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ECCO Guideline/Consensus Paper

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3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations

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Abstract

This paper is the second in a series of two publications relating to the European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on the diagnosis and management of Crohn's disease [CD] and concerns the surgical management of CD as well as special situations including management of perianal CD and extraintestinal manifestations. Diagnostic approaches and medical management of CD of this ECCO Consensus are covered in the first paper [Gomollon *et al*. JCC 2016].

Key Words: anti-integrins; anti-TNFs; biologics; budesonide; Crohn's disease; diagnosis; immunosuppressant; investigations; steroids; thiopurine; treatment

7 Surgery for Crohn's disease [CD]

7.1 Introduction

The following section provides a condensed summary of the ECCO guideline on surgery for CD which will soon appear in JCC. The care of CD is now primarily in the hands of medical gastroenterologists. However, many patients will require multiple surgeries during the course of their disease. Ileocaecal CD carries a 90% likelihood of requiring surgery while recurrent inflammation requiring another resection affects every second patient.[1–5] This mandates the gastroenterologist to understand the value of surgery in terms of symptom relief, and balance this against the risks of the procedure, so that the best therapy can be offered at the optimal time. The evidence for type of surgical therapy includes very few prospective randomized studies. However, there is good evidence that extensive resection is no longer necessary and potentially harmful.[6]

7.2 Small intestinal or ileo-colonic disease

7.2.1 Localized ileal or ileocaecal disease

ECCO Statement 7A

Surgery is the preferred option in patients with localised ileocaecal Crohn's disease with obstructive symptoms, but no significant evidence of active inflammation [EL4]

Patients with inflammatory CD confined to the ileocecal region but no imminent obstruction respond well to medical treatment. However, this patient group often require surgery during the course of their disease. Following resection, long-term studies have demonstrated that there is a 50% chance that the patient will never require a further operation [i.e. have symptoms of the same severity again].[7–10] In contrast there are no long-term follow-up studies [i.e. >15 years] of the outcome of medical treatment. In addition, it is not known whether there are long-term differences in the quality of life of patients treated by medical as opposed to surgical therapy.[11] Primary surgery should be considered as the first choice for patients with refractory obstructive symptoms after initial medical treatment in ileocaecal CD. Likewise, patients presenting with obstruction without inflammatory activity, for example assessed by C-reactive protein [CRP] levels,[12–14] can also be treated with primary surgery.

7.2.2 Concomitant abscess

Drainage followed by medical treatment should be considered if there are no obstructive symptoms, depending on the clinical situation. Some abscesses do not lend themselves to percutaneous drainage. There are no randomized studies in the literature to clarify whether percutaneous or surgical drainage should always be followed by a delayed resection, and although most case series favour a delayed elective resection, opinions vary.[15–20]

ECCO Statement 7B

Active small bowel Crohn's disease with a concomitant abdominal abscess should preferably be managed with antibiotics, percutaneous or surgical drainage followed by delayed resection if necessary [EL3]

7.2.3 Strictureplasty

ECCO Statement 7C

Strictureplasty is a safe alternative to resection in jejuno-ileal Crohn's disease, including ileocolonic recurrence, with similar short-term and long-term results. Conventional strictureplasty is advised when the length of the stricture is <10 cm. However, in extensive disease with long strictured bowel segments where resection would compromise the effective small bowel length, non-conventional stricturoplasties may be attempted [EL3]

Most authors limit conventional stricturoplasties to strictures <10 cm in length. The majority opinion is that strictureplasty is inadvisable for longer [>10 cm] strictures. However, there are now series reported with non-conventional stricturoplasties for longer bowel segments, reporting good results.[21–26] Indeed, a meta-analysis comparing conventional and non-conventional stricturoplasties in 1616 Crohn's patients who underwent 4538 stricturoplasties showed similar results for both techniques: the rates of small bowel obstruction, sepsis, reoperation, recurrence, carcinoma and mortality were similar.[27] A phlegmon in the bowel wall, carcinoma or active bleeding with mucosal disease are contraindications to strictureplasty. Where there are multiple strictures in a short segment and where bowel length is sufficient to avoid short bowel syndrome, resection may be preferable. Systematic reviews[28,29] and patient series[30] comparing strictureplasty and resection have confirmed the safety and bowel-sparing potential of strictureplasty for small bowel CD. The question of whether resection may induce a longer recurrence-free survival has not been resolved.[29,31] There are several case reports of adenocarcinoma at strictureplasty sites,[32] rendering the need for caution regarding the long-term consequences of this procedure.

7.2.4 Anastomotic technique

ECCO Statement 7D

Wide lumen stapled ileocolic side-to-side (functional end-to-end) anastomosis is the preferred technique [EL1]

The observation that recurrent CD almost invariably appears just proximal to the anastomosis has led to the assumption that the width of the anastomosis matters. Several studies have tried to address this.[33–38] A meta-analysis of eight comparative studies including two randomized trials compared end-to-end anastomosis with stapled side-to-side anastomosis in 661 patients. It showed that end-to-end anastomosis after ileocolonic resection for CD was associated with increased anastomotic leak rates and overall postoperative complications. There was no significant difference with regard to peri-anastomotic recurrence rates.[39] A second meta-analysis comparing stapled versus hand-sewn ileocolic anastomosis in 1125 randomized patients [seven randomized control trials [RCTs]) showed a marked superiority for stapled side-to-side anastomosis.[40] The clinical leak rate was 2.3% for stapled and 4.2% for hand-sewn anastomosis. A prospective cohort study showed no difference in safety and recurrence rate between hand-sewn side-to-side and stapled side-to-side anastomosis,[34] suggesting that a wide anastomotic luminal diameter is an important discriminating factor, whatever anastomotic technique is used.

7.2.5 'Coincidental' ileitis and appendectomy

ECCO Statement 7E

Terminal ileitis resembling Crohn's disease found at a laparotomy for suspected appendicitis should not routinely be resected [EL5]

The finding of terminal ileitis or caecitis at laparoscopy or laparotomy for a clinical suspicion of appendicitis is non-specific, and it is virtually impossible to differentiate between CD and infectious [e.g. *Yersinia* species] enteritis. Even if it were to be Crohn's ileitis, resection might not be the most appropriate strategy if the dominant symptoms relate to inflammation. Only when the patient's history indicates obstructive symptoms for more than a few days, or the proximal intestine is dilated and the inflamed bowel wall looks typical of CD with mesenteric fat wrapping, is an experienced surgeon justified in performing a primary resection.[41] In the presence of clinical features suggestive of appendicitis, standard appendectomy may safely be performed. While population-based studies have suggested a controversial association between appendectomy and a subsequent diagnosis of CD,[42–44] this association vanishes after 5 years in a meta-analysis.[45]

7.2.6 Laparoscopic resection

ECCO Statement 7F

A laparoscopic approach is to be preferred for ileocolic resections in Crohn's disease [EL 2] where appropriate expertise is available. In more complex cases or recurrent resection, there is insufficient evidence to recommended laparoscopic surgery as the technique of first choice [EL3]

Several studies during the last few years have shown that laparoscopic resection gives substantial benefits in addition to a shorter scar. Three meta-analyses of up to 15 studies, including a meta-analysis of two randomized controlled trials following 120 patients for up to 10 years,[46,47] showed benefits in the postoperative period for the laparoscopic group. Advantages included earlier recovery of normal intestinal function, shorter hospital stay and lower postoperative morbidity.[48–50] Reoperations for incisional hernia or adhesions were also markedly lower in the laparoscopy groups. This was confirmed in a US nationwide registry study of 49 609 resections for CD.[51] The 2826 laparoscopic cases [6%] were associated with shorter length of stay, lower charges, a lower complication rate [8 vs 16%] and reduced mortality [0.2 vs 0.9%, $p < 0.01$]. The 10-year follow-up of two randomized controlled trials comparing open and laparoscopic resection for ileo-colic Crohn's showed equal rates of surgical recurrence.[47,52] This is an important finding, as it alleviates the concern of potentially missing occult segment of disease during laparoscopy. Moreover, better cosmesis scores and body image in the laparoscopy groups have also been reported.[46,53] Thus, although laparoscopic surgery for CD is technically demanding, there is growing evidence for significant advantages with the technique for primary ileocolonic resections. Evidence for feasibility and safety in complex Crohn's is scarce with recurrent disease and intra-abdominal abscess or fistulae being important risk factors for conversion to open laparotomy.[54,55] Repeat irritable bowel disease [IBD] surgery via the laparoscopic approach appears feasible and safe in experienced hands, although a high conversion rate is more appropriate to ensure patient safety.[55,56]

7.3 CD of the colon

7.3.1 Localized colonic disease

ECCO Statement 7G

If surgery is necessary for localised colonic disease (less than a third of the colon involved) then resection of the affected part only is preferable [EL3]. Two segmental resections can be considered for a patient with an established indication for surgery when macroscopic disease affects two separate segments of the colon [EL3]. Strictureplasty in the colon is not recommended [EL3]

Limited colonic CD treated by segmental resection results in a higher and earlier rate of recurrence than a proctocolectomy.[57–61] However, most agree that the avoidance of a permanent stoma usually outweighs the increased risk of recurrence. There is some support for separate segmental resection in the literature.[57,62,63] In particular, loss of the colon in a patient with significant prior small bowel resection may impair functional results. Conversely, a more aggressive approach [subtotal colectomy up to proctocolectomy] may be considered in patients with diffuse and distal Crohn's colitis. In properly selected patients, this may translate into a lower risk of, and later time to, recurrence.[64] Ultimately, decisions should take into account preferences of the patient and surgeon.

7.3.3 Dilatation of strictures

Endoscopic dilatation is an accepted technique for the management of mild to moderate stenosing disease. Most reports of endoscopically dilated strictures have been at the proximal side of a surgical anastomosis. Locations of choice are the terminal ileum or the colon, although double balloon enteroscopic dilatation of the small bowel has been attempted. Outcomes suggest short- to mid-term benefit with long-term surgery-free interval achieved in up to 50% of the patients.[65–68] Most experts consider that endoscopic dilatation of a

ECCO Statement 7H

Endoscopic dilatation is a preferred technique for the management of symptomatic and short anastomotic strictures It should only be attempted in institutions with surgical back-up [EL3]

stenosis in CD should only be attempted in institutions with a 24-h surgical service. The largest single-centre study reported 237 dilatations in 138 patients with rates of success at first dilatation of 97%, and perforation in 5%. At 6 years of follow-up, repeat dilatation was required in every second patient, while surgery was performed in every fourth patient.[65] Similarly, a review of 23 studies enrolling 574 Crohn's patients treated with endoscopic dilatation reported a 90% technical success rate with 4% major complications [perforation, severe bleeding]. At 2 years of follow-up every fourth patient had required surgery. Another systematic review concluded that a stricture length of, or below, 4 cm predicted endoscopic success, delaying surgery by a mean of 3 years.[69]

7.3.5 Ileo pouch-anal anastomosis [IPAA]

ECCO Statement 7I

Patients with a (unsuspected) diagnosis of Crohn's disease after IPAA present markedly higher complication and failure rates. An IPAA may be discussed in highly selected and motivated patients with Crohn's colitis, pending proof of absent small bowel disease and no existing or previous evidence of perineal involvement. Intensive combined management by IBD physicians is mandatory to maintain an acceptable pouch function in those patients [EL4]

Most IPAA series include some patients with CD. Retrospective analyses show that these patients suffer a higher complication rate, with pouch failure reported in up to 56%.[70–74] The largest prospective series of IPAA published a pouch failure rate of 13.3% in 150 Crohn's patients [5.1% in ulcerative colitis [UC]). Quality of life was, however, excellent for both Crohn's and UC patients with IPAA.[75] Recent meta-analysis and systematic reviews of outcomes of IPAA in CD did, however, show more anastomotic strictures and incontinence in patients with CD. Moreover, pouch failure was up to six-fold more frequent than with UC and indeterminate colitis.[76,77] Half the experts are prepared to recommend an IPAA for a patient with long-standing Crohn's colitis, provided there is no sign of small bowel or perianal disease, and that the patient is willing to accept an increased risk of complications and pouch failure.

ECCO Statement 7J

Whether there is a higher rate of postoperative complications from abdominal surgery during or after anti-TNF therapy remains controversial [EL3]

Most probably, complications after surgery can be minimized with optimal preparation.[78] Whether anti-tumour necrosis factor alpha [TNFα] therapy increases the risk of postoperative complications in CD is a matter of debate.[79] Anti-TNF therapy increases the risk of complications in some[80–83] but not all studies.[84,85] In a recent meta-analysis with a total of eight studies including 1641 patients, preoperative infliximab therapy demonstrated a trend toward an increased rate of total complications, with a modestly increased risk of infectious complications mostly remote from the surgical site.[86]

ECCO Statement 7K

Prednisolone 20mg daily or equivalent for more for more than six weeks is a risk factor for surgical complications [EL2]. Therefore, corticosteroids should be weaned if possible [EL5]

Uncontrolled or retrospective series indicate that patients taking ≥20 mg prednisolone for >6 weeks do have an increased risk for surgical complications.[35,84,87]

ECCO Statement 7L

Thiopurines can safely be continued in the peri-operative period and beyond [EL3]

Most publications agree that thiopurines do not increase the risk of surgical complications,[87–89] although some question this.[90]

8 Risk factors, prophylaxis, diagnosis and management of post-operative recurrence of CD

8.1 Epidemiology of post-operative CD

Unfortunately, surgery is not curative as the disease inexorably recurs in many patients. The post-operative recurrence [POR] rate varies according to the definition used, be it clinical, endoscopic, radiological or surgical. It is lowest when measured by repeat resection, intermediate when clinical indices are used and highest when endoscopy is employed as the diagnostic tool. Overall, in population-based studies, the clinical POR rate ranged from 28 to 45% and from 36 to 61% at 5 and 10 years, respectively. It has been demonstrated that the post-operative clinical course of CD is best predicted by the severity of endoscopic lesions.[91] Clinical recurrence should be suspected with digestive CD symptoms, which may be difficult to assess in the post-operative period, and can be delayed as symptoms may appear only when severe lesions are present.[92] Clinical indices such as the Crohn's Disease Activity Index [CDAI] have low sensitivity at discriminating between patients with or without POR and have not been validated in the post-operative setting.[93] Strategies to reduce POR have yet to be defined, with a recent randomized study demonstrating the value of treatment modulation following colonoscopy 6 months after surgery.[94,95]

8.2 Risk factors for first surgery and POR

ECCO statement 8A

Current smoking [EL1], penetrating and stricturing disease behaviour [EL1], early steroid use [EL2], ileal disease [EL2], jejunal disease [EL3] and young age at diagnosis [EL3] are risk factors for surgery in Crohn's disease

Risk factors for surgery were investigated in three population-based cohorts.[96–98] Ileal disease and in some studies ileocolonic disease, oral corticosteroid therapy within 3 months of diagnosis, early use of thiopurines within the first year of diagnosis, age younger than

40 years or older than 30 years, as well as stricturing or penetrating disease behaviour, were independent factors for having surgery in CD. Jejunal disease is a significantly greater risk factor for stricturing disease and multiple abdominal surgeries than either oesophagogastroduodenal or ileal [without proximal] disease.[99] In a population-based cohort from Olmsted County, MN, USA, non-colonic disease extent, current smoking, penetrating disease behaviour and early steroid use were significantly associated with major abdominal surgery.[100] Anti-TNF treatment was associated with a reduction in the need for surgery in patients newly diagnosed with CD, and azathioprine when compared with anti-TNF had modest efficacy in reducing this risk.[101] Lakatos *et al*. showed also that early azathioprine therapy was a significant predictor for time to first surgery in CD patients.[102]

ECCO statement 8B

The following are considered predictors of early post-operative recurrence after ileocolonic resection: smoking, prior intestinal surgery, absence of prophylactic treatment [EL1], penetrating disease at index surgery, perianal location [EL2], granulomas in resection specimen [EL2], and myenteric plexitis [EL3]

ECCO statement 8C

Early treatment with thiopurines [EL2] is associated with reduced risk of first surgery. Treatment with anti-TNF reduces the risk of surgery [EL2]

Patients with CD who smoke have a 2.5-fold increased risk of POR and a 2-fold risk of clinical recurrence compared to non-smokers,[103] smoking being the only consistently reported factor in clinical trials.[95,104] A number of observational studies have shown that a history of prior resection is a risk factor associated with POR.[105,106] In the same way, a controlled clinical trial showed that azathioprine was more effective than mesalamine in preventing clinical recurrence in those with a previous intestinal resection, suggesting a more aggressive outcome for those previously submitted to surgery. Perforating disease is an independent risk factor for postoperative recurrence.[107,108] Conflicting data exist with regards to the early recurrence of perforating disease.[107,108] Perianal disease,[96,109,110] and extensive small bowel resection [>50 cm] [4] are also established predictors for POR. A meta-analysis found a significantly higher recurrence and reoperation rate in patients with granulomas[111] and three studies showed myenteric plexitis as an independent predictor;[106,112,113] new studies need to clarify the real value of histology to predict recurrence.[114] Inconsistent data exist for the age at onset of the disease,[115,116] gender,[117,118] duration of the disease,[119–121] resection margins[122–124] or type of surgery.[48,125]

8.3 Diagnosis of POR

Diagnosis of POR may be based on clinical symptoms, serum and faecal markers, or radiological and endoscopic findings. Symptoms are not always easily distinguishable from other post-operative conditions [such as pain due to adhesional obstruction, calculi or dysmotility, and diarrhoea due to bile-salt malabsorption or bacterial overgrowth].

Ileocolonoscopy remains the gold standard to diagnose recurrence after surgery and several studies have shown that colonoscopy is the most sensitive tool to document morphological recurrence. Histological or endoscopic recurrence may occur within a few weeks to months after surgery.[126–131] Endoscopic recurrence precedes clinical recurrence and severe endoscopic recurrence predicts a poor prognosis.[129,130] Rutgeerts *et al*. developed an endoscopic scoring system to assess endoscopic recurrence.[129] The patients were stratified into five groups [i0–i4] according to the endoscopic severity. An endoscopic score of i0 or i1 correlated with a low risk of endoscopic progression and had clinical recurrence rates of less than 10% over 10 years.[129]

ECCO statement 8D

Ileocolonoscopy is the gold standard in the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course [EL2]. Ileocolonoscopy is recommended within the first year after surgery where treatment decisions may be affected [EL2]

ECCO statement 8E

Calprotectin, "trans-abdominal" ultrasound, MR enterography, small bowel capsule endoscopy (SBCE) are less invasive diagnostic methods emerging as alternative tools for identifying postoperative recurrence [EL3]

Faecal calprotectin was shown to remain elevated in some patients after surgery,[132] and later a correlation was found between endoscopic severity and calprotectin levels.[133] Several recent studies and meta-analyses confirm the usefulness of calprotectin as a diagnostic and monitoring tool in CD patients after surgery.[134–139]

Radiology and imaging (ultrasound [US], magnetic resonance [MR], computed tomography [CT]) are being evaluated as independent diagnostic methods for POR. US has been used with high accuracy for the diagnosis of postsurgical recurrence in CD, and can differentiate with high sensitivity and specificity mild from severe recurrence.[140–143] Severe anastomotic stenosis and anastomotic wall thickening > 3 mm are the two most sensitive computed tomography enterography [CTE] findings for the diagnosis of a diseased anastomosis, inflammatory recurrence and fibrostenosis.[144] CTE complemented with water enema showed high accuracy (92%] in evaluating anastomotic disease recurrence.[145] Magnetic resonance enterography [MRE] allows assessment of disease recurrence after ileocolonic resection with high agreement to the endoscopic Rutgeerts score.[146] Capsule endoscopy in the postoperative setting is able to detect proximal lesions, beyond the reach of the colonoscope in two-thirds of patients.[147]

8.4 Medical prophylaxis

ECCO statement 8F

All patients with Crohn's disease should be informed of the risk associated with smoking and smoking cessation should be encouraged and supported [EL1]

A meta-analysis of 16 studies including 2962 patients reported that smokers had a 2-fold increased risk for clinical and a 2.5-fold increased risk for surgical POR within 10 years[103] and interestingly the rate of clinical POR among ex-smokers was not different from

patients who had never smoked.[148] Smoking's key role in POR is confirmed in the setting of randomized clinical trials.[95]

ECCO statement 8G

Prophylactic treatment is recommended after ileocolonic intestinal resection in patients with at least one risk factor for recurrence [EL2]. To prevent post-operative recurrence the drugs of choice are thiopurines [EL2] or anti-TNFs [EL2]. High dose mesalazine is an option for patients with an isolated ileal resection [EL2]. Imidazole antibiotics have been shown to be effective after ileocolic resection but are less well tolerated [EL1]

A recent multi-centre, randomized trial has shown that treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up if there is disease recurrence, is better than conventional therapy alone for prevention of post-operative CD recurrence.[95]

ECCO statement 8H

Long-term prophylaxis should be recommended [EL2]

8.4.1 Mesalazine

Seven controlled trials have evaluated the role of mesalazine on POR.[131,149–154] In a 2009 meta-analysis, pooling the results of the five available RCTs,[155] the relative risk of clinical recurrence was reduced with mesalazine compared to placebo and the number needed to treat [NNT] to prevent a single clinical recurrence was 12. The relative risk of severe endoscopic recurrence [score ≥ i3] was significantly less with mesalazine with an NNT of 8, although the relative risk of any endoscopic recurrence was not significantly reduced. Some studies were open, however. The largest multi-centre controlled trial to date enrolled 318 patients and did not find any significant difference in cumulative clinical relapse rates after 18 months in the mesalazine 4 g and placebo groups, at 24.5 and 31.4%, respectively.[151]

8.4.2 Sulphasalazine

The effect of sulphasalazine versus placebo on POR was studied by Ewe *et al*.[156] in 232 patients. An early difference in the rate of recurrence [identified by either clinical, radiological or endoscopic means] was observed with sulphasalazine at 1 year but significant loss to follow up and withdrawals beyond this time point made subsequent results difficult to interpret.[155]

8.4.3 Corticosteroids

Two studies examined the effect of oral budesonide on rates of POR. Hellers *et al*.[157] randomized 130 patients to budesonide 6 mg daily or placebo for 12 months. The second study[158] showed the impact on clinical and endoscopic recurrence of budesonide at a dose of 3 mg daily or placebo. Taken together [n = 212], the relative risk of severe endoscopic recurrence at 12 months was not significantly different with budesonide relative to placebo.[155,159].

8.4.4 Antibiotics

Metronidazole [20 mg/kg/day] administered for 3 months after surgery significantly reduced the incidence of severe endoscopic recurrence at 1 year in 60 patients, although the effect was not sustained beyond 12 months.[160] Clinical recurrence was also delayed, which was the most important effect. Ornidazole 1 g/day administered for 1 year has also shown efficacy in the prevention of POR in 80 patients with CD at 1 year. Clinical recurrence was again only decreased at 1 year and not at 2 or 3 years. Neither antibiotic was well tolerated,[161] and beneficial effects did not persist after the interruption of therapy. On the basis of this finding, imidazoles seem clearly effective, at least delaying POR, but long-term use is precluded by very common side effects. Ciprofloxacin was not more effective than placebo for the prevention of POR.[162]

8.4.5 Thiopurines

Azathioprine/mercaptopurine

Thiopurines [azathioprine and 6-mercaptopurine] are widely recommended for reducing the risk of POR after surgery, while available data are controversial.[104] In the first trial, there was a trend for 6-mercaptopurine 50 mg/day to be more effective than placebo and mesalazine in preventing clinical POR.[152] A second prospective study randomized 142 patients to receive azathioprine 2 mg/kg/day or mesalazine 3 g/day for 24 months and showed comparable rates of clinical and surgical recurrence. However, subgroup analysis showed a favourable effect of azathioprine for patients who had a previous resection.[163] In the Herfarth *et al*. study the failure rate was equally high with azathioprine [2.0–2.5 mg/kg/day] and mesalazine [4 g/day].[164] D'Haens *et al*. compared the combination of azathioprine for 12 months with metronidazole for 3 months to metronidazole alone in 81 'high-risk' patients. There was no difference in endoscopic recurrence between the two groups at 3 months; however, patients treated with azathioprine experienced a significantly lower rate of endoscopic recurrence at 12 months [55%] than did the patients who received placebo [78%].[165] Another trial of 39 patients receiving either azathioprine [50 mg] or mesalazine [3 g] failed to detect any significant difference in endoscopic recurrence at 2 years, although the dose of azathioprine was lower than recommended in CD.[166] Reinisch *et al*. randomized 78 CD patients who developed endoscopic recurrence [Rutgeerts score ≥i2] to receive azathioprine 2–2.5 mg/kg or mesalazine 4 g/day. Therapeutic failure [as defined by CDAI ≥200 or increase ≥60 points from baseline] during the first year did not differ between the two groups. Azathioprine treatment was associated with a significant decrease in the endoscopic score [decrease ≥1] and lower rates of severe endoscopic lesions [≥i3]. There was no difference in mucosal healing between the two groups.[167]

The Cochrane's meta-analysis comparing the effectiveness of azathioprine/6-mercaptopurine relative to mesalazine showed no significant increase in the relative risk of clinical recurrence within 12 months but the relative risk of any endoscopic recurrence at 12 months was significantly increased with mesalazine relative to azathioprine/6-mercaptopurine. Azathioprine failed to show benefits over mesalazine for more severe degrees of endoscopic recurrence.[155] In the meta-analysis by Peyrin-Biroulet *et al*.,[168] in the overall analysis, thiopurines were more effective than control arms in the prevention of clinical recurrence at 1 year [NNT = 13] and in the prevention of severe endoscopic recurrence [i2–i4] at 1 year but not effective in the prevention of very severe [i3–i4] POR at 1 year. If only studies comparing placebo arms are considered, the efficacy of purine analogues was superior to that of placebo for clinical and endoscopic recurrence at 1 year [NNT = 7, NNT = 4, respectively].

8.4.6 Anti-TNF agents

One pilot RCT has shown efficacy of infliximab in preventing POR.[169] Twenty-four patients with CD who had undergone ileocolonic resection were randomized to receive intravenous infliximab [5 mg/kg], administered within 4 weeks of surgery and continued 8-weekly for 1 year, or placebo. The rate of endoscopic recurrence at 1 year [chosen as the primary end-point] was significantly lower in the infliximab group [9%] compared with the placebo group [85%]. There was a non-significant higher proportion of patients in clinical remission in the infliximab group [80%] compared with placebo [54%]. In follow-up for at least 4 years, five stopped infliximab. All had endoscopic recurrence and four had another surgery. Conversely, of the seven who continued infliximab, none required surgery and all maintained the same endoscopic score.[170] In one trial, 31 patients after surgery received infliximab [5 mg/kg for 36 months] or no treatment.[171] The infliximab group achieved higher endoscopic remission at 12 months, 78.6 vs 18.8%, respectively, but the CDAI at 1 year [primary end point] was similar between both groups.[172] Sorrentino *et al*., in an open-label trial, treated seven CD patients with infliximab [5 mg/kg] and oral methotrexate 10 mg/week, and compared them with 16 patients treated with mesalamine 2.4 g/day. At the end of 2 years, none of the infliximab/methotrexate-treated patients had clinical or endoscopic recurrence, whereas 75% of the patients in the mesalazine group had clinical or endoscopic recurrence.[173] In the long-term follow-up the discontinuation of infliximab in 12 patients, after 3 years of treatment, caused endoscopic recurrence after 4 months in 83% and all were retreated successfully with infliximab.[174]

More recently, a multi-centre, randomized, placebo-controlled trial, to evaluate the efficacy of infliximab in preventing POR of CD in 297 patients, has shown that infliximab was not superior to placebo to prevent clinical recurrence at 76 weeks, but was able to reduce endoscopic recurrence. A smaller proportion of patients in the infliximab group had a clinical recurrence before or at week 76 compared with the placebo group, but this difference was not statistically significant (12.9 vs 20.0%; absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval [CI]: 1.3–15.5%; $p = 0.097$). A significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group [30.6 vs 60.0%; ARR with infliximab, 29.4%; 95% CI: 18.6–40.2%; $p < 0.001$]. Additionally, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based only on Rutgeerts scores >_i2 [22.4 vs 51.3%; ARR with infliximab, 28.9%; 95% CI: 18.4–39.4%; $p < 0.001$].[175]

In a multi-centre, prospective observational trial, 29 CD patients considered at high-risk received adalimumab [40 mg every 2 weeks with an initial induction dose 160/80 mg] after ileal or ileocolonic resection. Endoscopic recurrence [≥ i2] after 1 year was observed in 20.7%.[176] A pilot, open-label study with eight high-risk patients received adalimumab from post-operative day 14. At 6 months, endoscopic POR [≥ i2] was seen in 12.5% of patients.[177] Savarino *et al*. randomly assigned 51 patients with CD who had undergone ileocolonic resection to receive adalimumab 160/80/40 mg every 2 weeks, azathioprine at 2 mg/kg/day, or mesalazine at 3 g/day, starting 2 weeks after surgery with follow up for 2 years. The rate of endoscopic recurrence was significantly lower in the adalimumab [6.3%] compared with azathioprine [64.7%] or mesalazine groups [83.3%]. Furthermore, there was a significantly lower proportion of patients with clinical recurrence in the adalimumab group [12.5%] compared with azathioprine [64.7%] or mesalazine (50%).[178] Recently, a multi-centre trial, carried out in 101 patients at high risk of disease recurrence [smoker, perforating disease, ≥ 2nd operation], has shown that adalimumab was superior to thiopurine in preventing early endoscopic recurrence.[179] Although data are limited,[104] anti-TNFs are the most effective treatment according to indirect comparisons.[180]

8.4.7 Other therapies

Five studies evaluated the effect of probiotics in the post-operative setting, namely *Lactobacillus johnsonii*,[181,182] *Lactobacillus rhamnosus*,[183] and the probiotic cocktails Synbiotic 2000'[184] and VSL#3.[185] A recent trial suggests a modest effect for VSL#3 if administered early after surgery.[186] The subcutaneous administration of recombinant human IL-10 in a randomized controlled trial of 58 patients after ileocolonic resection did not prevent endoscopic recurrence at 12 weeks.[187]

9 Diagnosis and management of fistulating CD

9.1 Introduction

Fistula pose a considerable morbidity in patients with CD including permanent sphincter and perineal tissue destruction, often causing significant impairment in quality of life with serious clinical and psychological consequences. While currently there are more treatment options, overall progress in this area is limited. The unresolved challenges in fistula treatment warrant RCTs for future treatment strategies as well as better classification systems to compare studies, as several recent reviews acknowledge.[188–191]

Fistulizing CD comprises fistulae arising in the perianal area, together with those communicating between the intestine and other organs or the abdominal wall. The main aspects to be taken into account when planning a strategy for the management of CD fistulae are:

1. Locate origin of the fistula and its anatomy
2. Evaluate originating intestinal loop [inflammation or stenosis]
3. Identify or exclude local sepsis [abscess]
4. Determine which organs are affected and the contribution to systemic symptoms or impairment of quality of life
5. Assess nutritional status of the patient

Most emphasis is placed on perianal fistulae complicating CD, since these are most common and supported by the largest body of literature.[188,192] Nevertheless, the greatest limiting factor for this Consensus again was the scarce controlled data regarding combined medical and surgical management.

9.1.1 Perianal fistulae

In a series of 202 consecutive patients with CD at a teaching hospital, up to 54% suffered perianal complications.[193] In population-based studies,[194–196] the occurrence varies between 21 and 23%, with a cumulative frequency of 12% at 1 year, 15% at 5 years, 21% at 10 years and 26% at 20 years. Prevalence varies according to disease location. Perianal fistulae were noted in 12% with isolated ileal disease, 15% with ileocolonic disease, 41% with colonic disease and rectal sparing, and 92% with colonic disease involving the rectum.[194] Perianal disease may precede or appear simultaneously with intestinal symptoms.[196,197]

9.1.2 Non-perianal fistulae

This includes fistulae communicating with other viscera [urinary bladder, vagina], intestine [entero-enteric fistulae] or the abdominal wall [entero-cutaneous fistulae]. There is a notable lack of controlled data in this field.

9.2 Diagnosis of perianal fistulae

9.2.1 Initial diagnostic approach

ECCO statement 9A

Contrast-enhanced pelvic magnetic resonance imaging (MRI) is considered the initial procedure for the assessment of perianal fistulising CD [EL2]. If rectal stenosis is excluded, endoscopic anorectal ultrasound (EUS) is a good alternative [EL2]. The specificity and sensitivity of both imaging modalities is increased when combined with examination under anaesthetic (EUA) [EL1]. Fistulography is not recommended [EL3]. If a perianal fistula is detected, EUA is considered the gold standard in the hands of an experienced surgeon [EL5]

ECCO statement 9B

Since the presence of concomitant rectosigmoid inflammation has prognostic and therapeutic relevance, proctosigmoidoscopy should be used routinely in the initial evaluation [EL2]

The diagnostic approach is crucial in the management of fistulizing perianal CD, since the findings influence the therapeutic strategy. Various tools have been described, including EUA, fistulography and imaging by EUS or MRI.[189] Since inflammation in the affected bowel segment determines whether medical therapy is combined with surgical drainage, endoscopy is best combined with anatomical definition of the fistulous track.[188]

EUA is reported to be the most sensitive, with an accuracy of 90%.[195,197] It has the advantage of allowing concomitant surgery, but care must be taken to obtain appropriate informed consent before the operation in case of unexpected findings. When perianal pain is present an abscess is almost always the cause. If an abscess is present or suspected, prompt EUA including drainage is the procedure of choice to prevent the destructive effective of undrained sepsis. It should not be delayed until an MR scan has been performed, unless the scan is immediately available. Nevertheless, MRI has an accuracy of 76–100% compared to EUA[198,199] for fistulae and may provide additional information. Anorectal ultrasound has an accuracy of 56–100%, especially when performed by experts in conjunction with hydrogen peroxide enhancement.[200] Any of these methods can be combined with endoscopy to assess the presence or absence of inflammation in the rectosigmoid colon. Anecdotal experience indicates that treatment of fistulae is unsuccessful without treatment of underlying, active disease.[201,202]

9.2 2 Classification of perianal fistulae

ECCO statement 9C

There is no consensus for classifying perianal fistulae in CD. In clinical practice most experts use a classification of simple or complex [EL5]

Various classifications have been proposed, either relating fistulae to the anorectal ring [high or low], or in more precise anatomical terms where the external sphincter is the reference point, as described by Parks.[203] A more empiric and easier classification into simple and complex fistulae has been proposed.[204] This includes the physical inspection of the area to detect fistulous connections, strictures and abscesses, together with endoscopic evaluation of the rectosigmoid area for the presence or absence of macroscopic inflammation.

ECCO statement 9D

Pelvic floor dysfunction can be addressed in individual patients and in cases of severe impairment a specific rehabilitation program is recommended [EL4]

Individual patients may suffer from pelvic floor dysfunction upon recurrent or severe perianal disease. Specific rehabilitation programmes have proven to be effective in other indications and may be suggested to CD patients.

9.3 Treatment of fistulating disease

9.3.1 Simple perianal fistulae

ECCO statement 9E

In an uncomplicated low anal fistula, simple fistulotomy may be discussed [EL5]. The presence of a perianal abscess should be ruled out and if present should be drained [EL5]

ECCO statement 9F

Symptomatic simple perianal fistulae require treatment. Seton placement in combination with antibiotics (metronidazole and/or ciprofloxacin) is the preferred strategy [EL3]. In recurrent refractory simple fistulising disease not responding to antibiotics, thiopurines or anti-TNFs can be used as second line therapy [EL4]

Asymptomatic fistulae in CD patients do not require specific treatment.

In contrast, when a simple perianal fistula is symptomatic, opinion favours a combined medical and surgical strategy. Pain in patients with a simple fistula is most often caused by an underlying abscess and most agree that this must be ruled out by EUA complemented with pelvic MRI or ano-rectal ultrasound when indicated. Surgical drainage of the abscess is the first step in therapy. Seton placement has proven to be effective in simple perianal fistula,[205] but criteria for seton removal have not been defined.

9.3.2 Complex perianal disease

ECCO statement 9G

Seton placement after surgical treatment of sepsis is recommended for complex fistulae [EL2]. The timing of removal depends on subsequent therapy

ECCO statement 9H

Active luminal Crohn's disease should be treated if present, in conjunction with appropriate surgical management of fistulae [EL5]

ECCO statement 9I

In complex perianal fistulising disease infliximab [EL1] or adalimumab [EL2] can be used as first line therapy following adequate surgical drainage if indicated. A combination of ciprofloxacin and anti-TNF improves short term outcomes [EL1]. To enhance the effect of anti-TNF in complex fistulising disease, combination of anti-TNF treatment with thiopurines may be considered (EL5]

ECCO statement 9J

Imaging before surgical drainage is recommended. EUA for surgical drainage of sepsis is mandatory for complex fistulas [EL4]. In complex fistulas, abscess drainage and loose seton placement should be performed [EL4]

9.3.3 Medical therapy

Metronidazole and or ciprofloxacin

Uncontrolled case series are the only real evidence for using these agents in these patients.[206–208] A small RCT comparing metronidazole 500 mg [*n*=8] and ciprofloxacin 500 mg [*n*=10] to placebo [*n*=7] twice daily showed no significant benefit of either antibiotic therapy over placebo for cessation of drainage or for improvement.[209] Taken together, antibiotics are effective for improving symptoms of the disease, but rarely induce complete healing. Exacerbation is the rule when these drugs are discontinued. In an updated and comprehensive systematic review of all RCTs evaluating antibiotics for induction and maintenance in IBD, there were three trials evaluating perianal CD fistula in 123 patients, using either ciprofloxacin or metronidazole. There was a statistically significant effect in reducing fistula drainage (relative risk [RR]=0.8; 95% CI=0.66–0.98] with no heterogeneity [I2=0%] and an NNT of 5 [95% CI=3–20].[210]

Azathioprine/mercaptopurine: There are also no RCTs assessing the effect of azathioprine or 6-mercaptopurine on the closure of perianal fistulae as the primary end-point in CD. Data favouring the use of these drugs come from a meta-analysis of five RCTs where perianal fistula closure was assessed as a secondary end-point,[211] in addition to uncontrolled case series. In this context, azathioprine and 6-mercaptopurine appear to be effective in both closing and maintaining closure of perianal fistulas.[212]

Anti-TNF agents

Infliximab: Infliximab was the first agent shown to be effective in an RCT for inducing closure of perianal fistulae and for maintaining this response over 1 year. For treatment of simple or complex perianal fistulae, 5 mg/kg infusions at weeks 0, 2 and 6 induced complete closure [cessation of all drainage at two visits, 1 month apart] in 17/31 (55%] of cases.[213] The ACCENT II trial confirmed this initial response [69%, or 195/306 at 14 weeks], and randomized responders to receive 5 mg/kg every 8 weeks, or placebo.[214,215] At week 54, 33/91 [36%] receiving infliximab had complete closure compared to 19/98 [19%] on placebo [*p*=0.009]. Response, defined as >50% closure on clinical assessment, was seen in 46% with pnfliximab [23% placebo, *p*=0.01]. Maintenance infliximab reduces hospitalization and surgery.[216] These effects have been confirmed in clinical practice by several uncontrolled case series.[217,218] There are no data on the effect of infliximab on simple Crohn's perianal fistulas. In a recent retrospective study, long-term outcome after infliximab treatment for fistulizing perianal CD was evaluated in 156 patients. After a median follow-up of 250 weeks, about two-thirds of patients had fistula closure, though one-third had fistula recurrence. Combination therapy, seton drainage less than 34 weeks and long-term treatment with infliximab were associated with better outcomes[219].

Adalimumab: Despite the lack of RCTs where closure or improvement of drainage from perianal disease has been the primary endpoint, compete closure [cessation of drainage from all fistula orifices] and fistula improvement has been a secondary endpoint in two short-term [4 week] clinical trials comparing adalimumab to placebo. In CLASSIC-1[220] and GAIN,[221] adalimumab was no better than placebo, but only 32 [naïve for anti-TNF] and 45 [infliximab-failure] patients with fistulae were evaluated, respectively. In the more extensive CHARM trial, 117 of the 778 patients had actively draining perianal fistulae.[222,223] Fistula remission was more often observed in adalimumab-treated patients at week 26 [30 vs 13%, $p<0.04$] and at week 56 [33 vs 13%, $p<0.02$]. In an open-label trial [22 patients, treated with 160/80 mg induction], 23% had fistula remission at 4 weeks.[224] In an open-label trial to evaluate adalimumab therapy for clinical effectiveness, fistula healing, patient-reported outcomes and safety in 304 CD patients, including 68 patients with fistula, fistula healing rates at week 12 were 48% for anti-TNF-naive patients and 36% for infliximab-experienced patients. At week 24, fistula healing rates were significantly greater for the anti-TNF-naive group [60 vs 28%; $p<0.01$].[225] The CHOICE trial was an open-label, single-arm, multi-centre, phase IIIb trial evaluating the safety and effectiveness of adalimumab in patients with moderate-to-severe CD who had failed to respond or had lost response to infliximab. In total, 83 patients with a draining fistula were assessed. Draining fistula decreased by 41.3% at the last visit compared with baseline, at which time approximately 40% of patients [34 of 88 patients] had complete fistula healing.[226]

Certolizumab: One 20-week trial with open-label induction [PRECiSE 2] and one induction and maintenance trial [PRECiSE 1] assessed certolizumab [CZP] 400 mg at 0, 2 and 4 weeks [compared with placebo in PRECiSE 1] and then 400 mg or placebo every month.[227,228] In PRECiSE 1, 107 patients had draining fistulae at baseline; at week 26, 30% of CZP and 31% of placebo patients achieved fistula remission. In PRECiSE 2, 58% of patients had perianal fistulae draining at baseline; at week 20, 54% [CZP] vs 43% [placebo] (n.s.] had achieved fistula remission. A limitation of these studies is that they were not powered for finding a difference in fistula remission, but the results do not support benefit. A subanalysis from patients with draining fistula responding to treatment after open-label induction, thereafter randomized to CZP 400 mg [n = 28] or placebo [n = 30] every 4 weeks, demonstrated that 36% of patients in the CZP group had complete fistula closure at week 26, compared with 17% of patients receiving placebo [p = 0.038]. However, protocol-defined fistula closure [>/=50% closure at two consecutive post-baseline visits >/=3 weeks apart] was not statistically different [p = 0.069] with 54 and 43% of patients treated with CZP and placebo achieving this end point, respectively.

Combination of ciprofloxacin and anti-TNF

One pilot trial and one RCT evaluating the additive effect of ciprofloxacin to anti-TNFs showed that combination therapy is more effective than anti-TNF monotherapy to achieve fistula closure in CD at week 12.[229,230]

Cyclosporin (CsA]: The only data on intravenous CsA in perianal CD come from several uncontrolled case series which include fewer than 100 patients.[231] Patients who responded were converted to oral CsA, but response was rapidly lost on drug withdrawal.

Tacrolimus: Uncontrolled case series indicated that tacrolimus may be effective for perianal disease, and a subsequent small, placebo-controlled trial showed that oral tacrolimus 0.2 mg/kg/day enabled disease response [closure of at least 50% of fistulae] but not remission [closure of 100% of fistulae] at 4 weeks.[232–236]

Other treatments: Case reports and uncontrolled case series have reported benefit from enteral or parenteral nutrition, mycophenolate mofetil, methotrexate, thalidomide, granulocyte colony-stimulating factor and hyperbaric oxygen, but they are not recommended for standard practice.[237] Initial experience with locally injected stem cells, both with expanded adipose-derived allogeneic mesenchymal stem cells and with autologous bone marrow-derived mesenchymal stromal cells, have shown beneficial effects.[191,238,239]

9.3.4 Surgical procedures for perianal CD

Surgical treatment is sometimes necessary for simple fistulae, but is always necessary for complex perianal disease. It includes abscess drainage and seton placement, according to the symptoms and complexity of the fistulae.[240] Fistulectomy and fistulotomy should only be performed very selectively, because of the risk of incontinence. A diverting stoma or proctectomy may be necessary for severe disease refractory to medical therapy. Uncontrolled evidence suggests that local injection of infliximab close to the fistula track may be beneficial in patients not responding to or intolerant of intravenous infliximab.[241,242] Similar beneficial results have been reported with locally injected adalimumab.[243,244]

During the last 10 years, several small cohort studies have shown that the combination of seton placement *and* infliximab is superior to either strategy alone, probably because of better drainage of abscesses and fistulae.[245] This combination gives better response, longer effect duration and lower recurrence rates.[246–248] Moreover, reparative surgery [e.g. mucosal flap or fistula plug] during infliximab therapy may improve long-term healing rates.[248] More recently, a systematic review confirmed that combined surgical and medical therapy may have beneficial effects on perianal fistula healing in patients with CD compared with surgery or medical therapy alone.[249] The important principle is that undrained perianal sepsis is destructive to perianal structures, including sphincters, and optimal management involves both colorectal surgeons and gastroenterologists experienced in the management of CD. Collaboration between surgeons and physicians, and particularly a multidisciplinary approach, is important.[190] Nevertheless, a recent retrospective study has reported that only a minority of CD complex perianal fistulas were in remission after conventional treatment strategies.[250]

9.3.5 Monitoring the therapeutic response

ECCO statement 9K

In evaluating the response to medical or surgical treatment in routine practice, clinical assessment (decreased drainage) is usually sufficient [EL2]. MRI [EL2] or anal endosonography [EL3] in combination with clinical assessment is recommended to evaluate the improvement of fistula track inflammation [EL5]

Consensus views

Most participants report using more that one method to assess the therapeutic response. Clinical assessment, as described by Present,[76] which defines cessation of drainage despite gentle pressure in >50% fistulae after treatment, or MRI were preferred by 59 and 53%, respectively. Some [34%] use the Perianal [Crohn's] Disease Activity Index [PCDAI] alone or in combination with other techniques. Endoanal ultrasound was used by <20%. The PCDAI has the advantage of providing a quantitative assessment and encompasses several criteria of disease activity including discharge, pain, restriction of sexual activity, induration and type of fistula.

9.4 Continuing therapy for perianal CD

ECCO statement 9L

Thiopurines [EL2], infliximab [EL1] or adalimumab [EL2], seton drainage, or a combination of drainage and medical therapy [EL3] should be used as maintenance therapy

There are no data on the effect of azathioprine/6-mercaptopurine as maintenance therapy for fistulae after induction with infliximab, or during infliximab maintenance therapy. Around 75% of patients in the ACCENT II trial were already on azathioprine/6-mercaptopurine[214,215] prior to recruitment, but this medication was continued together with infliximab in only 30%. This implies that although infliximab maintained longer fistula closure than placebo in this trial, it occurred with azathioprine/6-mercaptopurine as background therapy in some cases.[214] Nevertheless for perianal disease, only maintenance therapy with infliximab has been shown to reduce hospitalization and surgery.[216] For adalimumab, controlled maintenance data with perianal fistulizing disease as a primary endpoint indicate efficacy but data on reduction of hospitalization and surgery for patients with fistulizing disease are not available.

9.4.1 Therapeutic approach in the event of medical treatment failure

ECCO statement 9M

Patients refractory to medical treatment should be considered for a diverting ostomy, with proctectomy as the last resort [EL5]

9.4.2 Surgical intervention in conjunction with infliximab treatment

There is real concern about the use of anti-TNF treatment in the presence of perianal sepsis. It is, therefore, important to exclude sepsis with MRI or EUS, and if found perform surgery [EUA] including abscess drainage and seton placement before, or at the start of, infliximab therapy, to avoid septic complications and optimize therapeutic results.

9.5 Management of non-perianal fistulating CD

There are no RCTs on the effect of medical treatment for non-perianal fistulating CD other than the subgroups of several trials.

9.5.1 Enterocutaneous fistulae

Enterocutaneous fistulae can be primary, early postoperative [within 7–14 days of surgery] and late [≥3 months following surgery]. They can be complicated by abscess or the high output of small intestinal content. The management of enterocutaneous fistulae in CD is complex and requires a combined medical and surgical approach. In cases of low output fistulae not complicated with abscess, they can be treated with immunomodulators and biologics, but respond less well than perianal fistulae. In case of high output fistulae and fistulae complicated with abscess or bowel stricture, they have to be treated surgically.

Fewer than 10% of the patients in the ACCENT II trial receiving infliximab had abdominal enterocutaneous fistulae.[214]

In the CLASSIC I trial, there were 32 patients with enterocutaneous and perianal fistula, assessed together with response to adalimumab no different from placebo.[220] The same results were observed in the CLASSIC II trial, again with all types of fistula in one group.[251] In the GAIN trial, a group of 45 patients with abdominal or perianal fistulas had better results in the placebo group compared with adalimumab group.[221] In the CHARM study, there were 130 patients with enterocutaneous or perianal fistulas, where fistula closure occured more frequently in patients receiving adalimumab maintenance therapy compared with those receiving placebo. Again, there was no breakdown of this subgroup.[222] In the ACCESS trial, there were 69 patients with draining fistula, where anti-TNF-naive patients had better healing rates [60%] than anti-TNF-experienced [28%], but subgroups cannot be analysed regarding the type of fistulae.[225] In the CARE trial, the fistula healing rate was 33% in the anti-TNF-naive group and 22% in the anti-TNF-experienced group, again without analysis by the type of fistula.[252] There is a small study from Poland with 29 patients who were treated with infliximab and adalimumab with 28% healing of enterocutaneous fistula.[253] A multi-centre study from Spain with 26 patients with enterocutaneous fistula showed 67% of patients with improvment of drainage with infliximab.[254]

9.5.2 Enteroenteric fistulae

Enteroenteric fistulas are common in CD, the most common being ileo-ileal or ileo-caecal. They do not bypass long segments of intestine, often are asymptomatic and usually do not require surgery. They cause major problems if complicated with abscess.

Duodeno-colic and ileo-sigmoid fistulas are less common but can cause excessive diarrhoea and severe malabsorption due to intestinal bypass and small intestinal bacterial overgrowth. Surgery is indicated for entero-enteric fistulas if associated with abscess or stricture, often following attempts to drain the abscess prior to surgery. Medical therapy includes thiopurine and anti-TNF agents. Internal fistulas respond less well to anti-TNF treatment than perianal fistulas and often require resective surgery.

9.5.3 Enterovesical fistulae

Medical therapy for enterovesical fistula includes antibiotics to treat urinary tract infection, immunomodulators and biologics. Surgery is needed in cases or recurrent urosepsis or abscess development.

ECCO statement 9N

Enteroenteric and enterovesical fistulae often require resective surgery [EL5]. Surgery is strongly recommended for enteroenteric fistulas if associated with abscess and bowel stricture and if they cause excessive diarrhea and malabsorption [EL5]

ECCO statement 9O

Asymptomatic low anal-introital fistulae do not need surgical treatment [EL5]. If a patient has a symptomatic rectovaginal fistula, surgery is usually necessary (including diverting ostomy) [EL5]. Active CD with rectal inflammation should be treated medically prior to surgery and after surgery to prevent recurrence [EL5]

9.5.3 Enterogynaecological fistulae

Intestinal small bowel or sigmoid gynaecological fistulae can usually be treated with resection of the diseased bowel segment. The data on medical treatment are scarce.

For the 25 patients with rectovaginal fistulae [out of 282] in the ACCENT II trial, infliximab was only modestly effective [45% closure at week 14].[214] A Spanish study with 47 patients with 75% rectovaginal fistulas, 21% anovaginal/anovulvar fistulas and with 4% enterovaginal fistulas showed that antibiotics were without effect. Thiopurine therapy resulted in complete remission in 13% and in partial response in 24% of patients. Infliximab therapy resulted in 17% patients with complete response and in 30% with partial response.[255]

Complete closure of rectovaginal fistula with anti-TNF agents can occur rarely. Surgical repair of fistulas with mucosal advancement flaps are succesfull in only 50% of cases. Recurrence rates are very high unless bowel CD is controlled with medical therapy.

10.0 Extraintestinal manifestations of CD

10.1 Introduction

The following section provides a condensed summary of the ECCO extraintestinal manifestation [EIM] guideline published in 2015.[256] EIMs are common in CD affecting up to 35% of patients [257–259] and their prevalence accumulates during the disease course. EIMs may even precede the diagnosis of IBD; for example, in a paediatric IBD registry 6% of IBD patients presented with at least one EIM before the diagnosis of IBD. The cumulative incidence of EIMs was 9, 19 and 29% after 1, 5 and 15 years of disease duration, respectively.[260] Most reports are retrospective and based on reviews of patients' files. The occurrence of one EIM seems to predispose to others; in addition family history of IBD was reported as a predisposing factor.[261] Some EIMs are related temporally to CD activity, while others more usually run an independent course. Peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis belong to the former group, while pyoderma gangrenosum, uveitis, axial arthropathy and primary sclerosing cholangitis [PSC] are characteristic of the latter.

For those EIMs closely related to CD activity, treatment can parallel that of the underlying disease. Treatment otherwise is mainly on a 'case by case' basis as RCTs are lacking.

10.2 Arthropathy

ECCO Statement 10A

Diagnosis of arthropathy associated with IBD is made on clinical grounds based on characteristic features and exclusion of other specific form of arthritis [EL3]

Arthropathy associated with CD belongs to the concept of spondylarthritis and includes axial arthropathy [EL2]. Type I is pauciarticular and affects large joints acutely at times of IBD activity, while type II is polyarticular, affecting a larger number of peripheral joints independently of IBD activity [EL2]. Axial arthritis, including sacro-iliitis and ankylosing spondylitis [AS], is diagnosed on conventional rheumatological grounds, and is supported by characteristic radiological changes, MRI being the most sensitive [EL2]. Although HLA-B27 is over-represented in axial arthritis related to CD, it is without diagnostic value [EL2]

10.2.1 Peripheral arthropathy

The Oxford group classified peripheral arthropathy into type I and type II, but only type I is associated with intestinal disease activity.[262,263] Type 1 is pauci-articular and affects large [predominantly weight-bearing] joints including the ankles, knees, hips, wrists and sometimes elbows and shoulders. By convention fewer than five joints are affected. The arthritis is acute, self limiting [weeks rather than months] and typically asymmetric. This arthropathy is observed in 4–17% of patients with CD[257,263,264] and may be present in around 15% at the time of diagnosis.[257,264] Type II is a polyarticular arthritis mainly affecting the small joints of the hand but independent of CD activity and is observed in about 2–4% of patients with CD. The diagnosis of arthritis is made clinically on finding painful swollen joints [synovitis]. The differential diagnosis includes osteoarthritis, rheumatoid arthritis and arthritis associated with connective tissue diseases, such as lupus. It has to be differentiated from arthralgia [which may complicate corticosteroid withdrawal], osteonecrosis related to corticosteroids and infliximab related lupus-like syndrome.[265]

10.2.2 Axial arthropathy

Axial arthropathy includes sacroiliitis and spondylitis. Irrespective of the presence of inflammatory back pain, isolated radiographic sacroiliitis has been found in 25–50% of patients with CD.[263,266,267] The diagnosis of AS according to the modified Rome criteria[268] includes a chronic inflammatory back pain [at night and at rest, improving by exercise], morning stiffness, limited spinal flexion and, in later stages, reduced chest expansion. Radiographs demonstrate sacroiliiits, syndesmophytes and bone proliferation evolving to ankylosis ['bamboo spine']. The current gold standard of diagnostic modalities is MRI due to its ability to demonstrate inflammation before bone lesions occur.[269,270] The overall prevalence of AS in IBD ranges from 4 to 10%.[257,263,267] HLA-B27 is found in 25–75% of patients with CD and AS[263,271,272] but only in 7–15% of patients with isolated sacroiliitis. HLA-B27-positive IBD patients seem to be at risk for the development of AS.[272]

10.2.3 Treatment of arthropathy related to CD

ECCO Statement 10B

In the case of peripheral arthritis there is general support for use of physiotherapy, short term treatment with non-steroidal anti-inflammatory agents, and local steroid injections [EL4]. The emphasis should be on treating the underlying Crohn's disease [EL2]. Sulfasalazine has a role in persistent peripheral arthritis [EL2]

Recommendations for the treatment of IBD-related arthropathy are based on studies in spondyloarthropathy, predominantly AS.[273] No single prospective RCT in IBD patients is available in the literature. Only small open-label trials or case reports are published.[264,274–276]

The treatment of arthropathy should be based on the severity of symptoms and association with the IBD activity.[277] The primary aim is symptomatic control and preservation of mobility and function. In peripheral arthritis the emphasis should be on the treatment of the underlying CD, including corticosteroids, immunomodulators and anti-TNF agents as appropriate. Symptomatic relief may be obtained by rest and physiotherapy. If arthropathy exists or persists independent of active intestinal disease, it is best treated, with caution, as a primary articular disease. This represents an important dilemma in CD patients with peripheral arthritis, where non-steroidal anti-inflammatory drugs

ECCO Statement 10C

In axial arthropathy evidence supports the use of intensive physiotherapy [EL2], and NSAIDs, but due to safety concerns long-term treatment with NSAIDs is best avoided if possible [EL2]. Anti-TNF is the preferred treatment of ankylosing spondylitis intolerant or refractory to NSAIDs [EL2]. Sulfasalazine [EL2], methotrexate [EL2] and thiopurines [EL4] are only marginally effective

[NSAIDs] remain the mainstay of therapy. Although there is concern that NSAIDs may aggravate the underlying CD,[278–280] this risk seems low, particularly if prescribed at low dose and for short duration.[281] The use of COX-2 inhibitors such as etoricoxib and celocoxib[282,283] is controversial due to long-term safety concerns. A beneficial effect of sulfasalazine on large joint arthropathy has been reported.[284,285] Several open-label studies and some controlled trials have demonstrated a significant effect of infliximab on peripheral arthritis.[286]

Recently an integrated management of different clinical scenarios in patients with IBD and spondyloarthritis has been proposed.[273] A multidisciplinary approach with a joint outpatient clinic with gastroenterologist and rheumatologist would be ideal, but is not always achievable. However, strict cooperation is necessary, because often patients with IBD and spondyloarthritis are underdiagnosed and effective treatment is delayed, which may lead to a chronic debilitating disease course and decreased quality of life.[287]

Treatment of axial arthropathy in CD is based on evidence from AS. It should include intensive physiotherapy. NSAIDs are the mainstay of medical therapy and recommended as first-line therapy in AS. However, long-term treatment with high-dose NSAIDs is generally inadvisable in patients with CD. Local corticosteroid injections can be considered. Systemic steroids, sulfasalazine, methotrexate and azathioprine are considered to be ineffective or only marginally effective in AS with axial symptoms.[288] In patients with active AS refractory to or intolerant of NSAIDs, anti-TNF agents are recommended. The efficacy and safety of infliximab and adalimumab in AS is now well established.[286,288–293] and open-label studies demonstrate their efficacy also in treating AS in patients with CD. Etanercept is not recommended because of the lack of effect in CD and its association with a possible flare up of IBD.[293]

10.3. Metabolic bone disease

Low bone mass and osteoporosis are common in both male and female patients with CD (20–50%].[294] Contributing factors include chronic inflammation, corticosteroid treatment, extensive small bowel disease or resection, age, smoking, low physical activity and nutritional deficiencies.[295] Diagnosis of osteoporosis is best made by a T score <–2.5 on bone densitometry [dual-energy X-ray absorptiometry scanning] in patients over 50 years old; in patients under 50 'low bone mass' is defined by a Z-score < 2.0 [EL1]. The precision and reproducibility of ultrasound and quantitative-CT is not sufficient for repeated clinical measurements.[296] In patients undergoing contrast-enhanced CT enterography, bone mineral density can be determined with good accuracy.[297]

The presence of osteoporosis is one [but not the only] risk factor for fractures of the spine and peripheral long bones. In recent studies, vertebral fractures have been documented in patients with reduced and normal bone density, challenging the concept that osteoporosis is the main risk factor for vertebral fractures in young patients with IBD.[298–300] The strongest predictor of future fracture is a prior vertebral fracture. There is, therefore, a need for prospective studies in young and premenopausal IBD patients to establish a valid assessment tool [e.g. FRAX index].[301]

ECCO Statement 10D

Patients on corticosteroid therapy or those with reduced bone density should receive calcium and vitamin D supplements [EL2]. Isotonic exercise [EL2] and cessation of smoking [EL2] are beneficial. Patients with established fractures should be treated with bisphosphonates [EL2]. The efficacy of primary prevention of fracture with bisphosphonates has not been demonstrated. Routine hormone replacement in postmenopausal women is not warranted due to the risk of side effects. Men with low testosterone may benefit from its therapeutic administration [EL3]

Treatment with calcium 500–1000 mg/day and vitamin D [800–1000 IU/day] increase bone density in patients with IBD.[295] The value of calcium and vitamin D in preventing fractures has not been demonstrated in patients with IBD, although they have value in postmenopausal or steroid-induced osteoporosis. Vitamin D supplementation may improve bone turnover parameters.[294,302] Various bisphosphonates increase bone density in patients with CD [for review see reference[295]. Fracture prevention with bisphosphonates has been clearly established in postmenopausal women and steroid-induced osteoporosis but not in young, premenopausal patients with CD, although pooled data suggest efficacy in preventing vertebral fractures.[303] Therefore, a general recommendation of treatment with bisphosphanates on the basis of reduced bone density is not feasible. In individual patients with low bone density and additional risk factors treatment should be considered.[304] Prolonged steroid treatment should be avoided in patients with chronic active disease. It has been shown that a significant proportion of patients with CD are able to normalize their bone density after 3 years in stable remission.[305]

10.4. Cardiopulmonary disease

Cardiac involvement is considered rare and many times is subclinical [EL3]. While increased risk of venous thromboembolic events is now well established, the risk of cardiovascular disease has been debated. Since the publication of a meta-analysis reporting no increased risk of cardiovascular mortality[306] several studies,[307–311] but not all,[312] have reached opposite conclusions, and shown an increase risk of ischaemic heart disease. The treatment of IBD-related cardiac involvement depends on the specific pattern of involvement and patients should be referred to a cardiologist.

Pulmonary disease represents a rare extraintestinal manifestation of IBD, but its true prevalence is unknown. Respiratory symptoms may be present in >50% of IBD patients[313,314] [EL3], and although these are often mild, attributed to smoking or ignored, more recent studies suggested a possible association between airways disease and CD, for example asthma in population-based studies.[315–319]

10.5 Hepatobiliary disease

ECCO Statement 10E

Magnetic resonance cholangiography is now established as the first-line diagnostic test for primary sclerosing cholangitis [EL2]. Primary sclerosing cholangitis substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma [EL1]

Liver test abnormalities are common in IBD although more often associated with hepatobiliary disease in UC than in CD, and are associated with a small but significant reduction in survival [EL2]. PSC[320] is less common in CD than in UC. However, pericholangitis, steatosis, chronic hepatitis, cirrhosis and gallstone formation are also over-represented. In addition, many of the drugs used for CD have the potential to cause hepatotoxicity. In most cases, PSC will be suspected by abnormal liver function tests [predominantly obstructive pattern] on routine screening rather than symptoms or signs of liver disease. If ultrasound scanning is normal and drug side effects have been thought unlikely, and serological tests for other primary liver disease are negative then the probability of PSC is significantly increased. The most accurate imaging diagnostic test is magnetic resonance cholangiography [MRCP], which will show the characteristic pattern of irregular bile ducts, with zones of both narrowing and dilatation.[321,322] If MRCP is normal, a liver biopsy should be considered [given probable predominant small duct disease] to confirm a suspected diagnosis. Its accuracy is superior to that of a diagnostic endoscopic retrograde cholangiography [ERCP].[322,323] PSC is a major risk factor for cholangiocarcinoma and colon cancer.[323,324]

ECCO Statement 10F

Ursodeoxycolic acid improves abnormal liver function tests [EL1] but not histology and prognosis in PSC. ERCP should be used to treat dominant strictures by dilatation and/or stenting [EL4]. Advanced liver disease may necessitate transplantation [EL2]

Ursodeoxycholic acid [UDCA; ursodiol] (up to 20 mg/kg daily] was shown to improve liver enzymes, reduce liver fibrosis and reduce progression in cholangiographic appearances.[325,326] In a placebo-controlled trial, UDCA at high daily doses (28–30 mg/kg] led to worse outcomes [e.g. liver transplantation, oesophageal varices] in endstage PSC patients[327] and therefore should be avoided. Ursodiol may also reduce colon cancer risk,[328] although recent data are conflicting,[329,330] because data are limited.[331] ERCP may retain a place in the management of dominant biliary strictures[323] as dilatation of dominant strictures has been suggested to improve the course of the disease as well as survival.[332,333] In advanced disease with liver failure there is no alternative to liver transplantation.[323] A detailed clinical guideline has been published recently.[334]

10.6 Cutaneous manifestations

10.6.1. Erythema nodosum [EN]

ECCO Statement 10G

Diagnosis of the cutaneous manifestations of IBD are made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy can be helpful in atypical cases [EL3]

ECCO Statement 10H

Treatment of erythema nodosum is usually based on that of the underlying Crohn's disease. Systemic steroids are usually required [EL4]. Pyoderma gangrenosum is initially treated with systemic steroids [EL4], infliximab [EL2], adalimumab [EL4] or calcineurin inhibitors [EL4]

EN is usually readily recognized. It is characterized by raised, tender, red or violet subcutaneous nodules 1–5 cm in diameter. It commonly

affects the extensor surfaces of the extremities, particularly the anterior tibial areas and usually occurs at times of CD activity. A firm clinical diagnosis can normally be made and biopsy is not usually appropriate. If performed, the histology reveals a non-specific focal panniculits.[335,336] In recent publications the prevalence of EN in IBD and CD, respectively, ranged from 4.2 to 7.5%[258,261,337] and seems to be higher in CD than in UC.[337] The differential diagnosis includes metastatic CD, which may appear at any site as solitary or multiple nodules, plaques, ulcers or violaceous perifollicular papules, the histology of which includes non-caseating granulomas.[338] Because EN is closely related to disease activity despite a genetic link,[339] treatment is based on that of the underlying CD. Systemic steroids are usually required. In resistant cases or when there are frequent relapses, immunomodulation with azathioprine and/or infliximab can be tried,[340,341] but it is exceptional to need such measures solely to treat EN.

10.6.2. Pyoderma gangrenosum [PG]

Lesions are often preceded by trauma at the site through a phenomenon known as pathergy.[342] PG can occur anywhere on the body, including the genitalia, but the commonest sites are on the shins and adjacent to stomas. Initially they take the form of single or multiple erythematous papules or pustules, but subsequent necrosis of the dermis leads to the development of deep excavating ulcerations that contain purulent material that is sterile on culture unless secondary wound infection has occurred. In recent publications, 0.6–2.1% of CD patients developed PG.[261,337,343,344,345] PG may parallel the activity of the underlying CD or run a course that is independent of it. PG is a diagnosis of exclusion and might be misdiagnosed in a substantial percentage of cases.[346] Histopathological findings in PG are non-specific, but biopsy should be considered to exclude other specific skin disorders, although complications have been reported.[347]

Rapid healing should be the therapeutic goal, because PG can become a debilitating skin disorder. There is no evidence that the efficacy of treatment strategies for PG differs between IBD and non-IBD patients. Immunosuppression is the mainstay of treatment. The most commonly used drugs with the best clinical experience are systemic corticosteroids and ciclosporin.[348] Corticosteroids have been considered first-line treatment, with intravenous ciclosporin and tacrolimus reserved for refractory cases.[349–351] Infliximab has, however, changed the management of PG in patients with CD. Its effectiveness was first reported in small case studies.[352,353] A randomized, placebo-controlled trial with infliximab including 30 patients [19 with IBD][354] demonstrated at week 2 better significant response with infliximab (response 46% vs 6%, p=0.025]. After week 2 open-label infliximab in 29 patients led to 69% response and 31% remission at week 6, with better response in shorter duration lesions. In recent years, some case-series have demonstrated the efficacy of adalimumab in the treatment of PG.[355–357] No comparative trial of different drugs has been reported to date, but anti-TNF showing good and quick results should be considered in steroid non-responders.[358] In patients with peristomal PG, closure of the stoma might lead to resolution of the PG lesions.[359]

10.6.3. Sweet's syndrome

Sweet's syndrome is characterized by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face or neck.[360] It has only been recognized as an extraintestinal manifestation of IBD relatively recently.[361,362] It is part of the group of acute neutrophilic dermatoses that includes PG, but can be distinguished by its appearance, distribution and histological features. There is a strong predilection for women and patients with colonic involvement and other extraintestinal manifestations. The rash is mostly associated with active disease. Systemic corticosteroids have been reported to be effective. Immunosuppressants should be considered in resistant or highly relapsing cases.[363]

10.7 Venous thromboembolism

ECCO Statement 10l

Antithrombotic prophylaxis should be considered in all hospitalised and outpatients with severe disease [EL4]. Treatment of venous thromboembolism in IBD should follow established antithrombotic therapy options [EL1]

Patients with IBD are at increased risk for venous thromboembolism [VTE], which represents an important cause of morbidity and mortality,[364,365] but prophylaxis has been found to be clearly suboptimal.[366] The prevalence of VTE in IBD ranges between 1.2 and 6.7% in clinical studies, and the relative risk when compared to controls varies between 1.5 and 4.6 with higher figures in ambulatory patients.[364,367,368] However, this reflects the low risk in ambulatory control populations, and the absolute risk is clearly higher in hospitalized patients.([364,369] Pregnant IBD patients have a higher risk than controls;[370] paediatric IBD patients are at lower risk.[371,372] Deep venous thromboses [DVTs] of the leg and pulmonary emboli [PE] are the most common thromboembolic manifestations, but unusual sites of VTE, such as cerebrovascular, portal, mesenteric and retinal veins, have also been described.[364,371] The reason for the increased risk is not completely understood. Acquired risk factors appear to be most relevant and many of the haemostatic alterations parallel inflammatory activity.[373] Steroid use [compared with biological agents] has recently been identified as an important independent risk factor.[369,374] Active inflammation affects the clot lysis profile, and infliximab treatment significantly improves this.[375] Thus, the majority of VTE occurs during the active phase of IBD,[364] but a significant number of cases do occur in ambulatory, non-active cases.[376] Patients with CD should be informed about thrombotic risk factors such as oral contraceptive use and long-distance travel.

The diagnosis of VTE is not considered in further detail and should follow international guidelines[377,378] based on appropriate imaging techniques.

The mainstay of therapy of acute DVT and PE is anticoagulation and should follow guidelines.[379,380] The benefit of anticoagulant treatment is independent of the diagnosis of CD. In patients with acute DVT and/or PE, anticoagulant therapy should be continued, if possible, for at least 3 months using low-molecular-weight heparin, unfractioned heparin or fondaparinux for initial treatment followed by vitamin K antagonists. Long-term treatment should especially be considered for patients with a second episode of unprovoked VTE.[381] The risk of bleeding complications of IBD patients taking anticoagulant therapy compared to non-IBD patients is not known, although observational data suggest this is not higher than in controls.[382]

Hospitalization for an acute medical illness is independently associated with an 8-fold increased risk for VTE.[377] This risk can be reduced by anticoagulant prophylaxis with low-molecular-weight heparin, unfractioned heparin or fondaparinux.[377,383,384] There is recent evidence that this risk is clearly underestimated [384] and undertreated[366,368,383,385] in IBD patients. The number of IBD patients included in the studies was too small to draw any sufficient conclusions about the efficacy of anticoagulant prophylaxis specifically in

IBD.[364] However, hospitalized IBD patients have a higher rate of VTE than non-IBD hospitalized patients, with an associated increased age- and comorbidity-related excess mortality from VTE.[364] Hospitalized patients with acute severe or fulminant disease, as well as those with active fistulizing CD, are most appropriately treated with anticoagulant prophylaxis with low-molecular-weight heparin, unfractioned heparin or fondaparinux, especially in the event of prolonged immobilization.[384] Anticoagulant prophylaxis after abdominal surgery should follow established guidelines.[386]

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The CoI 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 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

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