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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 relating to 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 previous guidelines.

**Key Words:** Crohn's disease; surgery; inflammatory bowel disease [IBD]

## 1. Introduction

The incidence and prevalence of Crohn's disease [CD] is rising globally, with yearly increases in incidence ranging from 4% to 15% over the past three decades.[1] A cure remains elusive, and efficient management of CD is essentially multidisciplinary and interprofessional. At least half of patients with CD undergo one or more surgical procedures during their lifetime. CD patients frequently suffer from malnutrition and psychological comorbidities, and may have to live with a stoma.[2–5] Care for CD has become more complex for both medical and surgical disciplines. Several new drugs have entered the market, and surgical subspecialisation for inflammatory bowel disease has evolved. The best possible outcomes are currently achieved within dedicated expert centres providing personalised medicine.[6–10] Care for CD is exemplary in an interrelated clinical world where the actions of individual health care providers need coordination, common knowledge, and shared expectations to optimise clinical management and research in terms of diagnosis, treatment, and side-effects. The European Crohn's and Colitis Organisation [ECCO] provides an interdisciplinary framework with the present evidence-based Consensus Guidelines to inform and guide clinicians and allied health care providers caring for patients with CD. The present Guidelines focus on surgery for CD, including preoperative aspects and drug management before surgery, and provide technical advice for a variety of common clinical presentations. Further guidance on most aspects of interdisciplinary and interprofessional care for CD has been elaborated by ECCO in separate publications.[3,11–16]

## 2. Methods

A detailed description of the methodology used is presented in the Supplementary materials, available at *ECCO-JCC* online. This article is the second in a series of two publications relating to the ECCO evidence-based consensus on the management of CD. The first article [Torres J *et al*. ECCO guidelines on therapeutics in Crohn's disease. *Journal of Crohn's and Colitis* 2020; in press] covered medical management; the present article addresses surgical management. Both articles together represent the evidence-based recommendations of the ECCO for CD and they update previous Guidelines published in 2016.[17,18] These Guidelines abide by 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 methodology (Oxford Centre for Evidence-Based Medicine: the Oxford 2011 Levels of Evidence 2—grading from evidence level [EL] 1: systematic review of randomised controlled trials to EL 5: expert opinion).[19] This allowed us to formulate statements and practice recommendations that can be operationalised and can guide clinical management.

## 3. Surgery for perineal disease

Section 1. Complex perianal fistula

**Medical therapy and surgical drainage**

> **Statement 1.1. ECCO CD Treatment GL [2019]**
>
> No prospective study directly compares medical or surgical treatment of complex perianal Crohn's disease fistulae, either in isolation or in combination with both modalities. Observational studies support a combined medical/surgical approach to control sepsis and luminal activity [EL5].

No randomised controlled trials [RCT] or prospective studies were found which compared anti-tumour necrosis factor [TNF] treatment alone versus anti-TNF and surgery combined to treat complex perianal CD fistulae. A heterogeneous group of retrospective studies that compared anti-TNF treatment with a variety of surgical approaches was combined in a meta-analysis published in 2014.[20] The results of this analysis suggest that combined treatment 'may have additional beneficial effects compared to surgical or medical treatment alone'. However, the heterogeneity of the included studies, the retrospective nature of the included analysis, and low study quality preclude any firm conclusions or recommendations. Recently, results of the PISA study were presented as an abstract.[21] PISA randomised patients with high perianal CD fistula and a single internal opening initially drained for 6 weeks to: chronic seton drainage; or anti-TNF for 1 year; or advancement plasty under anti-TNF for 4 months. Primary outcome was fistula-related re-intervention [surgery and/or re-initiation of anti-TNF]. This RCT was stopped after inclusion of 44 of 126 planned patients, based on futility analysis. Chronic seton drainage was associated with the highest re-intervention rate within 1.5 year [10/15 patients vs 6/15 anti-TNF patients and 3/14 advancement plasty + anti-TNF patients; $p$ = 0.02]. No differences in quality of life and perianal disease activity index were observed. In a further prospective analysis of 50 patients, inferiority of chronic seton treatment could not be observed any more for any outcome. The authors concluded that chronic seton treatment should not be recommended as the sole or superior treatment for perianal CD fistula.

In practice, management decisions remain with the physician and surgeon, considering clinical information and any resource implications. The key role of surgery is in controlling perianal sepsis by examination under anaesthesia and appropriate seton drainage. In this regard, successful medical therapy and minimising the risk of anti-TNF therapy depend upon a close liaison between the physician and surgeon. According to the summary of product characteristics registered and approved by the regulatory agencies, active sepsis or any infection is a clear contraindication to the use of infliximab or adalimumab. Therefore, any procedure likely to treat and prevent perianal sepsis is recommended as good clinical practice and must be performed swiftly in the presence of signs of infection.

## Surgical techniques

> **Statement 1.2. ECCO CD Treatment GL [2019]**
>
> Advancement flaps are a therapeutic option for patients with Crohn´s disease and complex perianal fistulae [EL4].

A systematic review identified 11 retrospective studies that reported data from 135 patients with CD perianal fistulae treated with an advancement flap.[22] The pooled success rate was 66%. However, definitions of success and length of follow-up were highly variable, the results were heterogeneous, and the overall evidence level was low. In a more recent meta-analysis, Stellingwerf *et al.* observed a 61% success rate in 35 patients with CD perianal fistula, which did not differ significantly from the success rate of a ligation of the intersphincteric fistula tract [LIFT] procedure [53%]. However, incontinence rates were significantly higher after flaps [7.8% versus 1.6%].[23]

As an RCT comparing advancement flap to no surgery would be unethical, collaborative efforts to collect larger numbers of cases undergoing advancement flap for perianal CD, with defined outcomes and follow-up, are required to better define the role of this technique in CD.

> **Statement 1.3. ECCO CD Treatment GL [2019]**
>
> Fibrin glue may be a potential treatment, with limited efficacy, for patients with complex perianal Crohn's disease [EL4].

The use of fibrin glue for the treatment of CD perianal 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 removal of seton.[24] Overall clinical remission rates at Week 8 were 38% for fibrin glue and 16% in the observation group [$p$ = 0.04]. There was no significant difference in adverse events, which were non-significantly higher in the observation group. Follow-up length in this RCT was insufficient for a definitive judgement on the true success rate. Several cohort studies with small numbers of CD patients reported a wide range of success rates with fibrin glue treatment. A uniform characteristic of all these studies is the relatively good safety profile of this technique, with no reported injury to the sphincter muscles, which may potentially justify attempting this technique in cognisant patients.[25]

> **Statement 1.4. ECCO CD Treatment GL [2019]**
>
> Ligation of the intersphincteric fistula tract is an option for treatment of patients with Crohn's disease and complex perianal fistulae [EL4].

LIFT is a recent option in the armamentarium of surgical treatments for perianal fistulae. Sirany *et al.* performed a systematic literature

review and identified 26 studies that included a total of 713 patients, of whom 13 had CD.[26] Among these studies was a single RCT [which however excluded CD patients] and 25 cohort or case series. Studies were heterogeneous, with a wide range of outcome measures and follow-up times. The techniques used were only partially described and included seven technical variations. Primary healing rates ranged from 47% to 95%; thus even the lower end of this range appears promising when compared with other therapeutic options. Very few and minor complications were associated with classic LIFT or any of its variations [three complications were reported in six studies]. Göttgens *et al.* recently reported a retrospective cohort series of 46 patients mainly operated on for high trans-sphincteric fistulae [87%], excluding CD patients.[27] The primary healing rate was disappointingly low [37%] and the median time to failure was 4.2 months. Moreover, 20% had new, mildly impaired faecal continence postoperatively. Conversely, a prospective study by Gingold *et al.* on 15 CD patients with complex perianal fistulae treated with LIFT revealed a 67% healing rate at 12 months and a significant improvement of faecal continence.[28] Overall, due to the paucity of data, the role of LIFT for the treatment of perianal CD fistulae remains unclear, although the complication rate seems to be reasonably low. RCTs are needed to clarify the role of LIFT in CD fistulae, perhaps by comparing LIFT with advancement flap as a control arm.

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**Statement 1.5. ECCO CD Treatment GL [2019]**

Anal fistula plugs [AFP] should not be routinely considered for ano-perineal fistula closure in Crohn's disease, as seton removal alone is equally effective [EL3].

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The use of collagen anal fistula plugs [AFP] in patients with CD perianal fistulae was assessed in a single RCT, which compared seton removal and insertion of AFP into the fistula tract with seton removal and observation only, in 106 CD patients.[29] After 12 weeks, the fistula closure rate 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, perhaps because of an underpowered trial design. Importantly, there was a trend towards more adverse events at 12 weeks in the AFP group [17% vs 8%; *p* = 0.07]. However, cumulative adverse event rates at 12 months follow-up were similar.

A systematic review of 12 observational studies included 84 patients with a median follow-up time of 9 [3–24] months.[30] The overall fistula closure rate was 58.3%, with 40% success in the very small subgroup with a recurrent anal fistula after previous treatments. However, there was no uniform definition for fistula closure or follow-up regimen. The quality of evidence for this systematic review was rated low due to the risk of bias and imprecision.

In the three largest studies that included both CD fistulae and non-CD fistulae,[31–33] the overall healing rate for CD fistulae was 47.0% versus 72.2% for non-CD fistulae. Repeating the plug procedure produced a lower success rate. Finally, an RCT that excluded CD compared 48 patients treated with a plug versus 46 patients treated with an advancement flap. Quality of life and anal pain improved in both groups, but the fistula closure rate at 1 year was significantly lower in the plug group than in the advancement flap group [34% vs 62%; *p* = 0.006].

The use of AFP in patients with CD appears to be relatively safe and may be considered for selected patients aware of the low success rate.

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**Statement 1.6. ECCO CD Treatment GL [2019]**

Ano- and rectogenital fistulae related to Crohn's disease are very complex and rare; accordingly, they should be treated by an experienced multidisciplinary team [EL5].

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There is limited scientific evidence on the treatment of CD-associated rectovaginal fistulae. A systematic review by Kaimakliotis identified 23 studies [including one RCT, six prospective studies, and 16 retrospective studies], with 137 CD-associated rectovaginal fistulae.[34] Of 23 reported studies, three studies included 43 rectovaginal fistulae, focused on combined medical and surgical treatment, and revealed a healing rate of 44.2%.

Hotouras *et al.* reviewed 17 studies, including 106 patients, on the use of gracilis muscle interposition for rectovaginal fistulae.[35] Most studies were retrospective and non-randomised, and only 34 patients with CD fistulae were included. At a median follow-up of 21 months, 50% of the CD fistulae undergoing gracilis muscle interposition had healed, as compared with 60–90% for non-CD rectovaginal fistulae.

The repair of rectovaginal fistulae of CD is challenging, and the selection of medical and/or surgical treatment should be considered on a case-by-case basis within an expert multidisciplinary team.

## Stem cell therapy

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**Statement 1.7. ECCO CD Treatment GL [2019]**

Allogeneic adipose-derived stem cell therapy could be an effective and safe treatment for complex perianal fistulae in patients with Crohn's disease [EL2].

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The use of allogeneic adipose-derived stem cells in patients with perianal fistulae of CD was assessed in a pivotal phase 3 RCT [ADMIRE CD trial] including 212 patients.[36,37] All patients underwent curettage of the fistula tract and closure of the internal opening and were randomised to injection of stem cells or placebo around the internal opening and alongside the fistula tracts. Patients with more than two internal and three external openings, patients with rectovaginal fistula, and those with anal and rectal stenosis or proctitis were excluded from the study. At 1 year, there was significantly higher combined remission (defined as closure of the external opening on physical examination and absence of abscess in magnetic resonance imaging [MRI]) in the stem-cell treated patients compared with placebo [56.3% vs 38.6%; *p* = 0.010].

A meta-analysis of 11 studies, including three RCTs of which the ADMIRE CD was the largest,[38] showed improved healing rates when compared with the control arms.

Allogeneic stem cell therapy seems to be safe. In the ADMIRE CD trial, serious adverse events did not significantly differ between the two groups, although the adverse event rate, mainly abscesses and fistulae, was slightly and not significantly higher in the treatment group compared with placebo [24.3% vs 20.6%]. There

are currently no long-term follow-up data available on safety and effectiveness.

The mode and technique of delivery of stem cells was not compared in any of the studies. Dozois *et al.* reported higher healing rates when stem cells were combined with fibrin glue or impregnated on a Gore Bio-A fistula plug versus direct injection [71% and 83%, respectively, vs 50%].[39] Allogeneic stem cell therapy may be an effective and safe approach to treat complex perianal fistula and patient selection, optimal mode of delivery, and dose and frequency of injections should be determined in further studies.

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**Statement 1.8. ECCO CD Treatment GL [2019]**

Autologous adipose-derived stem cells may have positive effect for patients with Crohn's disease and complex perianal fistulae with good tolerability and safety [EL4].

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Autologous adipose-derived stem cells [ASC] have the advantage of originating from the patient considered for treatment, as opposed to donor-based therapy. Yet, both autologous and allogenic stem cells require cost- and resource-intensive culture, expansion, and cryopreservation of the harvested ASC.[40]

The best evidence on the use of ASC for perianal fistula of CD comes from an open-label, phase 2 study including 43 patients.[41] Treatment included curettage, irrigation, and suturing of the internal opening. The fistula tract was filled with a mixture of ASCs and fibrin glue. ASCs were injected into the lesion site[s]. A second injection of ASCs was performed for patients who did not show complete closure of the fistula at 8 weeks. After 12 months, 88.5% of the patients showed sustained fistula healing. A second trial was performed in six hospitals and included 24 patients, also allowing repeat ASC treatment when fistula closure was incomplete at Week 12. At 6 months of follow-up, 56.3% achieved complete clinical and MRI-confirmed healing of the treated fistula.[42] A further phase 1 study included 12 patients and applied ASC in a bioabsorbable matrix [fistula plug] placed into the fistula, obtaining clinical and MRI-confirmed healing at 6 months in 10 of 12 patients [83%].[43] In contrast to allogeneic stem cells, the use of autologous stem cells requires cell harvesting that entails an additional procedure [liposuction]. Overall, the procedures appeared safe, and the most common AEs were postoperative pain and anal bleeding. There are no studies comparing autologous and allogeneic stem cells for CD perianal fistula.

Last, a recent prospective study investigated the effects of injecting freshly collected autologous adipose tissue into perianal CD fistulas. A total of 21 patients were treated with repeat injections offered when no healing was observed at 6 weeks, or later relapse occurred. Six months following the last adipose tissue injection, 12/21 patients [57%] had complete fistula healing confirmed by MRI, and AE were minimal.[44] Harvesting, preparation, and administration of adipose tissue were performed as a single and inexpensive procedure. Further studies are required to define the true potential of this approach.

### Key points for clinical practice

Complex perineal disease remains a challenging CD presentation. Innovative approaches, such as LIFT and stem cell-based treatment, have enriched the therapeutic armamentarium. However, such novel approaches have yet to demonstrate effectiveness and consistent results in a properly designed RCT with an adequate follow-up time [more than 1 year] and consistent imaging [MRI].

### Section 2. Refractory pelvic sepsis

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**Statement 2.1. ECCO CD Treatment GL [2019]**

Pelvic sepsis and symptoms from complex perineal Crohn's disease refractory to medical or surgical interventions can be controlled by a diverting stoma. However, the fistula healing rate and stoma closure rate are limited [EL4].

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The quality of evidence for the use of defunctioning stoma in perianal CD is low, and no RCTs have compared defunctioning stoma with other surgical or medical interventions. There are several small and heterogeneous case series[45–47] with variable stoma types and definitions of success. A meta-analysis of 16 cohort series including 556 patients reported a clinical response in 63.8% of patients.[48] Clinical response was similar in the pre-biologic era and in the biologic era, respectively, and in patients failing biologics as in those not receiving biologics.[48,49] Restoration of bowel continuity was attempted in 34.5% of patients but was successful in only 16.6%. Absence of rectal involvement was consistently associated with restoration of continuity. Moreover, a quarter of the reversed patients required re-diversion [without proctectomy] because of severe recurrence. Ultimately, 41.6% of patients failed temporary diversion and required proctectomy. Similar results were reported in a later single-centre report of 77 patients, of whom 57 were concomitantly treated with biologics. Here, successful restoration of continuity was somewhat higher [27%] and reached 48% in the absence of ongoing perineal disease.

Quality of life was not discussed in any of the studies. Despite the low evidence and the low rate of fistula healing, diverting stoma may offer an alternative to extensive resection or proctocolectomy and may allow time for acceptance of a permanent stoma.[46]

### Key points for clinical practice

The control of pelvic sepsis is multidisciplinary and draws from interventional radiology, infectious disease, gastroenterology, and surgery. Nutritional support is often key for optimal outcomes in this context, particularly if a stoma is created. Imaging [pelvic MRI or endosonography], swift seton drainage, antibiotics, intensified medical therapy, and specialist nursing care are the mainstay of treatment [Torres J. *et al.* ECCO guidelines on therapeutics in CD. *Journal of Crohn's and Colitis* 2020; in press]. In cases of poor sepsis control, a diverting stoma can provide relief and allow for clinical optimisation before undertaking pelvic surgery.

## 4. Surgical management of abdominal Crohn's disease

### Section 3. Approach to intra-abdominal abscess

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**Statement 3.1. ECCO CD Treatment GL [2019]**

Percutaneous image-guided drainage of well-defined accessible intra-abdominal abscesses is recommended as the primary approach [EL4].

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The treatment of active CD complicated by intra-abdominal abscesses is challenging. Immunosuppression can be hazardous and antibiotic therapy may be insufficient for large abscesses. Furthermore, surgical drainage has an additional risk in the emergency setting/unfit patient, including the potential need for a stoma. Percutaneous drainage [PD] is advised as the primary treatment for well-defined unilocular abscesses when accessible by interventional radiology, and has reported successful drainage rates of 74–100%.[50] PD under ultrasonographic or computed tomographic guidance is a safe procedure with a low complication rate. When successful, PD may avoid subsequent emergency surgery in 14–85% of patients with CD-related intra-abdominal abscesses.[50,51]

> **Statement 3.2. ECCO CD Treatment GL [2019]**
>
> Following successful image-guided drainage of an intra-abdominal abscess, medical management without surgery may be considered. A low threshold for surgery is recommended in the event that medical management is not successful [EL4].

There is a limited evidence on the optimal management of CD patients with intra-abdominal abscess who have undergone PD. In particular, the optimal timing of surgical intervention after abscess drainage is unknown. Up to 30% of patients may avoid surgery following successful PD.[52] Identifying those who may be treated without further surgery is challenging and presently relies on clinical judgment rather than on evidence. Nevertheless, elective surgery should be considered after sepsis control/resolution by PD and antibiotic therapy, as abscess recurrence is up to 6.5 times greater following PD as stand-alone therapy than PD followed with surgical resection. Medically refractory disease, the presence of stenosis, or an enterocutaneous fistula—be it primary established or as a consequence of PD—increase the likelihood of surgery. Conversely, emergency surgery without preceding PD and sepsis control is associated with a higher rate of complications and stoma than with initial PD followed by surgery.[53] Successful PD can be considered as a bridge to elective surgery, allowing nutritional and medical optimisation and hence improved postoperative outcomes.[3,54]

### Key points for clinical practice

The control of intra-abdominal abscesses resembles the approach to pelvic sepsis with interventional radiology, infectious disease, gastroenterology, and surgery involved, together with nutritional support. Frequent monitoring and surgical consultation are critical. Fortunately, surgery can be deferred in most cases. Definitive non-surgical management may be successful but must be carefully balanced and discussed with the individual patient.

### Section 4. Preoperative optimisation

> **Statement 4.1. ECCO CD Treatment GL [2019]**
>
> Preoperative nutritional assessment should be performed for all patients with Crohn's disease who need surgery. Nutritional optimisation prior to surgery, with enteral or parenteral nutrition, is recommended for those patients with nutritional deficiencies [EL3].

Nutritional deficiencies are common in CD patients who require surgery. Persistent or recurrent mucosal inflammation, enteric fistulae or strictures, chronic diarrhoea, and medication side effects impede nutritional status, which in turn is a major driver of medical and surgical outcomes.[55,56] Although RCTs are lacking, IBD referral centres have long integrated nutritional support into multidisciplinary teams. Several observational studies have shown that preoperative optimisation in malnourished patients improves outcomes, including a meta-analysis of 1111 CD patients who received preoperative enteral or parenteral supplementation versus standard care.[57] Preoperative nutritional supplementation reduced postoperative complications (20% vs 61.3%, odds ratio [OR] 0.26, 95% confidence interval [CI] 0.07–0.99; $p$ <0.001). Enteral nutrition in particular led to markedly reduced postoperative morbidity [21.9% vs 73.2%, OR 0.09, 95% CI 0.06–0.13, $p$ <0.01] with a number needed to treat of two. Goal-driven parenteral nutrition should be considered whenever enteral nutrition is hampered. Perioperative dietary therapy, including systematic nutritional screening, correction of deficits, and optimal preparation for surgery have been covered by Adamina *et al.* in a recent ECCO topical review addressing the needs of IBD patients before and after surgery.[3]

> **ECCO Statement 4.2.**
>
> Preoperative corticosteroid use is associated with increased risk of postoperative complications [EL3]. Preoperative reduction of corticosteroid doses may reduce postoperative complications but should be monitored carefully to avoid increasing disease burden [EL4].

Treatment with 20 mg prednisolone daily, or equivalent, for >6 weeks is an acknowledged risk factor for surgical complications and hyperglycaemia, as reported in previous ECCO Guidelines.[11,18] This has been extensively reported, although no large RCTs were dedicated to this issue. Two meta-analyses of prospective and retrospective cohort studies, including 1714 IBD patients[58] and 3807 CD patients,[59] reported up to a doubling of surgical site infections for patients on steroids. Cut-offs for increased surgical complications were observed between 10 mg and 40 mg prednisolone daily for more than 3–6 weeks, together with a uniform recommendation of tapering down steroids whenever possible before surgery. Conversely, thiopurines can be safely continued perioperatively.[7,11,18,58–62] A staged procedure with a temporary stoma may be considered when high-dose steroids cannot be weaned [emergency surgery] and/or when other risk factors are present [e.g., sepsis, malnutrition, smoking]. Last, little evidence supports the common practice of steroid stress dose administration perioperatively for patients on long-term corticosteroids over plain continuation of the preoperative dose, converted to intravenous equivalents where necessary.[63] Two small RCTs [37 patients] and five cohort studies [462 patients] did not demonstrate any benefit of steroid stress dose administration.[64] Testing of the hypothalamic-pituitary-adrenal axis can be considered on an individual basis to assess adrenal suppression.[65]

> **Statement 4.3. ECCO CD Treatment GL [2019]**
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> Current evidence suggests that preoperative treatment with anti-TNF therapy [EL3], vedolizumab [EL4], or ustekinumab [EL4] does not increase the risk of post operative complications in patients with CD having abdominal surgery. Cessation of these medications prior to surgery is not mandatory.

## Anti-TNF therapy

The use of biologics in CD patients scheduled for surgery has been controversial. Concern was raised that by modulating the immune response, biologics may increase surgical site infections and morbidity. Some recent guidelines still caution against the use of anti-TNF therapy in this context; however, the safest period of omission remains unknown.[11] The most recent meta-analysis on this subject included 18 non-randomised controlled studies with 1407 patients who were receiving infliximab and 4589 who were not.[66] There were no differences in the occurrence of any complications between patients on infliximab or not: OR for major complications 1.41, 95% CI 0.85–2.34; OR for minor complications 1.14, 95% CI 0.81–1.61; OR for infectious complications 1.23, 95% CI 0.87–1.74; OR for non-infectious complications 1.06, 95% CI 0.88–1.28; OR for readmission 1.46, 95% CI 0.8–2.66. This was also true for reoperation and mortality considered alone or included into major complications. Finally results from the large prospective PUCCINI cohort study presented as an abstract at the 2019 Digestive Disease Week, which included 955 IBD patients, showed that exposure to anti-TNF therapy, including the measurement of drug levels, had no effect on the occurrence of any surgical site infection or anastomotic leak.

## Vedolizumab

Early data, including a retrospective multicentre analysis comparing the postoperative outcomes of 146 patients receiving vedolizumab versus 289 patients on anti-TNF therapy, revealed a significantly increased rate of surgical site infections after abdominal surgery in patients on vedolizumab.[67] However the most recent meta-analysis, comparing 307 IBD patients treated with vedolizumab versus 490 patients on anti-TNF and 535 patients not exposed to preoperative biologic therapy, revealed no differences in postoperative infectious and overall complications between vedolizumab patients and patients without biologic therapy [OR 0.99, respectively 1.00]. A similar outcome was observed, when comparing patients on vedolizumab with those on anti-TNF therapy, for the occurrence of postoperative infectious and overall complications [OR 0.99, resp. 0.92].[68] Although larger, randomised studies including perioperative drug monitoring remain necessary, treatment with vedolizumab appears to be safe in the surgical context.

## Ustekinumab

Two retrospective multicentre cohort studies compared CD patients exposed preoperatively to either ustekinumab [for 3–6 months] or to anti-TNF therapy [follow-up to 6 months postoperatively]. In univariate analysis, patients on ustekinumab were more likely to receive a stoma [70% vs 12.5%; *p* <0.001], to be on combination therapy [25% vs 2.5%; *p* = 0.01],[69] and to be reoperated [16% vs 5%; *p* = 0.01].[70] Nevertheless, no increases in early or late postoperative complications were noted in multivariate analysis when comparing the surgical outcomes of those 60 patients on ustekinumab versus 209 patients receiving anti-TNF therapy.[69,70] Again, studies of better design and larger patient numbers are required to confirm these results.

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**Statement 4.4. ECCO CD Treatment GL [2019]**

Preoperative control of sepsis is recommended prior to abdominal surgery for Crohn's disease [EL4].

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Surgery in the context of sepsis carries a high risk for postoperative complications, including anastomotic leaks and continued abdominal sepsis.[59] Preoperative control of sepsis with antibiotic therapy and PD of intra-abdominal abscess followed by elective surgery leads to lower rates of stoma creation, fewer complications, and shorter hospital length of stay when compared with emergency surgery and surgical drainage.[53,59,71] Prolonged [>6 weeks] and high-dose [≥20 mg prednisolone equivalent] steroids use are associated with poorer control of preoperative sepsis.[62]

## Key points for clinical practice

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,[72] 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].[54,73] A good relationship across disciplines and professions is critical.

## Section 5. Small-bowel obstruction

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**Statement 5.1. ECCO CD Treatment GL [2019]**

Deferred surgery is the preferred option in adult patients with Crohn´s disease presenting with acute small-bowel obstruction without bowel ischaemia or peritonitis [EL4].

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Intestinal stenosis frequently occurs in the course of CD. Acute small-bowel obstruction typically presents with intractable nausea/vomiting, abdominal distension, and absence of gas or stool passage per anum. Conservative management is the preferred option in the absence of peritonitis, including bowel rest, gastric decompression, and intravenous fluid therapy. In the presence of active inflammatory disease, intravenous steroids should be considered[11,17][and Torres J. *et al*. ECCO guidelines on therapeutics in CD *Journal of Crohn's and Colitis* 2020; in press]. Primary conservative management allows optimisation of the nutritional and immunosuppression status before a potential elective surgery.[3] Conversely, whenever clinical or radiological signs indicate an intestinal perforation, emergency surgery and resection of the diseased bowel loop are required. Early surgical consultation is strongly recommended to assess surgical indication and to jointly monitor the progress of a conservative approach. Episodes of [sub]acute small-bowel obstruction also tend to recur over time; hence surgical advice is important in the context of interdisciplinary care and discussion of treatment options.

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**Statement 5.2. ECCO CD Treatment GL [2019]**

Endoscopic balloon dilatation or surgery are both suitable treatment options for patients with short [<5 cm] strictures of the terminal ileum in Crohn's disease. The choice of treatment depends on local expertise and patient preference [EL5].

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Although symptomatic short strictures are frequent in CD patients, no RCT comparing surgery versus balloon dilatation has

been performed. The largest study investigating the benefits and risks of balloon dilatation is a pooled analysis published in 2017 by Bettenworth *et al.*, with 1493 patients who underwent a total of 3213 endoscopic balloon dilatations.[74] A total of 98.6% the strictures were ileal and 62% were anastomotic. The primary technical success rate [passage of the endoscope through the stricture] was 89.1% and was 80.8% for clinical efficacy [symptom-free at completion of follow-up]. Complications [perforation and/or bleeding] occurred in 2.8% of the procedures. Despite the high initial success rate, 73.5% of the patients underwent re-dilatation within 24 months and 42.9% required surgical resection.

Similar results were reported in a systematic review by Morar *et al.* who analysed 1089 patients and 2664 dilatations and reported a technical success rate of 90.6% and a clinical success rate of 70.2%. Complications occurred in 6.4% of the balloon dilatations. At 5 years of follow-up, 75% of the patients had undergone surgery.[75] There were no differences in outcomes when primary or anastomotic strictures were dilated. Recent observational studies revealed comparable results[76-79],[76-79] Hence, balloon dilatation of both primary and anastomotic short CD strictures appears safe and effective in the short term. However, recurrence is the rule and the need for surgery is frequent in the following 5 years.

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**Statement 5.3. ECCO CD Treatment GL [2019]**

Strictureplasty is a safe option to treat small-bowel strictures related to Crohn's disease. Strictureplasty may be preferable to resection of long segments of bowel, with potential reduction in surgical recurrence rates [EL3].

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Strictureplasty is an established and safe surgical option for treating strictures related to CD and is an alternative to bowel resection.[80,81] Strictureplasty is recommended whenever reasonable and technically feasible, particularly with multiple fibrotic strictures that would otherwise require more than a minimal bowel resection.[11,82] A meta-analysis of 1112 patients who underwent 3259 strictureplasties [81% HeinekeMikulicz, 10% Finney, 5% side-to-side isoperistaltic] before the biologic era revealed a 5-year recurrence rate of 28%.[83] HeinekeMikulicz is the preferred technique for stenotic segments up to 6–8 cm, whereas Finney and side-to-side isoperistaltic techniques address longer or multiple strictures and require more expertise.[84] Surgical morbidity is in the range of 8–15% and is unrelated to stricture length.[84,85] Favourable long-term results have been reported[81,84,85] and suggest better results for strictureplasty compared with resection. A large Japanese series reviewed 526 patients, of whom 435 underwent only bowel resections and 91 had a total of 199 strictureplasties. At 10 years, the site-specific cumulative rate of reoperation was 18% at the anastomosis site versus 7% at the strictureplasty site [*p* <0.01].[86]

## Key points for clinical practice

Whenever possible, elective surgery is preferable to an emergency procedure in acute small-bowel obstruction due to a CD stenosis. This can be achieved in most scenarios with primary conservative management, such as rehydration and nasogastric decompression. An interdisciplinary discussion of the treatment options, which should also include the patient's views, should follow. 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. Assessing the bowel during surgery can also be very useful in identifying strictures. To maximise bowel preservation, the IBD surgeon should be familiar with the different kinds of strictureplasties, including nonconventional strictureplasties. Nonetheless, strictureplasty of the colon is not recommended.[11]

## Section 6. Surgical techniques for abdominal CD

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**Statement 6.1. ECCO CD Treatment GL [2019]**

Laparoscopic surgery should be offered as the first-line approach in surgery for Crohn's disease, dependent on appropriate expertise [EL2].

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A meta-analysis and a Cochrane review of two RCTs[87,88] showed no statistical difference in any outcomes between laparoscopic and open surgery for small-bowel CD. A more recent meta-analysis, which included RCTs and observational studies, revealed fewer complications and fewer incisional hernias in favour of the laparoscopic approach.[89] A further meta-analysis assessed laparoscopic resection for recurrent CD, confirming feasibility and safety in the presence of appropriate expertise.[90] Conversion to open surgery was 2.5 times more frequent in this context, although complications did not increase. Hence, patients benefit from a laparoscopic approach in surgery for primary and recurrent small-bowel CD, with fewer postoperative complications and fewer incisional hernias. In the absence of expertise to perform laparoscopic surgery, emergency operations should not be delayed.

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**Statement 6.2. ECCO CD Treatment GL [2019]**

A temporary stoma should be considered if steroids cannot be withdrawn or significantly reduced prior to surgery [EL5].

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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 no data comparing strategies between primary anastomosis or secondary anastomosis, in CD patients treated with steroids. However, prolonged [>6 weeks] and high-dose [≥20 mg prednisolone equivalent] steroid use are associated with postoperative infectious complications, including anastomotic leakage.[58,59,61,62]

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**Statement 6.3. ECCO CD Treatment GL [2019]**

Primary anastomosis may safely be performed in the presence of anti-TNF therapy [EL3], vedolizumab [EL4], and ustekinumab [EL4], provided other risk factors have been accounted for.

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As discussed earlier in these Guidelines, the effect of anti-TNF therapy on anastomosis healing has been largely studied, although large RCTs that definitively address this important issue are lacking. Overall, the administration of anti-TNF therapy does not seem to increase anastomotic risk. However, anti-TNF therapy cannot be isolated from its clinical context, either when facing an individual patient or in appraising the literature in which several biases confound the evaluation of the true effect of anti-TNF therapy [e.g., heterogeneity of inclusion criteria and clinical presentation/risk factors, duration and dose of anti-TNF therapy administered, combination therapy, absence of drug monitoring]. The same considerations apply to vedolizumab and ustekinumab, in which the challenges of data evaluation are further compounded by less clinical experience and lower patient numbers[59,67,68,70,91-118] [59,67,68,70,91-118].

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**Statement 6.4. ECCO CD Treatment GL [2019]**

Laparoscopic resection in patients with limited, non-stricturing, ileocaecal Crohn's disease [[diseased terminal ileum <40 cm] is a reasonable alternative to infliximab therapy [EL2].

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Previous ECCO Guidelines have declared [laparoscopic] resection as the preferred option in patients with localised ileocaecal CD with obstructive symptoms but no active inflammation.[11]

For active non-stenotic disease, a recent randomised multicentre European trial compared 143 patients with active, non-stricturing disease involving <40 cm of the terminal ileum, in whom conventional therapy had failed, randomized to either infliximab or laparoscopic ileocaecal resection.[119] There was no difference in the primary outcome of quality of life on the Inflammatory Bowel Disease Questionnaire at 12 months nor in general quality of life as measured by the Short Form-36 Health Survey. However, operated patients scored 3.1 points better [95% CI 4.2–6.0] in the physical subscale of this survey. Serious complications were not different between medical and surgical groups. Over a median follow-up of 4 years, 37% of the infliximab-treated patients required resection, whereas 26% of the primarily resected patients were put on infliximab. Hence, laparoscopic resection of both stricturing, fibrotic disease of the terminal ileum and of an actively diseased terminal ileum [<40 cm] can be offered as a sound therapeutic option in an interdisciplinary context, with a benefit and risk profile comparable to medical therapy.

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**Statement 6.5. ECCO CD Treatment GL [2019]**

Stapled small-bowel or ileocolic side-to-side anastomoses are associated with lower rates of postoperative complications than end-to-end anastomoses, in Crohn's disease [EL3].

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Technical aspects are important to surgeons and can be influenced by many factors, including previous training, personal experience, available resources, and clinical situation. The optimal choice of anastomosis technique in small-bowel and ileocolic resection has been controversial. In the past 10 years, evidence in favour of a side-to-side anastomosis has emerged and was confirmed over time. The first large meta-analysis by Simillis *et al.* included 661 patients and revealed that the anastomotic leak rate was higher for an end-to-end anastomosis versus side-to-side anastomosis [OR 4.37; *p* = 0.02], including the subgroup of ileocolic anastomosis [OR 3.8; *p* = 0.05].[120] Overall postoperative complications [OR 2.64; *p* <0.001] and length of hospital stay were accordingly higher [by 2.81 days; *p* = 0.007] when an end-to-end anastomosis was performed. A later meta-analysis by Guo *et al.* confirmed the superiority of a side-to-side anastomosis over other configurations in terms of overall postoperative complications [OR 0.6; *p* = 0.01]. However, there were no statistically significant differences for leak rate, endoscopic and symptomatic recurrence, and reoperation for recurrence.[121] A further meta-analysis by He *et al.* compared 396 stapled side-to-side with 425 hand-sewn end-to-end anastomoses. Stapled side-to-side anastomoses were superior in all endpoints: 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].[122] Finally, a network meta-analysis of 11 trials and 1113 patients confirmed the superiority of stapled side-to-side anastomosis in terms of overall complications, clinical recurrence, and reoperation for recurrence. Leak rate, surgical site infections, mortality, and length of stay were not affected by the choice of the anastomosis technique.[123] The quality of the studies included in all meta-analyses was low, with a minority of patients included in RCTs. The general conclusion favours stapled side-to-side anastomosis. The diameter of the anastomosis likely plays a role, with an assumption that a wider anastomosis will have a lower rate of clinical and surgical recurrences.

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**Statement 6.6. ECCO CD Treatment GL [2019]**

Segmental colectomy is appropriate for patients with a single involved colonic segment in Crohn's disease [EL3].

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When a single colonic segment is involved, a segmental colectomy is indicated. Multiple involved colon segments generally indicate a [sub]total colectomy as the preferred approach. A meta-analysis by Tekkis *et al.* compared between 223 subtotal/total colectomies with ileorectal anastomosis and 265 segmental colectomies for colonic CD.[124] Although the recurrence rates, complications, and need for a permanent stoma were not different, recurrence occurred 4.4 years later in the subtotal/total colectomy [*p* < .001]. A recent meta-analysis by Angriman *et al.* evaluated 1436 patients who received segmental colectomy [*n* = 500], subtotal colectomy [*n* = 510], or total proctocolectomy [*n* = 426].[125] Complications were more frequent after segmental colectomy than after subtotal colectomy [OR 2.84, 95% CI 1.16–6.96] and after proctocolectomy than after subtotal colectomy [OR 0.19, 95% CI 0.09–0.38]. Hence, subtotal colectomy appeared to be the safer procedure, although segmental colectomy resulted in fewer permanent stomas than subtotal colectomy [OR 0.52, 95% CI 0.35–0.77]. Regarding CD recurrence, subtotal colectomy showed higher 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, whereas no difference in recurrence was observed between segmental colectomy and subtotal colectomy. In the rare situation where two distinct colon segments are involved, two segmental resections can be considered instead of a subtotal colectomy,[11] particularly for the patient who has suffered

an extensive loss of small bowel. In summary, the extent of colonic resection is indicated by the clinical situation [elective vs emergency surgery] and the number of colonic segments involved. Segmental colectomy is preferred whenever possible.

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**Statement 6.7. ECCO CD Treatment GL [2019]**

A defunctioning stoma for non-acute refractory Crohn's colitis may delay or avoid the need for colectomy [EL5].

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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.[126] A diverting ileostomy may delay further procedures, facilitate perioperative optimisation, and allow for a limited resection if required at a later stage [i.e., segmental colectomy]. The clinical scenario in which a diverting stoma is performed to aid the management of extensive perineal disease is covered elsewhere and is not the focus of the present statement.

The literature preceding the biologic era reports initial remission rates of up to 90%[45,127–129] following creation of a defunctioning stoma, which is less than the 50–80% reported in more recent series.[130,131] Lasting restoration of bowel continuity/stoma reversal was effective in up to two-thirds of the patients but was much less when perineal disease was also present [i.e. 29–42%].[130,131] Surgical complications of defunctioning stoma creation were in the expected range of 3–10% for stoma prolapse/hernia and <5% renal failure due to high-output stoma.[130] Further bowel resection was reported in up to half of the patients in recent series.[130,131] Risk factors for [procto]colectomy were severe refractory perineal 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.

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**Statement 6.8. ECCO CD Treatment GL [2019]**

Restorative proctocolectomy with ileal pouch-anal anastomosis can be considered in selected patients with refractory pancolonic Crohn's disease without history of perianal disease, taking into account the high risk of pouch failure [EL4].

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Several expert centres have reported their experience with restorative proctocolectomy and ileal pouch-anal anastomosis [IPAA] for refractory pancolonic CD. Previous ECCO Guidelines stressed the higher complication and failure rates of CD-IPAA, which should be restricted to highly motivated patients and to multidisciplinary teams, and only in the absence of small-bowel and perineal diseases.[11]

Panis *et al*. compared 31 CD-IPAA patients, without small-bowel or perianal involvement, with 71 ulcerative colitis IPAA [UC-IPAA] patients. No differences in postoperative outcomes were reported, whereas the 5-year definitive end ileostomy rate was 10% in CD-IPAA versus 2% in UC-IPAA patients.[132] At 10 years of follow-up, rates of CD-related complications were 35%, with 10% of the pouches excised.[133]

Manilich *et al*.[134] and Fazio *et al*.[135] reported two large comparative series from the same institution for a total of 3754 consecutive patients, of whom 150 were CD-IPAA patients. Again, no differences in early complications [pelvic sepsis, anastomotic leaks] were observed. However, CD-IPAA patients had a higher pouch failure rate [13.3%] compared with ulcerative colitis and indeterminate colitis patients [5.1% and 4.8%, respectively]. At 10 years, 80% of CD-IPAA patients retained a functional pouch versus 95% in UC-IPAA and indeterminate colitis IPAA.

Reese *et al*.[136] performed a meta-analysis of 3103 patients, of whom 225 were CD-IPAA and suffered in comparison from twice as many anastomotic strictures and six times more pouch failures [32% vs 4.8%, *p* <0.01]. However, in patients with isolated colonic CD, no significant difference in postoperative complications or pouch failure [8% in CD-IPAA patients vs 7.1% in UC-IPAA patients] was observed. Importantly, patients with isolated colonic CD did not have more complications or pouch failures than UC patients. Nevertheless, IPAA function was poorer in CD patients [two times more incontinence and urgency], although stool frequency did not differ. Similarly, no difference in quality-of-life scores were reported in the large Cleveland series, irrespective of the indication of IPAA.[135]

## 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 spirit in mind and summarise the current knowledge at hand. 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. Revealing gaps in evidence is the first step to resolution, 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 clinicians, who adapt expert knowledge and generic evidence 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 interests [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.

## Author Contributions

MA, GF, JT, and OZ coordinated the project; SB, TL, and MG-L provided expert methodology advice, trained the working group members, and performed the analysis of data; GD, TK, JPG, TR, AS, and JW coordinated the working groups; all the authors listed contributed to the identification of relevant data, data interpretation, and drafted and discussed the final recommendations; all the authors participated in the final Consensus; MA and OZ drafted this manuscript; all authors, the ECCO Guideline Committee [GuiCom], and the ECCO Governing Board approved the final version of the manuscript.

## Disclaimer

The ECCO Consensus Guidelines are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Consensus Guidelines. The ECCO and/or any of their staff members and/or any Consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines. This manuscript is a joint expert consensus activity. Hence all authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the concept, design, data interpretation, and writing of the manuscript.

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## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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