequently had proctocolectomy, six [28.6%] had their stoma in situ, and four [19%] had stoma reversal. In a large series of 138 patients who had initial FD, a total of 63 [45%] underwent subsequent total proctocolectomy, 45 [33%] had their stoma without proctectomy, and 30 [22%] had stoma reversal.[119] Independent predictors of lack of stoma reversal included proctitis [OR: 7.5; 95% CI: 2.4–33.4], one or two seton placements [OR: 3.3; 95% CI: 1.4–8.8], and two or more seton placements [OR: 6.9; 95% CI: 1.2–132.5]. Biologics were not associated with stoma closure [$p = 0.25$].

Few studies examined quality of life before and after FD in perianal CD. In a series of 34 patients with FD, compared

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with similar patients without FD, patients with FD had fewer perianal CD symptoms [44% vs 79%; $p < 0.05$], higher Gastrointestinal Quality of Life index scores [68 vs 62 points; $p < 0.001$], and higher gastrointestinal [GI] symptoms subscores [81 vs 67; $p < 0.0001$] compared with non-diverted patients.[120] The most recent meta-analysis, evaluating 1578 patients managed in the biologic era, similarly concluded that FD improved symptoms and quality of life, and bowel continuity could be successfully restored in a quarter of the patients.[121]

Statement 3.23: ECCO CD Treatment GL - SURGICAL [2024]
We suggest proctectomy for treatment of refractory, complex perianal CD despite defunctioning stoma [EL4]

Proctectomy may be recommended in many patients with perianal CD. However, proctectomy is associated with a substantial risk of a non-healing perineal wound in the short term and a risk of colonic or small-bowel recurrence in the long term. In a series of 127 patients with perianal CD, proctectomy was required in 32 [25.2%] patients.[122] Several studies discussed independent risk factors for proctectomy, including age at first perianal fistula [$p < 0.02$], perianal fistula at the time of CD diagnosis [$p < 0.04$], three or more fistulae during follow-up [$p < 0.01$], and proctitis [$p < 0.0001$].[123] Other studies also reported malignancy in the setting of perianal CD as an indication for an oncological proctectomy.[123–125]

Proctectomy for perianal CD is typically performed as an abdominoperineal resection [APR] with a colostomy or as a total proctocolectomy with end-ileostomy in case of extensive colonic involvement.[122–127] In terms of extent of bowel resection in the setting of perianal CD, a single study examined APR with colostomy and reported a clinical recurrence rate of colonic CD of 22% for an endoscopic colonic recurrence rate of 29%; overall, 5% of patients required completion total colectomy.[127] It is important to note that proctocolectomy does not cure CD; a multicentre, retrospective study of total proctocolectomy with end-ileostomy, including 193 patients with refractory perianal CD, reported a 23% small-bowel recurrence within 2 years.[126] Independent risk factors for recurrence included CD diagnosis at age < 18 years [HR: 2.56; 95% CI: 1.40–4.71] and previous small-bowel resection [HR: 2.61; 95% CI: 1.42–4.81].

Proctectomy for IBD is often performed as an intersphincteric dissection, limiting the size of the perineal incision.[122–127] The intersphincteric groove may not be identifiable due to scarring in up to 78% of patients with perianal CD, limiting the ability to perform an intersphincteric dissection and affecting wound healing.[125] Indeed, delayed perineal wound healing is often observed after proctectomy in perianal CD.[124,128–131] When wounds are left open to heal by secondary intention, an uncommon practice nowadays, only 58% of perineal wounds of patients with IBD were healed after 6 months of dressing changes.[129] Wound irrigation has also been explored in the 1980s, and half of perineal CD wounds were healed at 30 days compared with 87% after APR for cancer in the absence of radiotherapy.[131] Male gender was a risk factor for delayed healing, particularly when the drain exited through the wound instead of laterally. Higher success rates were observed when myocutaneous flaps were used, although patients are still at risk for subsequent fistulisation [20% in a small study].[130] In a large series of 126 patients, 72 [53%] wounds were healed at 12 weeks, and delayed healing was observed in 35 [26%] and non-healing in 29 [21%] patients.[124] Preoperative perianal sepsis was an independent predictor of a delayed- or non-healing wound [$p = 0.001$], suggesting FD prior to proctectomy.[128] For non-healing perineal wounds with metastatic CD, hyperbaric oxygen therapy may be an option.[132]

3.4. Practice points

Fistula treatment should start with insertion of a seton followed by medical treatment [preferably anti-TNF]. In the absence of proctitis, patients should be counselled for surgical closure.

Perianal fistulae in CD can have a substantial detrimental impact on patient quality of life. Current biological understanding of perianal fistulising CD remains inadequate, and previous classification systems have not provided clear guidance on therapy in clinical practice. A new classification presented in Figure 1 identifies four groups of patients.[133] Key elements include stratification according to disease severity and desired outcome. This classification can guide patients and clinicians in decision making on a 'treat to patient goal basis' by a combined medical and surgical approach.

All treatment should start with insertion of a seton to control sepsis and create a patent tract, followed by medical treatment [preferably anti-TNF with high trough level]. After good response to anti-TNF therapy, seton removal can be considered within 2–8 weeks to aim for closure with medication only.[134] Although clinical closure can be achieved in up to 60% by medication, it should be noted that MRI closure is rare [< 10%], with high risk of recurrence and surgical reintervention.[135] MRI closure is more frequently seen after surgical closure under anti-TNF therapy [up to 40%], with no recurrences after long-term follow-up in case of a completely fibrotic tract on MRI.[98] Therefore, in absence of proctitis, amenable patients should be counselled for surgical closure. For patients with an intersphincteric or low transsphincteric single fistula tract, fistulotomy can be considered as this procedure will have the highest success rate.

In case of complex perianal fistulae, AF or LIFT can be offered, depending on fistula characteristics. Stem cells can be an alternative, particularly in patients with multiple internal openings or pre-existing complaints of incontinence.

In case of anti-TNF failure and surgically refractory fistulae, more experimental approaches [such as hyperbaric oxygen therapy or new medical approaches] can be attempted, ideally in the context of a prospective clinical trial. An algorithm to guide the management of perianal CD is illustrated in Figure 2.

4. Surgical management of abdominal Crohn's disease

4.1. Preoperative optimisation

Statement 4.1: ECCO CD Treatment GL - SURGICAL [2024]
We recommend elective bowel resection over emergency surgery in patients with CD [EL2]

A meta-analysis of cohort series including 75 971 CD patients from 15 countries reported a significantly lower mortality among patients who underwent elective [0.6%; 95% CI: 0.2%–1.7%] vs emergent surgery [3.6%; 95% CI:

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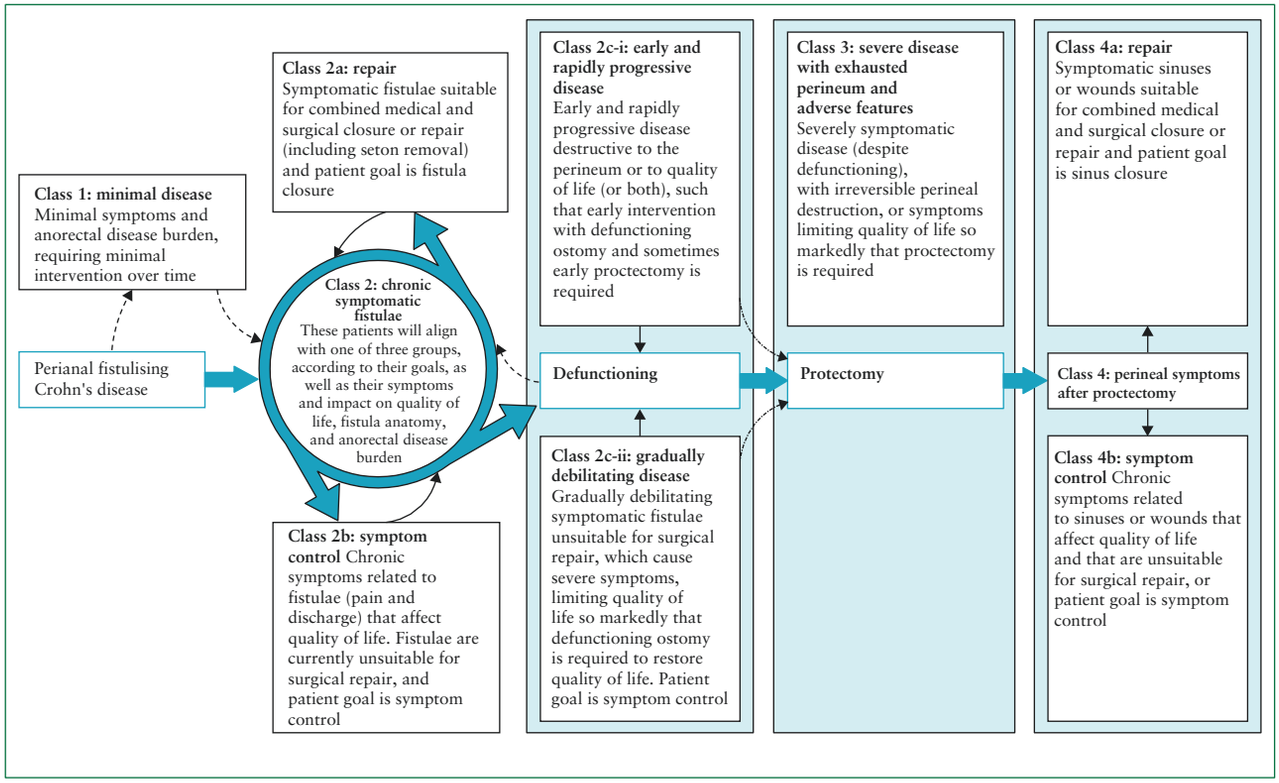


Figure 1 Classification of perianal fistulising Crohn's disease. At any moment throughout its disease course, perianal fistulising Crohn's disease can be classified into one of four classes.[133] [Reprinted with permission from Elsevier, License Number 5760781248280].

1.8%–6.9%], highlighting the importance of perioperative optimisation and avoidance whenever possible of emergent surgeries.[136]

Statement 4.2: ECCO CD Treatment GL - SURGICAL [2024]
Pre-operative optimisation should be initiated, followed by re-assessment of the patient for surgical intervention [EL3]

A recent meta-analysis showed that emergency bowel resection is associated with a higher risk of overall postoperative complications and abdominal septic complications.[137] This is consistent with a European Society of Coloproctology prospective snapshot audit, in which emergency surgical intervention was associated with unfavourable postoperative outcome.[138] Another, recent, multicentre, international, observational study concluded that emergency intervention in patients with an abdominal abscess increased the risk of postoperative complications and abscess recurrence.[139] Moreover, patients undergoing emergency surgery for CD have a higher rate of stoma formation.[140,141] Last, laparoscopic surgery in the emergency setting has a higher conversion rate and involves resection of longer segments of small bowel, which is a concern in CD due to a lifetime risk of short bowel.[140]

The drivers behind these unfavourable outcomes may be patient status and the environment of care typical of an emergency situation. Emergency resection [within 48 h of admission] is performed on tissue characterised by profuse oedema and acute inflammation, in a patient often in an unstable condition, by a team that may not be specialised in IBD or even colorectal surgery. Patients with CD who undergo emergency operation typically have a severe form of disease, are malnourished, and are often on steroids, immunomodulators, biologics, or combinations thereof, with a higher likelihood of undrained abscesses, fistulae, or both at time of emergency surgery. Drainage of an abscess and relieving obstruction, together with preoperative optimisation, should be initiated immediately on admission, as described in recent prospective cohort series[142,143] and advised in ECCO topical reviews.[144,145]

Preoperative optimisation of an emergency CD patient and transfer of care from the acute to the specialised/elective setting is key to improving short- and long-term postoperative outcomes. On the other hand, free bowel perforation is one of the few situations where urgent surgery may be mandatory, as bowel perforation is a very rare but serious and potentially life-threatening complication in CD. The literature is characterised by low-quality, heterogeneous studies based on historical data. A study from Korea estimated the incidence to be 2.15% in the Korean CD population.[146]

There are two important points to consider when CD leads to bowel perforation.

1. Bowel-wall thickness: bowel-wall thickening in CD occurs due to chronic inflammation and scarring and differs from ischaemic bowel perforation, which occurs when there is a decreased blood supply to the bowel, potentially resulting in a perforation. Symptoms, diagnostic approach, and treatment may also differ between these conditions.
2. Size of perforation: bowel perforation in CD can vary in size and presentation. Some cases may involve small or microscopic perforations, others can present as larger perforations. Timely diagnosis and appropriate treatment can prevent further complications and improve outcomes.

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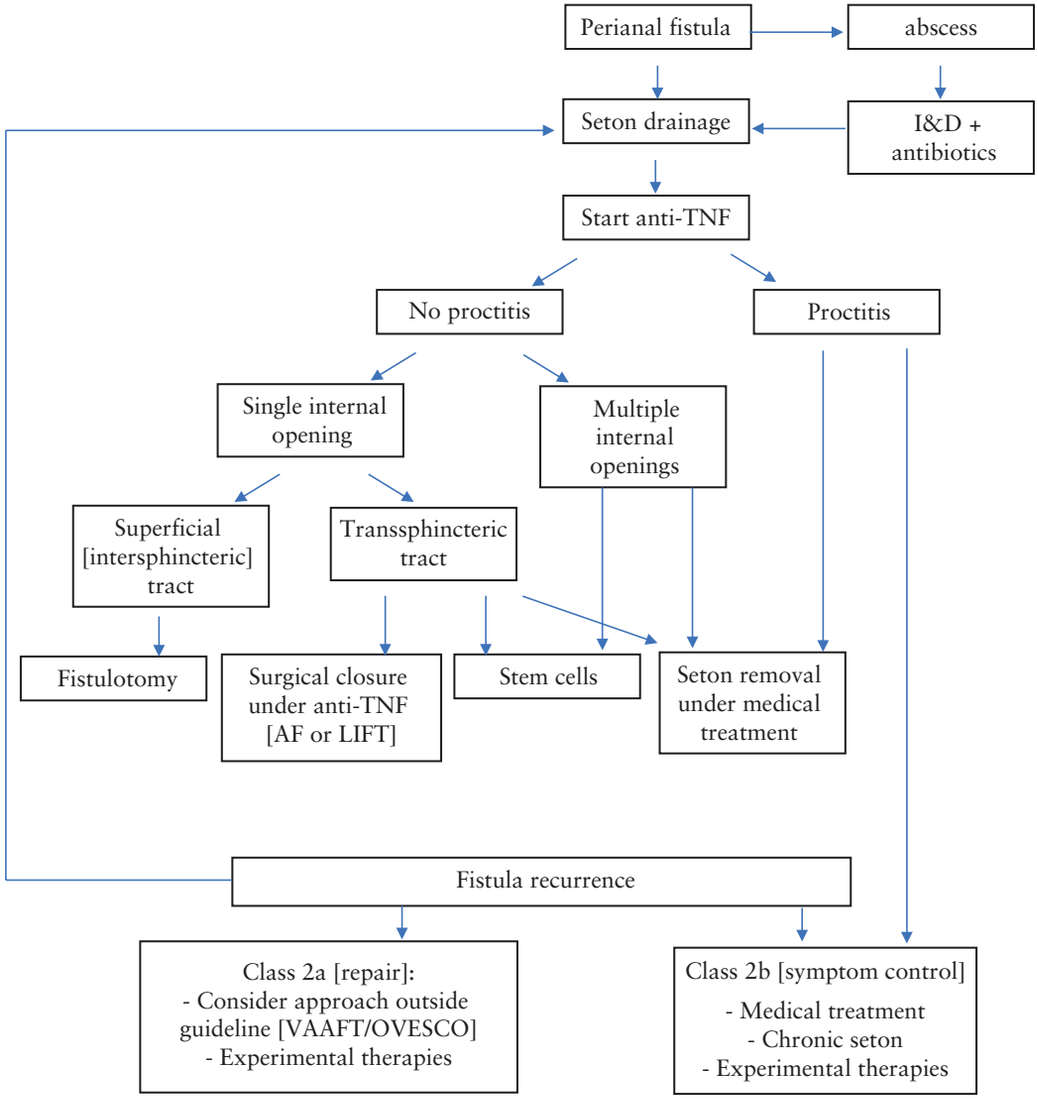


Figure 2 Treatment algorithm for Class 2A CD fistulae aiming for repair.

A small-bowel perforation can, in very selected situations and under supervision of an experienced colorectal surgeon, be managed conservatively. This mandates a very close clinical follow-up and the capacity to operate immediately should the patient deteriorate.

The early involvement of a multidisciplinary team consisting of an IBD gastroenterologist, an IBD surgeon, a radiologist, and a dietitian is mandatory in emergency presentation of CD, due to the complexity of the disease and management.

Statement 4.3: ECCO CD Treatment GL - SURGICAL [2024]
We recommend control of sepsis prior to abdominal surgery for CD [EL3]

Statement 4.4: ECCO CD Treatment GL - SURGICAL [2024]
We suggest use of intravenous antibiotics and percutaneous, image-guided drainage as the first-line treatment for intra-abdominal abscesses related to CD [EL3]

Statement 4.5: ECCO CD Treatment GL - SURGICAL [2024]
We suggest conservative treatment following successful percutaneous, image-guided drainage of an intra-abdominal abscess in carefully selected cases. A low threshold for surgery is recommended in the event of medically refractory cases [EL4]

Penetrating CD, complicated by intra-abdominal abscesses [IASC], represents a complex condition requiring involvement of interventional radiologists, gastroenterologists, and surgeons. An [elective] operative approach appears indicated in most patients, as conservative management leads to complete abscess resolution in less than 30% of selected cases, whereas delayed elective surgery is associated with improved postoperative outcomes, avoidance of a stoma, and abscess recurrence.[147–149]

Observational studies indicate that failure to control IASC preoperatively increases the risk of postoperative complications, anastomotic leaks, postoperative sepsis, and stoma formation, resulting in an increased length of hospital stay.[139,150–152] Percutaneous drainage [PD] under ultrasonographic or

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computed tomography [CT] guidance may be the primary approach for treatment of well-defined abscesses. Successful drainage rates of 74–100%, allowing avoidance of emergency surgery in 14–85% of patients, were reported.[18] PD with antibiotics to control IASC resulted in better quality of life than surgery alone, provided abscesses were completely drained.[139,150,153] PD and antibiotic therapy should be combined with perioperative optimisation, including nutritional support and stopping or decreasing corticosteroids. Despite PD, these patients still present with higher morbidity than those without preoperative IASC.[140]

It is worth noting that when performed by specialised, high-volume, IBD surgeons, early laparoscopic surgery [< 1 week after admission] was safe, feasible, and associated with similar morbidity rates when compared with delayed surgery [within 3 weeks after initial admission, including PD in 28% of patients].[154] However, steroid treatment before PD and short waiting interval [< 2 weeks] were associated with a higher risk of abscess recurrence, and anaemia and long waiting interval [> 4 weeks] increased the risk of stoma construction.[154] Overall, performing surgery 2–4 weeks after successful PD was associated with the lowest risk of postoperative IASC.[139] Identifying patients who may be treated without surgery is challenging and currently relies on clinical judgment rather than on evidence. In general, medically refractory disease, presence of stenosis, or an enterocutaneous fistula represent clear indications for surgery.[153]

Statement 4.6: ECCO CD Treatment GL - SURGICAL [2024]
We recommend endoscopic balloon dilatation as a treatment option for small-bowel strictures < 5 cm in length when technical expertise is available [EL2]

In a review of 1463 patients with CD who underwent 3213 endoscopic balloon dilatation [EBD] procedures, a stricture length < 5 cm was mostly amenable to EBD and associated with a surgery-free outcome; every additional centimetre in stricture length increased the need for surgery by 8% [$p = 0.008$].[155] This is consistent with other reviews.[156–158] Inflammation, disease activity, type of stricture, balloon diameter, and duration of inflation did not affect outcomes.[155,157]

Whereas therapeutic success can be achieved after a single dilation, several dilations may be necessary to resolve obstructive symptoms; however, repeat dilation may reduce quality of life.[159,160] Although accessory endoscopic techniques, including local steroid injection, cutting procedures [eg, Argon beaming], and stent implantation have been proposed to improve resolution,[155] the evidence is weak. Some retrospective cohort studies suggested that combined therapy with anti-TNF and EBD may prevent intestinal stricture recurrence and surgery in hospitalised patients with CD.[161,162]

An unresolved controversy is the dilatation efficacy of primary versus anastomotic strictures. Identification of predictive factors for the long-term success of EBD may assist clinical decision making and an individualised treatment approach in stricturing CD.[163]

In conclusion, short-term therapeutic success of EBD is high in a selected group of patients when technical expertise is available. However, the impact on long-term quality of life, need for repeat dilatations, and strictureplasty or bowel resection is less clear.

4.2. Practice point

Whenever possible, elective surgery is preferable to an emergency procedure in both fistulising and obstructive CD. The control of IASC is multidisciplinary and draws from interventional radiology, infectious disease, gastroenterology, and surgery. Imaging [sonography, CT, MRI], swift drainage, antibiotics, intensified perioperative therapy, and specialist care are the mainstays of treatment. PD is mostly a bridge intervention rather than a definitive solution; elective surgery performed 2–4 weeks thereafter minimises postoperative complications and need for a stoma.

Primary conservative management of bowel obstruction includes rehydration, nasogastric decompression, imaging, and consideration of high-dose steroid therapy. Frequent monitoring and surgical consultation are critical. Surgery can be deferred in most cases but should be considered during follow-up. Definitive non-surgical management may be successful but must be carefully balanced and discussed with the individual patient.

Statement 4.7: ECCO CD Treatment GL - SURGICAL [2024]
We recommend preoperative nutritional assessment and identification of nutritional risk by IBD-dedicated dietitians for patients with CD who need surgery [EL2]

Statement 4.8: ECCO CD Treatment GL - SURGICAL [2024]
When feasible, enteral nutrition should be the strategy of choice for preoperative optimisation in patients with CD [EL3]

Malnutrition is common in patients with CD requiring surgery and is a risk factor for adverse postoperative outcomes and complications. Systematic nutritional risk screening [body mass index, unintentional weight loss, reduced dietary intake, illness severity], together with perioperative nutritional support, may mitigate the perioperative risks associated with malnutrition. An ECCO consensus and topical review on perioperative dietary therapy in CD concluded than exclusive enteral nutrition [EEN] represented a valid preoperative optimisation strategy for reducing complications and improving nutritional status in patients with CD, likely by modulating inflammatory status and improving microbial composition.[145,164–166]

The benefits of preoperative EEN have been consistently reported, leading to a marked reduction of postoperative morbidity [21.9% vs 73.2%; OR: 0.09; 95% CI: 0.06–0.13; $p < 0.01$], although data on biochemical optimisation are still debatable.[167–169] Conversely, the role of parenteral nutrition [PN] in the preoperative optimisation strategy is more debated.[170] Importantly, EEN requires dedicated nutritional support and high patient compliance to be successful.

The use of PN in the perioperative period should be reserved for patients unable to tolerate EEN, who do not meet their nutritional requirements with EEN, or in whom EEN is contraindicated.[171] In a recent, prospective, multicentric, cohort study, preoperative EEN reduced morbidity for infection and temporary stoma requirement in malnourished patients with CD.[165] In another recent cohort study, patients receiving preoperative PN had significantly lower rates of non-infectious complications [OR: 0.07; 95% CI: 0.01–0.80;

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$p = 0.03$]. A subset of frail patients with severe CD, who did not tolerate EEN and required PN, presented a similarly high rate of IASC and primary stoma as when upfront surgery was elected. Hence, the advantage of providing PN to this subgroup of frail patients is questionable, as these patients may benefit from an early surgical approach followed by nutritional replacement.[172] Therefore, early surgery with postoperative optimisation may be considered in frail, severely ill patients who do not tolerate EEN and accept a diverting stoma.

Statement 4.9: ECCO CD Treatment GL - SURGICAL [2024]
We recommend that steroids should be tapered whenever possible before surgery to reduce the risk of complications [EL2]

Previous ECCO Guidelines have reported that treatment with > 20 mg prednisolone daily for > 6 weeks increases the risk of postoperative septic complications.[11,18,173] Whereas there is no large RCT confirming this position, one large, multicentre, cohort study and numerous retrospective cohort studies have identified this risk [summarised in three meta-analyses].[174–176]

Indeed, preoperative steroid use was a significant risk factor for major complications, including an overall increased risk of postoperative complications [OR: 1.41; 95% CI: 1.07–1.87] and a specifically increased risk of postoperative IASC [OR: 1.68; 95% CI: 1.24–2.28].[175,177] Patients who received > 40 mg perioperative oral steroids had the highest risk of overall complications [OR: 2.04; 95% CI: 1.28–3.26]. A meta-analysis confirmed an almost doubling of total wound infections [OR: 1.70; 95% CI: 1.38–2.09].[174] Similar to the results from the large, multicentre, cohort study, an increased risk for anastomotic leak was also observed [OR: 1.51; 95% CI: 1.02–2.25].[176]

Steroids should be reduced before surgery as part of a preoperative optimisation strategy in combination with nutritional optimisation and drainage of sepsis. If this is not possible, consideration should be given to a staged procedure with a temporary stoma.

Statement 4.10: ECCO CD Treatment GL - SURGICAL [2024]
We recommend against cessation of biologics prior to surgery, as current evidence suggests that preoperative treatment with anti-TNF therapy [EL3], vedolizumab [EL3], and ustekinumab [EL4] does not increase the risk of postoperative complications in patients with CD undergoing abdominal surgery

4.3. Anti-TNF therapy

Use of biologics in patients with CD undergoing surgery remains controversial. Concern exists over the desired modulation of the immune response and the potential to increase postoperative complications. Several retrospective studies regarding anti-TNF agents have been published over the past 20 years. Some suggested an increased incidence of complications in patients receiving anti-TNF agents preoperatively, and other studies showed no difference. Several meta-analyses have also reported varying conclusions.[178] Several prospective studies also reached inconsistent conclusions. This variation probably represents heterogeneous populations, different outcomes, and inconsistent definitions of outcomes. Most evidence is concentrated on infliximab and adalimumab.[178] The PUCCINI trial is the largest prospective trial to date and revealed no difference in the rate of any infection between patients using biologic therapy and those not so.[179] Detectable preoperative serum concentrations of anti-TNF agents also did not increase the risk of surgical site or overall infection rates.[179] Hence, anti-TNF therapy can be continued prior to surgery.

4.4. Vedolizumab

Although initial retrospective data suggest that VDZ leads to an increased risk of postoperative infection, subsequent studies showed no increased risk. These data were confirmed by most, but not all, recent meta-analyses.[180–183] The latest of these showed no significant differences in overall complications [OR: 1.04; 95% CI: 0.48–2.24],[181] infectious complications [OR: 1.00; 95% CI: 0.37–2.69], or surgical site infections [OR: 1.45; 95% CI: 0.33–6.32] for those receiving VDZ preoperatively. Therefore, VDZ can be continued prior to surgery.

4.5. Ustekinumab

Although one meta-analysis focused on ustekinumab and postoperative complications, the comparator was patients receiving anti-TNF therapy.[184] No difference in complications and infectious complications were identified. The only cohort study comparing ustekinumab with non-biologic therapy revealed that preoperative use of ustekinumab is an independent risk factor for intra-abdominal sepsis [OR: 2.93; 95% CI: 1.16–7.40; $p = 0.02$].[185] Although further studies are required to confirm the safety of ustekinumab and surgery, current data suggest that cessation before surgery may not be necessary.

There is no available evidence of the possible impact of preoperative use of CZP, rizankizumab, or JAK inhibitors on postoperative morbidity in patients with CD undergoing abdominal surgery. The safety of continuing newer biologic agents prior to surgery remains unknown.

4.6. Practice points

Preoperative optimisation is a key element in successful management of complex situations and chronic disease. Many aspects of optimal perioperative care are generic and common to all abdominal procedures,[186] although some aspects are particularly important in the context of CD [venous thromboembolism prophylaxis, nutrition, iron management, drug management, minimally invasive approaches, and bowel- and sphincter-sparing techniques].[187,188] High-dose steroids should be tapered to reduce surgical morbidity, but current biologic therapy can safely be continued perioperatively.

4.7. Surgical techniques

Statement 4.11: ECCO CD Treatment GL - SURGICAL [2024]
We recommend a laparoscopic approach as the first line in abdominal surgery for CD [EL2]

A Cochrane review of two randomised trials[189,190] showed no difference in complications between laparoscopic and open surgery for CD. A more recent review[191] showed a benefit

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for patients operated by laparoscopy, with fewer complications and lower rate of incisional hernia. This review included both randomised trials and observational studies. Although this may potentially introduce some bias, based on strong evidence for the benefits of laparoscopy, particularly in relation to reduced adhesions, the current evidence strongly supports recommending laparoscopy as the first-line approach. Laparoscopic resection for recurrent CD is also feasible but is associated with higher risk for conversion.[192] Importantly, in the absence of expertise to perform laparoscopic surgery, emergency operations should not be delayed.

Statement 4.12: ECCO CD Treatment GL - SURGICAL [2024]
We recommend laparoscopic resection as an alternative to infliximab [EL2] or adalimumab [EL4] therapy in patients with limited terminal ileal or ileocaecal disease

A randomised, controlled, open-label, multicentre trial assigned 143 patients with non-stricturing CD of the terminal ileum to receive either laparoscopic ileocaecal resection [$n = 73$] or infliximab [$n = 70$]. At 12-month follow-up, quality of life and body image perception were comparable.[193] Patients treated with infliximab had fewer days of sick leave from work. Serious complications related to treatment occurred in four resected patients versus two in the anti-TNF group. Crossover among groups was needed in 37% of patients treated with infliximab and in 26% of those who underwent surgery. Long-term data from the randomised trial revealed no surgical recurrence in the surgery group after 5 years, whereas 50% in the anti-TNF group had surgery at 5 years.[194] A recent meta-analysis suggests reduced risk of overall and surgical recurrence and reduced use of postoperative biologic therapy if surgery is performed early.[195] Based on these data, early surgery has a benefit in patients with limited terminal ileal CD and represents a reasonable alternative to escalating medical therapy. Patients should be advised early about a surgical option.

Statement 4.13: ECCO CD Treatment GL - SURGICAL [2024]
We suggest stapled side-to-side anastomoses in small-bowel or ileocolic resections for CD [EL3]

Surgeons place great importance on the technical aspects of their work, which can be influenced by various factors, including their training, personal experience, available resources, and the clinical scenario. The choice of the optimal anastomosis technique in small-bowel and ileocolic resections has been a subject of controversy. In recent years, there has been a growing body of evidence supporting the use of side-to-side anastomosis, and this support has been consistent over time.

A significant meta-analysis on 661 patients operated for cancer and CD revealed a significantly higher anastomotic leak rate in end-to-end anastomoses compared with side-to-side anastomoses [OR: 4.37; $p = 0.02$]. This was also observed in the subgroup of ileocolic anastomoses [OR: 3.8; $p = 0.05$].[196] Furthermore, overall postoperative complications [OR: 2.64; $p < 0.001$] and hospital stay length were higher [by 2.81 days; $p = 0.007$] when an end-to-end anastomosis was performed. A subsequent meta-analysis confirmed the superiority of side-to-side anastomosis in overall postoperative complications [OR 0.6; $p = 0.01$]. However, there were no statistically significant differences in leak rates, endoscopic and symptomatic recurrence, or reoperation for recurrence.[197]

A meta-analysis compared 396 stapled side-to-side anastomoses with 425 hand-sewn end-to-end anastomoses and found that stapled side-to-side anastomoses outperformed in all endpoints, namely overall postoperative complications [OR: 0.54; 95% CI: 0.32–0.93], anastomotic leak [OR: 0.45; 95% CI: 0.20–1.00], recurrence [OR: 0.20; 95% CI: 0.07–0.55], and reoperation for recurrence [OR: 0.18; 95% CI: 0.07–0.45].[198]

A network meta-analysis of 11 trials and 1113 patients further substantiated the superiority of stapled side-to-side anastomosis regarding overall complications, clinical recurrence, and reoperation for recurrence. However, the choice of anastomosis technique did not seem to affect leak rates, surgical-site infections, mortality, or length of hospital stay.[199] A more recent systematic review suggested that stapled side-to-side anastomoses may lower the risk of surgical recurrence in CD, potentially reducing rates of reoperations compared with hand-sewn end-to-end anastomoses [OR: 0.22; 95% CI: 0.05–0.95].[200] In case of emergency bowel resection, a retrospective study involving 92 bowel resections recommended use of stapled side-to-side anastomoses, which was associated with fewer endoscopic recurrences than use of hand-sewn end-to-end anastomoses [OR: 38.12; $p = 0.01$].[201] This was corroborated by another retrospective study.[202] However, a recent multicentre, retrospective, observational study examining 427 intestinal anastomoses in CD found no significant difference in postoperative complications.[203]

Overall, the quality of the studies included in systematic reviews and meta-analyses was notably limited, with only a minority of patients participating in RCTs and heterogeneous populations studied. Despite this limitation, the prevailing consensus leans toward a preference for stapled side-to-side anastomosis, which is associated with lower rates of postoperative complications and allows for an intracorporeal anastomosis. Furthermore, it was suggested that the diameter of the anastomosis may be a significant risk factor for recurrence, as a wider anastomosis is thought to be associated with a reduced likelihood of clinical and surgical recurrences. Importantly, the width of the anastomosis is determined by its inlet, more than by the length of a staple line or a suture line. Endoscopic appraisal of an early recurrence should consider the type of anastomosis healing. Indeed, stapled [everted mucosa] and hand-sewn [inverted mucosa] have a different healing pattern and healing time, which should neither be confused endoscopically with an early recurrence, nor lead to overtreatment.

Statement 4.14: ECCO CD Treatment GL - SURGICAL [2024]
We suggest that the Kono-S anastomosis can be an alternative surgical approach to other types of anastomoses after ileocaecal resection [EL3]

Kono-S anastomosis was first described in 2011 as a new, hand-sewn, anti-mesenteric, functional, end-to-end anastomosis designed with the aim to reduce anastomotic CD recurrence after ileocaecal resection.

In the first retrospective study,[204] Kono-S anastomosis was associated with a reduction in both median endoscopic recurrence score [Rutgeerts' score] and surgical recurrence rate

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at 5 years, with no safety issues. These findings were then confirmed by a larger, international, multicentre, retrospective study including 187 patients, reporting a 10-year surgical recurrence-free rate of 98.6%.[205]

Performing a Kono-S anastomosis was associated with longer operative time, similar short-term outcomes, and likely lower endoscopic recurrence rate than side-to-side anastomosis.[206] In another two retrospective cohort studies following patients for up to 5 years, Kono-S anastomosis was associated with a lower leak rate than end-to-end anastomosis[207] or stapled anastomosis,[208] which in the authors' opinion could explain the lower surgical recurrence rate observed in the long term.

More recently, early results from the first RCT[209] comparing Kono-S and side-to-side anastomoses demonstrated a significant reduction in the 6-month endoscopic recurrence rate and mean Rutgeerts' score, comparable postoperative outcomes, and a trend toward a reduced surgical recurrence rate, although this was not statistically significant. This and other trials are still ongoing, with definitive results expected in the near future.

Several meta-analyses, including the aforementioned RCT and observational studies, concluded that Kono-S anastomosis was associated with a reduced endoscopic recurrence rate and comparable short-term outcomes.[200,210,211] More limited evidence suggested a reduction in surgical recurrence and leak rate in Kono-S anastomosis than with conventional anastomoses. However, the most recent prospective study on Kono-S did not confirm a reduction in endoscopic recurrence rates and reported similar Rutgeerts' scores and clinical recurrence rates between conventional anastomosis and Kono-S.[212] Therefore, a definitive conclusion on the benefit of a Kono-S anastomosis cannot yet be made. Multicentre RCTs are currently ongoing across the USA and Europe and will probably provide definitive answers on the role of Kono-S anastomosis.[213–215]

Statement 4.15: ECCO CD Treatment GL - SURGICAL [2024]
There is insufficient evidence to recommend extensive mesenteric excision in surgery for ileocecal CD [EL4]

Extensive mesenteric excision may reduce the incidence of recurrence after resection by possibly removing a 'sump' of pro-inflammatory substances from the vicinity of the anastomosis. The current evidence for this is weak. Two systematic reviews addressed extensive mesenteric excision,[200,210] but both only included one small, historical, case-control study.[216] This single, case-control study compared 30 patients undergoing extensive mesenteric excision with a surgical recurrence rate of 2.9% at 5 years with a historical control group of 34 patients who had a 5-year recurrence rate of 40%.[216] Several ongoing trials address the possible benefit of a wide mesenteric excision in the context of CD. Such an excision cannot currently be recommended in routine care.

Statement 4.16: ECCO CD Treatment GL - SURGICAL [2024]
We suggest a temporary stoma formation in patients with CD if they are not sufficiently optimised for surgery [EL4]

The decision to create a stoma [primary anastomosis and protective stoma or no anastomosis and split stoma] in the context of steroid intake relies mostly on clinical grounds and experience. There are limited data comparing strategies between primary anastomosis or secondary anastomosis in patients with CD treated with steroids.[217] However, prolonged [> 6 weeks] and high-dose [≥ 20 mg prednisolone equivalent] steroid use are associated with postoperative infectious complications, including anastomotic leakage.[150,175,218,219]

Statement 4.17: ECCO CD Treatment GL - SURGICAL [2024]
We recommend strictureplasty as an alternative treatment option to resection in small-bowel CD [EL2]

Location of CD in the ileum, use of biologics before surgery, and non-conventional strictureplasty [SP] predict early site-specific recurrence after SP.[220,221] However, procedure-specific recurrence rates are available only for some SP techniques.[222] The wide range of recurrence rates after SP [3–25%] reflects the variability of the population case mix and, most importantly, of the follow-up length.[221] An extended follow-up time [> 5 years] is mandatory to appraise the true outcome of SP.[221] Morbidity and postoperative hospital length of stay were similar for bowel resection and SP.[222–224] Overall, the results of SP compare well with the recurrence rate after bowel resection, while preserving bowel length.

Statement 4.18: ECCO CD Treatment GL - SURGICAL [2024]
We suggest segmental colectomy in selected cases of colonic CD [EL4]

When a single colonic segment is affected, a segmental colectomy may be the recommended course of action. On the other hand, the involvement of multiple colon segments generally indicates [sub]total colectomy. A meta-analysis compared 223 cases of subtotal or total colectomies with ileorectal anastomosis and 265 cases of segmental colectomies in CD.[225] In this analysis, there were no significant differences in recurrence rates, complications, or need for a permanent stoma. However, it is worth noting that recurrence occurred on average 4.4 years later in patients who underwent a subtotal or total colectomy [$p < 0.001$].

A recent meta-analysis included patients who underwent segmental colectomy [$n = 500$], subtotal colectomy [$n = 510$], or total proctocolectomy [$n = 426$]. Complications were more frequent after segmental colectomy compared with subtotal colectomy [OR: 2.84; 95% CI: 1.16–6.96] and after proctocolectomy compared with subtotal colectomy [OR: 0.19; 95% CI: 0.09–0.38].[226] This indicates that subtotal colectomy is generally considered a safer procedure, although segmental colectomy resulted in fewer patients requiring permanent stoma [OR: 0.52; 95% CI: 0.35–0.77]. Subtotal colectomy had higher rates of CD recurrence [OR: 3.53; 95% CI: 2.45–5.10] and need for repeat surgery [OR: 3.52; 95% CI: 2.27–5.44] than total proctocolectomy. However, no significant difference in recurrence was observed between segmental and subtotal colectomy. In rare situations where two distinct colon segments are affected, it may be worth considering two segmental resections as an alternative to subtotal colectomy, particularly for patients who have extensive small-bowel loss.[11]

A recent retrospective analysis that included 55 [sub]total colectomies and 30 segmental colonic resections indicated a

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trend towards increased postoperative complications after segmental colectomy [Clavien–Dindo grade ≥ III] of 13.3% versus 7.3% after [sub]total colectomy. Additionally, there was a trend toward higher rates of hospital readmissions [13.3% vs 1.8%] and reinterventions [13.3% vs 3.6%] after segmental resection compared with [sub]total colectomy.[227] Another recent, multicentre, retrospective study including 687 patients concluded that segmental resection was a safe option compared with total colectomy, with the additional benefit of reducing ostomy formation without increasing the risk of surgical recurrence, particularly in the era of biologics.[228] However, the heterogeneity of the included patients was a limitation of this analysis.

A further, retrospective, single-centre study included 200 patients who underwent segmental colectomy. A surgical recurrence rate of 31% was observed. Risk factors of recurrence and subsequent [sub]total colectomy in multivariate analysis were the presence of three or more affected sites [HR: 2.47; 95% CI: 1.22–5.00; $p = 0.018$] and presence of perianal disease [HR: 3.23; 95% CI: 1.29–8.07; $p = 0.006$].[229]

In summary, the extent of colonic resection is determined by the clinical presentation [elective vs emergency surgery] and by the number of colonic segments involved [unisegmental vs pancolitis]. Segmental colectomy is generally favoured whenever feasible, as this does not increase the risk of recurrence, particularly in the modern era of biologics and when other risk factors for recurrence [such as number of affected locations and presence of perianal disease] are absent.

Statement 4.19: ECCO CD Treatment GL - SURGICAL [2024]
We suggest proctocolectomy as a treatment for CD-associated colorectal cancer or high-grade dysplasia and segmental colectomy followed by endoscopic surveillance in selected cases [EL3]

Patients with chronic inflammation of the large bowel are at an increased risk of development of colorectal cancer [CRC], as described in an European evidence-based consensus: IBD and malignancies.[230] Two meta-analyses of cohort studies have clarified the increased risk of CRC in patients with IBD.[231,232] The pooled standardised incidence ratio [SIR] for CRC was 1.7 [95% CI: 1.2–2.2] in all patients with IBD and 1.9 in CD [95% CI: 1.4–2.5]. However, the HR of CRC increased in all age groups [HR: 1.40; 95% CI: 1.27–1.53], consistent with a recent Scandinavian cohort study.[232] There was higher risk with extensive colitis and younger IBD diagnosis [age < 30 years], with a SIR of 6.4 [95% CI: 2.4–17.5] and 7.2 [95% CI: 2.9–17.8], respectively. Cumulative risks of cancer were 1%, 2%, and 5% after 10, 20, and > 20 years disease duration, respectively.

These reports indicate that the risk of CRC is increased in patients with IBD, but not to the extent previously reported and not in all patients.

In a Danish cohort,[233] CRC patients with CD had a lower frequency of Duke's A- and B-stage tumours [36% vs 42%] and a higher frequency of Duke's C- [31% vs 27%] and D-stage tumours [23% vs 21%], whereas the frequency of unknown-stage tumours [10%] resembled that of non IBD-related CRC. The 5-year adjusted mortality rate ratios for patients with ulcerative colitis [UC] or CD were increased by 1.14 [95% CI: 1.03–1.27] and 1.26 [95% CI: 1.07–1.49], respectively, compared with patients without IBD. In contrast, in an Irish population-based study, patients with IBD-related CRC were about 7 years younger at cancer diagnosis than patients with non-IBD CRC, but survived about 3 years longer. Older age, male sex, smoking, and advanced CRC grade and stage were independently associated with shorter survival times. When propensity score matching was used to analyse outcomes, the survival times of CRC patients with and without IBD were not significantly different.[234] Taken together, these results reveal that patients with IBD tend to develop CRC at younger ages than patients without IBD. However, no effect of IBD on patient survival has been consistently demonstrated.

The risk of CRC in CD increases with longer disease duration, extent of colitis, a familial history of CRC, coexistent primary sclerosing cholangitis, and the degree and duration of inflammation. CRC in CD tends to have higher histological grade and more often mucinous/signet-ring histological characteristics.[11,230,235–237]

The previous ECCO-ESCP consensus on surgery for CD[11] recommended proctocolectomy in fit patients with preoperative diagnosis of cancer or high-grade dysplasia, due to the multifocal nature of dysplasia in CD colitis and the reported high rate of metachronous colon cancer after segmental surgical resection.[238,239] However, caution is required when comparing cancer incidence between patients with CD undergoing regular colonoscopies and the general population offered cancer screening; lead time bias may overestimate a possible causal association. Furthermore, the onset of CD is often unclear, whereeas many cancers are diagnosed concomitantly or immediately after a diagnosis of CD and thus have a debatable association with CD. Indeed, the incidence of metachronous CRC after segmental resection is much lower than initially thought[240–242] and the prior reported high rate of metachronous cancer may be attributed to inadequate surgery or even underestimation of synchronous tumours. Furthermore, most of the available data originate from the early 1970s, when both endoscopic and therapeutic interventions were very different from current standards.

Therefore, segmental resections and endoscopic surveillance may be proposed in selected patients after proper consent or in patients who are at high risk for surgery.

Importantly, patients with CRC in CD should be operated according to the principles of oncological surgery, including adequate lymphadenectomy.[243,244] The same principles of oncological surgery should be considered in the presence of a colonic stenosis, and long-lasting extensive CD colitis can easily be missed upon endoscopic biopsy. Strictureplasty is not recommended in this context.[11,238]

Statement 4.20: ECCO CD Treatment GL - SURGICAL [2024]
We suggest a defunctioning stoma for non-acute refractory CD colitis, to delay or avoid the need for colectomy [EL5]

The following two options may be discussed in the presence of refractory CD colitis: a [sub]total colectomy, particularly as a potentially life-saving procedure in fulminant colitis, and a defunctioning ileostomy to divert the faecal stream and allow for remission, together with intensified medical therapy.[245] A diverting ileostomy may delay further procedures, facilitate perioperative optimisation, and allow for a limited resection if required at a later stage [ie, segmental colectomy]. The clinical scenario in which a diverting stoma is performed to aid

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the management of extensive perineal disease is covered elsewhere and is not the focus of the present statement.

The literature preceding the biologic era reported initial remission rates of up to 90%[246–249] following creation of a defunctioning stoma, which is more than the 50–80% reported in more recent series.[250,251] Lasting restoration of bowel continuity/stoma reversal was effective in up to two-thirds of patients, but was much lower when perianal disease was also present [ie, 29–42%.][6,7] Surgical complications of defunctioning stoma creation were in the expected range of 3–10% for stoma prolapse/hernia and < 5% for renal failure due to high-output stoma.[251] Further bowel resection was reported in up to half of the patients in recent series.[250,251] Risk factors for proctocolectomy were severe refractory perianal disease, requirement for combined medical therapy, and a history of more than one biologic drug. For these patients, early colectomy and end-ileostomy [as opposed to a defunctioning ileostomy] may be discussed.

The following factors should be taken into account when a proctocolectomy is required and ileal pouch-anal anastomosis [IPAA] is considered. In general, more patients have postoperative pelvic sepsis and a higher pouch failure rate when compared with patients with IPAA for UC. Patients also have more bowel movements and daytime incontinence when compared with patients with IPAA for UC. It is worth noting that in selected patients with isolated CD colitis without small-bowel or perianal involvement, outcomes similar to patients with IPAA for UC can be obtained [no difference in pelvic sepsis, stool frequency, incontinence, score on quality-of-life surveys, or pouch failure].[11,252–256]

Statement 4.21: ECCO CD Treatment GL - SURGICAL [2024]
We recommend CD surgery is performed in high-volume IBD centres [EL3]

The data and appreciation of the benefit of centralisation of IBD surgery in high-volume centres is controversial. Nationwide studies suggested lower mortality in high-volume centres, although patients who are frailer and sicker are overrepresented in these centres.[257,258] The definitions of a high-volume, expert centre and of referral criteria are particularly controversial. ECCO has defined quality-of-care criteria and standards for the care of IBD patients, including patient volume, in a position paper.[259]

4.8. Practice points

When surgery becomes necessary, it is important to thoroughly assess the bowel, ideally preoperatively with MRI enterography. MRI enterography may reveal a distinction between inflammatory strictures [amenable to intensified medical therapy] and fibrotic strictures. Systematically assessing the bowel during surgery may identify further strictures. To maximise bowel preservation, the IBD surgeon should be familiar with the different kinds of strictureplasties, including non-conventional strictureplasties. Nonetheless, strictureplasty of the colon is not recommended.

The anastomotic technique of choice is not firmly established, although a stapled side-to-side anastomosis is suggested in small-bowel or ileocolic resections. Whereas segmental colectomy is advisable when a single colon segment is involved, an oncological proctocolectomy is recommended when colonic dysplasia or a neoplasia is identified.

4.9. Postoperative management

Statement 4.22: ECCO CD Treatment GL - SURGICAL [2024]
We recommend endoscopic surveillance within 6–12 months after surgical resection in CD [EL2]

A systematic review that included one unblinded RCT and four retrospective cohort studies revealed a lower recurrence rate in the endoscopy-based management group than in the control group.[260] Similarly, another systematic review concluded that mucosal changes can be observed in up to 73% of cases within 1 year after surgical resection, when patients undergo endoscopic monitoring.[261]

In a study that randomised 174 patients in a 2:1 ratio, some underwent colonoscopy at 6 months with active therapy and others did not undergo colonoscopy and received standard care. At the 18-month time point, clinical recurrence was lower [37.7% vs 46.1%; RR 0.82; 95% CI: 0.56–1.18] in the colonoscopy group and endoscopic recurrence was higher in the group that received standard care compared with those under active surveillance [67% vs 49%; $p = 0.03$].[262]

Another systematic review that included 26 prospective studies reported the presence of mucosal lesions in up to 70% of cases with a median endoscopic follow-up of 12 months. Notably, more than 50% of these lesions were located at the anastomotic site. Interestingly, despite receiving medical treatment, 41% of patients exhibited significant lesions.[263] These findings are consistent with similar results presented by other studies.[264,265] Endoscopic monitoring within 6–12 months following surgical resection allows for identification of patients who may experience disease recurrence, even with ongoing medical therapy, enabling proactive intervention.

Statement 4.23: ECCO CD Treatment GL - SURGICAL [2024]
We suggest postoperative prophylactic medical therapy after ileocolic resection in patients with CD at high risk of recurrence [EL3]

Prophylaxis for postoperative recurrence is recommended in patients at high risk for recurrence. Thiopurines appear to be more effective than placebo in preventing postoperative recurrence, according to different studies.[266] Infliximab was more effective than placebo in preventing endoscopic, but not clinical, recurrence in the prospective PREVENT trial.[267] Overall, anti-TNF agents are the most effective therapy in preventing postoperative endoscopic recurrence.[268] More recent evidence from observational studies described the efficacy of biologics with different mechanisms of action [ustekinumab and VDZ] in prevention of recurrence.[269] A prospective study, presented in abstract form. demonstrated that VDZ was more efficacious than placebo in preventing endoscopic recurrence. Patients treated with VDZ had a 77.8% chance of having a lower Rutgeerts' score than patients with placebo 6 months after an ileocolic resection [$p < 0.0001$].[270] A retrospective multicentre study from Spain analysed postoperative recurrence rates in 40 patients treated with ustekinumab and 25 treated with VDZ [all had previous exposure to anti-TNF]. The cumulative probability of clinical postoperative recurrence at 12 months after surgery was 32% and 30% for ustekinumab and VDZ, respectively. The rate of endoscopic

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recurrence was 42% for ustekinumab and 40% for VDZ.[271] High-risk patients include those that smoke, have penetrating disease, or present with an IASC, fistula, or both.[272,273]

Statement 4.24: ECCO CD Treatment GL - SURGICAL [2024]
We recommend extended thromboembolism prophylaxis following hospital discharge after CD surgery [EL2]

Although thromboprophylaxis is well documented in patients who have surgery after CRC, there is limited evidence in IBD. A recent systematic review suggested that postoperative deep vein thrombosis [DVT] risk was similar in IBD to that of patients with advanced CRC. The risk was highest in those who had a subtotal colectomy or a proctectomy. The dosage of low molecular weight heparin was also assessed in a single-centre study, suggesting that a dose of 4000 IU/day of low molecular weight heparin was insufficient for IBD patients.[274] A minimal duration of thromboprophylaxis of 2 weeks postoperatively was suggested.[275]

5. Conclusion

There are many options and crossroads in decision making for surgery in CD. Some approaches have been tested over time and were described in these surgical Guidelines. Although sufficient training, technical expertise, and an adequate caseload to achieve and maintain subspecialisation in IBD surgery are important, the key to success in managing CD is a multidisciplinary team, as no specialist alone can solve the CD equation. The present Guidelines have been written with this interdisciplinary approach in mind and summarise the currently available knowledge. The degree of certainty in some aspects of surgery for CD is closer to eminence than evidence, thus paving the way for further research and better answers. Consideration of patient lifestyle preference is integral to shared decision making and key to achieve best standard of care. Revealing gaps in evidence is the first step, as research focused on clinical needs and gaps in the current evidence will inform Guideline updates. Meanwhile, dynamic integration of gains in knowledge into the ECCO e-Guide will allow for rapid dissemination. Guidelines provide guidance to the clinician, who adapts expert knowledge, generic evidence, and patient lifestyle preference to individualise care. It is hoped that the present work will contribute to optimising care for patients with CD.

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Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interest [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of *JCC*, but is also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of authors.

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Author Contributions

MA, PM, HG, and TR coordinated the project; SM provided expert methodology advice, trained the working group members, and performed the analysis of data; UK, BV, MC, CB, and JW coordinated the working groups; all the authors listed contributed to the identification of relevant data and data interpretation, and drafted and discussed the final recommendations; all authors participated in the final consensus; MA and PM drafted this manuscript.

SupplementaryData

Supplementarydata are available online at *ECCO-JCC* online.

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