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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 prior guidelines.

Introduction

The incidence and prevalence of Crohn's disease [CD] is rising globally, with yearly increases in incidence ranging from 4–15% over the last 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, 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 subspecialization for inflammatory bowel disease has evolved. The best possible outcomes are currently achieved within dedicated expert centres providing personalized 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 optimize 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. 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 CD, JCC 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 update prior 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 randomized controlled trials to EL 5: expert opinion[19]. This allowed us to formulate statements and practice recommendations that can be operationalized and can guide clinical management.

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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 randomized controlled trials [RCT] or prospective studies were found that compared anti-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 randomized patients with high perianal CD fistula and a single internal opening initially drained for 6 weeks to chronic seton drainage or anti-TNF for one 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 vs. 6/15 anti-TNF 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 anymore for any outcome. The authors concluded that chronic seton treatment should not be recommended as the sole or superior treatment for perianal CD fistulas.

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 minimizing the risk of anti-TNF therapy depends 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 a 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 randomized 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 cognizant 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 which 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 47–95%, 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 and any of its variations [3 complications were reported in 6 studies]. Göttgens et al. recently reported a retrospective cohort series of 46 patients mainly operated on for high transsphincteric 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 to advancement flap as a control arm.

Statement 1.5 ECCO CD Treatment GL [2019]

Anal Fistula Plugs (AFP) should not be routinely considered for ano-perineal fistulas closure in Crohn's disease, as seton removal alone is equally effective [EL3]

The use of collagen anal fistula plug [AFP] in patients with CD perianal fistulae was assessed in a single RCT, which compared seton removal with insertion of AFP into the fistula tract to 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 from 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, a RCT that excluded CD compared 48 patients treated with a plug to 46 patients treated with an

advancement flap. Quality of life and anal pain improved in both groups, whereas 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.

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]

There is limited scientific evidence on the treatment of CD-associated rectovaginal fistulae. A systematic review by Kaimakliotis identified 23 studies [including 1 RCT, 6 prospective studies, and 16 retrospective studies] with 137 CD-associated rectovaginal fistulae[34]. Of 23 reported studies, three studies included 43 rectovaginal fistulae that 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-randomized 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

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]

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 randomized 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 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 3 RCTs of which the ADMIRE CD was the largest[38], showed improved healing rates when compared to 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. to 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% vs. 50%][39]. While allogeneic stem cell therapy may be an effective and safe approach to treat complex perianal fistula, patient selection, optimal mode of delivery, and dose and frequency of injections should be determined in further studies.

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]

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 6 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, which 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. Twenty-one 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

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]

The quality of evidence for the use of defunctioning stoma in perianal CD is low, and no RCTs have compared defunctioning stoma to 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-biological era and in the biological 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 which 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, JCC 2020 in press*]. In cases of poor sepsis control, a diverting stoma can provide relief and allow for clinical optimization before undertaking pelvic surgery.

Surgical management of abdominal Crohn's disease

Section 3. Approach to intra-abdominal abscess

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]

The treatment of active CD complicated by intra-abdominal abscesses is challenging. Immunosuppression can be hazardous, 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 underwent 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 prior 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 optimization 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 optimization

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 optimization 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 optimization 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 2. 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 has 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 prior 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 prior to 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]. Lastly, 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]

Current evidence suggests that pre-operative 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-randomized controlled studies with 1407 patients on 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 PUCCINI RCT presented as an abstract at the 2019 Digestive Disease Week that 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, resp. 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, randomized 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 re-operated [16% vs. 5%; p = 0.01][70]. Nevertheless, no increase in early and 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.

Statement 4.4 ECCO CD Treatment GL [2019]

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

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 optimization 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

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]

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][+ *Torres J et al ECCO guidelines on therapeutics in CD, JCC 2020 in press*]. Primary conservative management allows optimization 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.

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]

While 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 dilatated. Recent observational studies revealed comparable results[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.

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]

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% Heineke-Mikulicz, 10% Finney, 5% side-to-side isoperistaltic] prior to the biologic era revealed a 5-year recurrence rate of 28%[83]. Heineke-Mikulicz is the preferred technique for stenotic segments up to 6–8 cm, while 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 which 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 maximize 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[11].

Section 6. Surgical techniques for abdominal CD

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]

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.

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]

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 with 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].

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

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, neither when facing an individual patient nor 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].

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]

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

For active non-stenotic disease, a recent randomized multicentre European trial compared 143 patients with active, non-stricturing disease involving < 40 cm of the terminal ileum in whom conventional therapy had failed 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 or 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 primary 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.

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]

Technical aspects are important to surgeons and can be influenced by many factors, including prior 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 last 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 re-operation 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.

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]

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 223 subtotal/total

colectomies with ileorectal anastomosis to 265 segmental colectomies for colonic CD[124]. While the recurrence rates, complications, and need for a permanent stoma were not different, recurrence occurred 4.4 years later in the subtotal/total colectomy [$p < 0.001$]. 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 subtotal colectomy [OR 2.84, 95% CI 1.16–6.96] and after proctocolectomy than 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 stoma 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.

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]

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 optimization, 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 prior to the biologic era reports initial remission rates of approximately 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 >1 biologic drug. For these patients, early colectomy and end ileostomy [as opposed to a defunctioning ileostomy] may be discussed.

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]

Several expert centres have reported their experience with restorative proctocolectomy and ileal pouch-anal anastomosis [IPAA] for refractory pancolonic CD. Prior 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 difference 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 which 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 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].

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 subspecialization 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 summarize 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 the clinician, who adapt expert knowledge and generic evidence to individualize care. It is hoped that the present work will contribute to optimizing care for patients with CD.

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Authors' contribution

Michel Adamina, Gionata Fiorino, Joana Torres, and Oded Zmora coordinated the project; Stefanos Bonovas, Theodore Lytras, and Marien Gonzalez-Lorenzo provided expert methodology advice, trained the working group members, and performed the analysis of data; Glen Doherty, Torsten Kucharzik, Javier P. Gisbert, Timothy Raine, Antonino Spinelli, and Janindra Warusavitarne 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; Michel Adamina and Oded Zmora drafted this manuscript; all Authors, the ECCO Guideline Committee [GuiCom], and the ECCO Governing Board approved the final version of the manuscript.

Conflict of interests

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.

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References

1. Ng SC, Shi HY, Hamidi N*, et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet* 2018;**390**:2769-78.
2. Frolkis AD, Dykeman J, Negron ME*, et al.* Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;**145**:996-1006.
3. Adamina M, Gerasimidis K, Sigall-Boneh R*, et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2019.
4. Bouguen G, Peyrin-Biroulet L. Surgery for adult crohn's disease: What is the actual risk? *Gut* 2011;**60**:1178-81.
5. Burke JP, Velupillai Y, O'Connell PR, Coffey JC. National trends in intestinal resection for crohn's disease in the post-biologic era. *Int J Colorectal Dis* 2013;**28**:1401-6.
6. Bemelman WA, collaborators SE. Evolving role of ibd surgery. *J Crohns Colitis* 2018;**12**:1005-7.
7. Lightner AL, Shen B. Perioperative use of immunosuppressive medications in patients with crohn's disease in the new "biological era". *Gastroenterol Rep (Oxf)* 2017;**5**:165-77.
8. Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2018;**24**:3567-82.
9. Reinglas J, Restellini S, Gonczi L*, et al.* Harmonization of quality of care in an ibd center impacts disease outcomes: Importance of structure, process indicators and rapid access clinic. *Dig Liver Dis* 2019;**51**:340-5.
10. Koltun WA. Better together: Improved care of the ibd patient using the multi-disciplinary ibd center. *Expert Rev Gastroenterol Hepatol* 2017;**11**:491-3.
11. Bemelman WA, Warusavitarne J, Sampietro GM*, et al.* Ecco-escp consensus on surgery for crohn's disease. *J Crohns Colitis* 2018;**12**:1-16.
12. Harbord M, Annese V, Vavricka SR*, et al.* The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:239-54.
13. Kemp K, Dibley L, Chauhan U*, et al.* Second n-ecco consensus statements on the european nursing roles in caring for patients with crohn's disease or ulcerative colitis. *J Crohns Colitis* 2018;**12**:760-76.
14. Maaser C, Sturm A, Vavricka SR*, et al.* Ecco-esgar guideline for diagnostic assessment in ibd part 1: Initial diagnosis, monitoring of known ibd, detection of complications. *J Crohns Colitis* 2019;**13**:144-64.
15. Sturm A, Maaser C, Calabrese E*, et al.* Ecco-esgar guideline for diagnostic assessment in ibd part 2: Ibd scores and general principles and technical aspects. *J Crohns Colitis* 2019;**13**:273-84.
16. Sturm A, Maaser C, Mendall M*, et al.* European crohn's and colitis organisation topical review on ibd in the elderly. *J Crohns Colitis* 2017;**11**:263-73.
17. Gomollon F, Dignass A, Annese V*, et al.* 3rd european evidence-based consensus on the diagnosis and management of crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3-25.
18. Gionchetti P, Dignass A, Danese S*, et al.* 3rd european evidence-based consensus on the diagnosis and management of crohn's disease 2016: Part 2: Surgical management and special situations. *J Crohns Colitis* 2017;**11**:135-49.
19. J. H, I. C, P. G*, et al.* Explanation of the 2011 oxford centre for evidence-based medicine (ocebm) levels of evidence (background document). https://www.cebm.net/index.aspx?o=5653 Accessed 09.11.2019, 2011.
20. Yassin NA, Askari A, Warusavitarne J*, et al.* Systematic review: The combined surgical and medical treatment of fistulising perianal crohn's disease. *Aliment Pharmacol Ther* 2014;**40**:741-9.

21. Wasmann K, de Groof EJ, Stellingwerf M*, et al.* Dop73 treatment of perianal fistulas in crohn's disease, seton vs. Anti-tnf vs. Surgical closure following anti-tnf (pisa): A randomised controlled trial. *Journal of Crohn's and Colitis* 2019;**13**:S074-S.
22. Rozalen V, Pares D, Sanchez E*, et al.* Advancement flap technique for anal fistula in patients with crohn's disease: A systematic review of the literature. *Cir Esp* 2017;**95**:558-65.
23. Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and crohn's high perianal fistulas. *BJS Open* 2019;**3**:231-41.
24. Grimaud JC, Munoz-Bongrand N, Siproudhis L*, et al.* Fibrin glue is effective healing perianal fistulas in patients with crohn's disease. *Gastroenterology* 2010;**138**:2275-81, 81 e1.
25. Fichera A, Zoccali M, Crohn's, Colitis Foundation of America I. Guidelines for the surgical treatment of crohn's perianal fistulas. *Inflamm Bowel Dis* 2015;**21**:753-8.
26. Sirany AM, Nygaard RM, Morken JJ. The ligation of the intersphincteric fistula tract procedure for anal fistula: A mixed bag of results. *Dis Colon Rectum* 2015;**58**:604-12.
27. Gottgens KWA, Wasowicz DK, Stijns J, Zimmerman D. Ligation of the intersphincteric fistula tract for high transsphincteric fistula yields moderate results at best: Is the tide turning? *Dis Colon Rectum* 2019;**62**:1231-7.
28. Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with crohn's disease. *Ann Surg* 2014;**260**:1057-61.
29. Senejoux A, Siproudhis L, Abramowitz L*, et al.* Fistula plug in fistulising ano-perineal crohn's disease: A randomised controlled trial. *J Crohns Colitis* 2016;**10**:141-8.
30. Nasseri Y, Cassella L, Berns M, Zaghiyan K, Cohen J. The anal fistula plug in crohn's disease patients with fistula-in-ano: A systematic review. *Colorectal Dis* 2016;**18**:351-6.
31. Cintron JR, Abcarian H, Chaudhry V*, et al.* Treatment of fistula-in-ano using a porcine small intestinal submucosa anal fistula plug. *Tech Coloproctol* 2013;**17**:187-91.
32. Ellis CN, Rostas JW, Greiner FG. Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. *Dis Colon Rectum* 2010;**53**:798-802.
33. Ky AJ, Sylla P, Steinhagen R*, et al.* Collagen fistula plug for the treatment of anal fistulas. *Dis Colon Rectum* 2008;**51**:838-43.
34. Kaimakliotis P, Simillis C, Harbord M*, et al.* A systematic review assessing medical treatment for rectovaginal and enterovesical fistulae in crohn's disease. *J Clin Gastroenterol* 2016;**50**:714-21.
35. Hotouras A, Ribas Y, Zakeri S*, et al.* Gracilis muscle interposition for rectovaginal and anovaginal fistula repair: A systematic literature review. *Colorectal Dis* 2015;**17**:104-10.
36. Panes J, Garcia-Olmo D, Van Assche G*, et al.* Long-term efficacy and safety of stem cell therapy (cx601) for complex perianal fistulas in patients with crohn's disease. *Gastroenterology* 2018;**154**:1334-42 e4.
37. Panes J, Garcia-Olmo D, Van Assche G*, et al.* Expanded allogeneic adipose-derived mesenchymal stem cells (cx601) for complex perianal fistulas in crohn's disease: A phase 3 randomised, double-blind controlled trial. *Lancet* 2016;**388**:1281-90.
38. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal crohn's disease: Progress made and future directions. *Dis Colon Rectum* 2018;**61**:629-40.
39. Dozois EJ, Lightner AL, Mathis KL*, et al.* Early results of a phase i trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transsphincteric cryptoglandular fistulas. *Dis Colon Rectum* 2019;**62**:615-22.
40. Tavares MMR, Barbosa LER. Adipose tissue-derived stem cells: A new approach to the treatment of crohn's disease-associated perianal fistulae. *Journal of Coloproctology* 2018;**38**:240-5.
41. Lee WY, Park KJ, Cho YB*, et al.* Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for crohn's fistula. *Stem Cells* 2013;**31**:2575-81.

42. de la Portilla F, Alba F, Garcia-Olmo D*, et al.* Expanded allogeneic adipose-derived stem cells (eascs) for the treatment of complex perianal fistula in crohn's disease: Results from a multicenter phase i/iia clinical trial. *Int J Colorectal Dis* 2013;**28**:313-23.
43. Dietz AB, Dozois EJ, Fletcher JG*, et al.* Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with crohn's disease. *Gastroenterology* 2017;**153**:59-62 e2.
44. Dige A, Hougaard HT, Agnholt J*, et al.* Efficacy of injection of freshly collected autologous adipose tissue into perianal fistulas in patients with crohn's disease. *Gastroenterology* 2019;**156**:2208-16 e1.
45. Edwards CM, George BD, Jewell DP*, et al.* Role of a defunctioning stoma in the management of large bowel crohn's disease. *Br J Surg* 2000;**87**:1063-6.
46. Hong MK, Craig Lynch A, Bell S*, et al.* Faecal diversion in the management of perianal crohn's disease. *Colorectal Dis* 2011;**13**:171-6.
47. Regimbeau JM, Panis Y, Cazaban L*, et al.* Long-term results of faecal diversion for refractory perianal crohn's disease. *Colorectal Dis* 2001;**3**:232-7.
48. Singh S, Ding NS, Mathis KL*, et al.* Systematic review with meta-analysis: Faecal diversion for management of perianal crohn's disease. *Aliment Pharmacol Ther* 2015;**42**:783-92.
49. Marti-Gallostra M, Myrelid P, Mortensen N*, et al.* The role of a defunctioning stoma for colonic and perianal crohn's disease in the biological era. *Scand J Gastroenterol* 2017;**52**:251-6.
50. de Groof EJ, Carbonnel F, Buskens CJ, Bemelman WA. Abdominal abscess in crohn's disease: Multidisciplinary management. *Dig Dis* 2014;**32 Suppl 1**:103-9.
51. Pugmire BS, Gee MS, Kaplan JL*, et al.* Role of percutaneous abscess drainage in the management of young patients with crohn disease. *Pediatr Radiol* 2016;**46**:653-9.
52. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A meta-analysis of percutaneous drainage versus surgery as the initial treatment of crohn's disease-related intra-abdominal abscess. *J Crohns Colitis* 2016;**10**:202-8.
53. He X, Lin X, Lian L*, et al.* Preoperative percutaneous drainage of spontaneous intra-abdominal abscess in patients with crohn's disease: A meta-analysis. *J Clin Gastroenterol* 2015;**49**:e82-90.
54. Zangenberg MS, Horesh N, Kopylov U, El-Hussuna A. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: A systematic review. *Int J Colorectal Dis* 2017;**32**:1663-76.
55. Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: Outcomes and post-operative complications following colectomy for ulcerative colitis. *Alimentary pharmacology & therapeutics* 2016;**44**:807-16.
56. Patel KV, Darakhshan AA, Griffin N*, et al.* Patient optimization for surgery relating to crohn's disease. *Nature reviews Gastroenterology & hepatology* 2016;**13**:707-19.
57. Brennan GT, Ha I, Hogan C*, et al.* Does preoperative enteral or parenteral nutrition reduce postoperative complications in crohn's disease patients: A meta-analysis. *Eur J Gastroenterol Hepatol* 2018;**30**:997-1002.
58. Subramanian V, Saxena S, Kang JY, Pollok RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol* 2008;**103**:2373-81.
59. Huang W, Tang Y, Nong L, Sun Y. Risk factors for postoperative intra-abdominal septic complications after surgery in crohn's disease: A meta-analysis of observational studies. *J Crohns Colitis* 2015;**9**:293-301.
60. Serradori T, Germain A, Scherrer ML*, et al.* The effect of immune therapy on surgical site infection following crohn's disease resection. *Br J Surg* 2013;**100**:1089-93.
61. Aberra FN, Lewis JD, Hass D*, et al.* Corticosteroids and immunomodulators: Postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003;**125**:320-7.

62. Rizzo G, Armuzzi A, Pugliese D*, et al.* Anti-tnf-alpha therapies do not increase early postoperative complications in patients with inflammatory bowel disease. An italian single-center experience. *Int J Colorectal Dis* 2011;**26**:1435-44.
63. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence - a systematic review. *Dan Med J* 2018;**65**.
64. Groleau C, Morin SN, Vautour L, Amar-Zifkin A, Bessissow A. Perioperative corticosteroid administration: A systematic review and descriptive analysis. *Perioper Med (Lond)* 2018;**7**:10.
65. Hicks CW, Wick EC, Salvatori R, Ha CY. Perioperative corticosteroid management for patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**:221-8.
66. Xu Y, Yang L, An P, Zhou B, Liu G. Meta-analysis: The influence of preoperative infliximab use on postoperative complications of crohn's disease. *Inflamm Bowel Dis* 2019;**25**:261-9.
67. Lightner AL, Mathis KL, Tse CS*, et al.* Postoperative outcomes in vedolizumab-treated patients undergoing major abdominal operations for inflammatory bowel disease: Retrospective multicenter cohort study. *Inflamm Bowel Dis* 2018;**24**:871-6.
68. Law CCY, Narula A, Lightner AL*, et al.* Systematic review and meta-analysis: Preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis* 2018;**12**:538-45.
69. Shim HH, Ma C, Kotze PG*, et al.* Preoperative ustekinumab treatment is not associated with increased postoperative complications in crohn's disease: A canadian multi-centre observational cohort study. *J Can Assoc Gastroenterol* 2018;**1**:115-23.
70. Lightner AL, McKenna NP, Tse CS*, et al.* Postoperative outcomes in ustekinumab-treated patients undergoing abdominal operations for crohn's disease. *J Crohns Colitis* 2018;**12**:402-7.
71. da Luz Moreira A, Stocchi L, Tan E, Tekkis PP, Fazio VW. Outcomes of crohn's disease presenting with abdominopelvic abscess. *Dis Colon Rectum* 2009;**52**:906-12.
72. Adamina M, Gie O, Demartines N, Ris F. Contemporary perioperative care strategies. *Br J Surg* 2013;**100**:38-54.
73. Barnes EL, Lightner AL, Regueiro M. Peri-operative and post-operative management of patients with crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol* 2019.
74. Bettenworth D, Gustavsson A, Atreja A*, et al.* A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing crohn's disease. *Inflamm Bowel Dis* 2017;**23**:133-42.
75. Morar PS, Faiz O, Warusavitarne J*, et al.* Systematic review with meta-analysis: Endoscopic balloon dilatation for crohn's disease strictures. *Aliment Pharmacol Ther* 2015;**42**:1137-48.
76. Hirai F, Andoh A, Ueno F*, et al.* Efficacy of endoscopic balloon dilation for small bowel strictures in patients with crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018;**12**:394-401.
77. Lan N, Stocchi L, Ashburn JH*, et al.* Outcomes of endoscopic balloon dilation vs surgical resection for primary ileocolic strictures in patients with crohn's disease. *Clin Gastroenterol Hepatol* 2018;**16**:1260-7.
78. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W*, et al.* Outcomes of endoscopic therapy for luminal strictures in crohn's disease. *Inflamm Bowel Dis* 2018;**24**:1575-81.
79. Lian L, Stocchi L, Remzi FH, Shen B. Comparison of endoscopic dilation vs surgery for anastomotic stricture in patients with crohn's disease following ileocolonic resection. *Clin Gastroenterol Hepatol* 2017;**15**:1226-31.
80. Ozuner G, Fazio VW, Lavery IC, Milsom JW, Strong SA. Reoperative rates for crohn's disease following strictureplasty. Long-term analysis. *Dis Colon Rectum* 1996;**39**:1199-203.
81. Bellolio F, Cohen Z, MacRae HM*, et al.* Strictureplasty in selected crohn's disease patients results in acceptable long-term outcome. *Dis Colon Rectum* 2012;**55**:864-9.
82. Schlussel AT, Steele SR, Alavi K. Current challenges in the surgical management of crohn's disease: A systematic review. *Am J Surg* 2016;**212**:345-51.

83. Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for crohn's disease: A systematic review and meta-analysis. *Dis Colon Rectum* 2007;**50**:1968-86.
84. Ambe R, Campbell L, Cagir B. A comprehensive review of strictureplasty techniques in crohn's disease: Types, indications, comparisons, and safety. *J Gastrointest Surg* 2012;**16**:209-17.
85. Campbell L, Ambe R, Weaver J, Marcus SM, Cagir B. Comparison of conventional and nonconventional strictureplasties in crohn's disease: A systematic review and meta-analysis. *Dis Colon Rectum* 2012;**55**:714-26.
86. Uchino M, Ikeuchi H, Matsuoka H*, et al.* Long-term efficacy of strictureplasty for crohn's disease. *Surg Today* 2010;**40**:949-53.
87. Dasari BV, McKay D, Gardiner K. Laparoscopic versus open surgery for small bowel crohn's disease. *Cochrane Database Syst Rev* 2011:CD006956.
88. Tan JJ, Tjandra JJ. Laparoscopic surgery for crohn's disease: A meta-analysis. *Dis Colon Rectum* 2007;**50**:576-85.
89. Patel SV, Patel SV, Ramagopalan SV, Ott MC. Laparoscopic surgery for crohn's disease: A meta-analysis of perioperative complications and long term outcomes compared with open surgery. *BMC Surg* 2013;**13**:14.
90. Shigeta K, Okabayashi K, Hasegawa H*, et al.* Meta-analysis of laparoscopic surgery for recurrent crohn's disease. *Surg Today* 2016;**46**:970-8.
91. Appau KA, Fazio VW, Shen B*, et al.* Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in crohn's patients. *J Gastrointest Surg* 2008;**12**:1738-44.
92. Billioud V, Ford AC, Tedesco ED*, et al.* Preoperative use of anti-tnf therapy and postoperative complications in inflammatory bowel diseases: A meta-analysis. *J Crohns Colitis* 2013;**7**:853-67.
93. Brouquet A, Maggiori L, Zerbib P*, et al.* Anti-tnf therapy is associated with an increased risk of postoperative morbidity after surgery for ileocolonic crohn disease: Results of a prospective nationwide cohort. *Ann Surg* 2018;**267**:221-8.
94. El-Hussuna A, Andersen J, Bisgaard T*, et al.* Biologic treatment or immunomodulation is not associated with postoperative anastomotic complications in abdominal surgery for crohn's disease. *Scand J Gastroenterol* 2012;**47**:662-8.
95. El-Hussuna A, Krag A, Olaison G, Bendtsen F, Gluud LL. The effect of anti-tumor necrosis factor alpha agents on postoperative anastomotic complications in crohn's disease: A systematic review. *Dis Colon Rectum* 2013;**56**:1423-33.
96. Fumery M, Seksik P, Auzolle C*, et al.* Postoperative complications after ileocecal resection in crohn's disease: A prospective study from the remind group. *Am J Gastroenterol* 2017;**112**:337-45.
97. Holubar SD, Holder-Murray J, Flasar M, Lazarev M. Anti-tumor necrosis factor-alpha antibody therapy management before and after intestinal surgery for inflammatory bowel disease: A ccfa position paper. *Inflamm Bowel Dis* 2015;**21**:2658-72.
98. Jouvin I, Lefevre JH, Creavin B*, et al.* Postoperative morbidity risks following ileocolic resection for crohn's disease treated with anti-tnf alpha therapy: A retrospective study of 360 patients. *Inflamm Bowel Dis* 2018;**24**:422-32.
99. Kanazawa A, Yamana T, Okamoto K, Sahara R. Risk factors for postoperative intra-abdominal septic complications after bowel resection in patients with crohn's disease. *Dis Colon Rectum* 2012;**55**:957-62.
100. Kasparek MS, Bruckmeier A, Beigel F*, et al.* Infliximab does not affect postoperative complication rates in crohn's patients undergoing abdominal surgery. *Inflamm Bowel Dis* 2012;**18**:1207-13.
101. Kotze PG, Magro DO, Martinez CAR*, et al.* Adalimumab and postoperative complications of elective intestinal resections in crohn's disease: A propensity score case-matched study. *Colorectal Dis* 2017.
102. Kotze PG, Saab MP, Saab B*, et al.* Tumor necrosis factor alpha inhibitors did not influence postoperative morbidity after elective surgical resections in crohn's disease. *Dig Dis Sci* 2017;**62**:456-64.

103. Myrelid P, Marti-Gallostra M, Ashraf S*, et al.* Complications in surgery for crohn's disease after preoperative antitumour necrosis factor therapy. *Br J Surg* 2014;**101**:539-45.
104. Norgard BM, Nielsen J, Qvist N*, et al.* Pre-operative use of anti-tnf-alpha agents and the risk of post-operative complications in patients with crohn's disease--a nationwide cohort study. *Aliment Pharmacol Ther* 2013;**37**:214-24.
105. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis. *J Crohns Colitis* 2013;**7**:868-77.
106. Scarpa M, Martinato M, Bertin E*, et al.* Intestinal surgery for crohn's disease: Role of preoperative therapy in postoperative outcome. *Dig Surg* 2015;**32**:243-50.
107. Yamamoto T, Spinelli A, Suzuki Y*, et al.* Risk factors for complications after ileocolonic resection for crohn's disease with a major focus on the impact of preoperative immunosuppressive and biologic therapy: A retrospective international multicentre study. *United European Gastroenterol J* 2016;**4**:784-93.
108. Ferrante M, de Buck van Overstraeten A, Schils N*, et al.* Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. *J Crohns Colitis* 2017;**11**:1353-61.
109. Kotze PG, Ma C, McKenna N*, et al.* Vedolizumab and early postoperative complications in nonintestinal surgery: A case-matched analysis. *Therap Adv Gastroenterol* 2018;**11**:1756284818783614.
110. Lightner AL, McKenna NP, Moncrief S*, et al.* Surgical outcomes in vedolizumab-treated patients with ulcerative colitis. *Inflamm Bowel Dis* 2017;**23**:2197-201.
111. Lightner AL, McKenna NP, Tse CS*, et al.* Postoperative outcomes in vedolizumab-treated crohn's disease patients undergoing major abdominal operations. *Aliment Pharmacol Ther* 2018;**47**:573-80.
112. Lightner AL, Raffals LE, Mathis KL*, et al.* Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *J Crohns Colitis* 2017;**11**:185-90.
113. Lightner AL, Tse CS, Potter DD, Jr., Moir C. Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease. *J Pediatr Surg* 2018;**53**:1706-9.
114. Mitsuya JB, Gonzalez R, Thomas R, El-Baba M. The effect of biologics on postoperative complications in children with inflammatory bowel disease and bowel resection. *J Pediatr Gastroenterol Nutr* 2019;**68**:334-8.
115. Park KT, Sceats L, Dehghan M*, et al.* Risk of post-operative surgical site infections after vedolizumab vs anti-tumour necrosis factor therapy: A propensity score matching analysis in inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;**48**:340-6.
116. Yamada A, Komaki Y, Patel N*, et al.* Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. *Am J Gastroenterol* 2017;**112**:1423-9.
117. Yung DE, Horesh N, Lightner AL*, et al.* Systematic review and meta-analysis: Vedolizumab and postoperative complications in inflammatory bowel disease. *Inflamm Bowel Dis* 2018;**24**:2327-38.
118. Zimmerman LA, Zalieckas JM, Shamberger RC, Bousvaros A. Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab. *J Pediatr Surg* 2018;**53**:1330-3.
119. Ponsioen CY, de Groof EJ, Eshuis EJ*, et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in crohn's disease: A randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;**2**:785-92.
120. Simillis C, Purkayastha S, Yamamoto T*, et al.* A meta-analysis comparing conventional end-to-end anastomosis vs. Other anastomotic configurations after resection in crohn's disease. *Dis Colon Rectum* 2007;**50**:1674-87.
121. Guo Z, Li Y, Zhu W*, et al.* Comparing outcomes between side-to-side anastomosis and other anastomotic configurations after intestinal resection for patients with crohn's disease: A meta-analysis. *World J Surg* 2013;**37**:893-901.

122. He X, Chen Z, Huang J*, et al.* Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for crohn's disease: A meta-analysis. *Dig Dis Sci* 2014;**59**:1544-51.
123. Feng JS, Li JY, Yang Z*, et al.* Stapled side-to-side anastomosis might be benefit in intestinal resection for crohn's disease: A systematic review and network meta-analysis. *Medicine (Baltimore)* 2018;**97**:e0315.
124. Tekkis PP, Purkayastha S, Lanitis S*, et al.* A comparison of segmental vs subtotal/total colectomy for colonic crohn's disease: A meta-analysis. *Colorectal Dis* 2006;**8**:82-90.
125. Angriman I, Pirozzolo G, Bardini R*, et al.* A systematic review of segmental vs subtotal colectomy and subtotal colectomy vs total proctocolectomy for colonic crohn's disease. *Colorectal Dis* 2017;**19**:e279-e87.
126. Uzzan M, Stefanescu C, Maggiori L*, et al.* Case series: Does a combination of anti-tnf antibodies and transient ileal fecal stream diversion in severe crohn's colitis with perianal fistula prevent definitive stoma? *Am J Gastroenterol* 2013;**108**:1666-8.
127. Harper PH, Truelove SC, Lee EC, Kettlewell MG, Jewell DP. Split ileostomy and ileocolostomy for crohn's disease of the colon and ulcerative colitis: A 20 year survey. *Gut* 1983;**24**:106-13.
128. Spivak J, Landers CJ, Vasiliauskas EA*, et al.* Antibodies to i2 predict clinical response to fecal diversion in crohn's disease. *Inflamm Bowel Dis* 2006;**12**:1122-30.
129. Burman JH, Thompson H, Cooke WT, Williams JA. The effects of diversion of intestinal contents on the progress of crohn's disease of the large bowel. *Gut* 1971;**12**:11-5.
130. Mennigen R, Heptner B, Senninger N, Rijcken E. Temporary fecal diversion in the management of colorectal and perianal crohn's disease. *Gastroenterol Res Pract* 2015;**2015**:286315.
131. Bafford AC, Latushko A, Hansraj N, Jambaulikar G, Ghazi LJ. The use of temporary fecal diversion in colonic and perianal crohn's disease does not improve outcomes. *Dig Dis Sci* 2017;**62**:2079-86.
132. Panis Y, Poupard B, Nemeth J*, et al.* Ileal pouch/anal anastomosis for crohn's disease. *Lancet* 1996;**347**:854-7.
133. Regimbeau JM, Panis Y, Pocard M*, et al.* Long-term results of ileal pouch-anal anastomosis for colorectal crohn's disease. *Dis Colon Rectum* 2001;**44**:769-78.
134. Manilich E, Remzi FH, Fazio VW, Church JM, Kiran RP. Prognostic modeling of preoperative risk factors of pouch failure. *Dis Colon Rectum* 2012;**55**:393-9.
135. Fazio VW, Kiran RP, Remzi FH*, et al.* Ileal pouch anal anastomosis: Analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;**257**:679-85.
136. Reese GE, Lovegrove RE, Tilney HS*, et al.* The effect of crohn's disease on outcomes after restorative proctocolectomy. *Dis Colon Rectum* 2007;**50**:239-50.