European evidence based consensus on the diagnosis and management of Crohn’s disease: special situations


This third section of the European Crohn’s and Colitis Organisation (ECCO) Consensus on the management of Crohn’s disease concerns postoperative recurrence, fistulating disease, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations, and alternative therapy. The first section on definitions and diagnosis reports on the aims and methods of the consensus, as well as sections on diagnosis, pathology, and classification of Crohn’s disease. The second section on current management addresses treatment of active disease, maintenance of medically induced remission, and surgery of Crohn’s disease.

8.0 RISK FACTORS, PROPHYLAXIS, DIAGNOSIS, AND MANAGEMENT OF POSTOPERATIVE RECURRENCE OF CROHN’S DISEASE (CD)

8.1 Epidemiology of postoperative CD

In the natural history of CD, intestinal resection is almost unavoidable as about 80% of patients require surgery at some stage. Surgery is unfortunately not curative as the disease inexorably recurs. The postoperative recurrence (POR) rate varies according to its definition: clinical, endoscopic, radiological, or surgical. It is lowest when the repeat resection rate is considered, intermediate when clinical indices are used, and highest when endoscopy is used as a diagnostic tool.1–10

Data from endoscopic follow up of patients after resection of ileocaecal disease have shown that in the absence of treatment, the POR rate is around 65%–90% within 12 months and 80%–100% within three years of the operation. The clinical recurrence without therapy is about 20%–25% per year.1–10 It has been shown that the postoperative clinical course of CD is best predicted by the severity of endoscopic lesions. Symptoms, in fact, appear only when severe lesions are present, but it is not uncommon to see patients with fairly advanced recurrent lesions at endoscopy who remain asymptomatic.1–10 For these reasons, the sensitivity of the CDAI is poor at discriminating between patients with or without postoperative recurrence.11

8.2 Predicting postoperative recurrence

ECCO Statement 8A

Of the risk factors evaluated, four are considered predictors of early postoperative recurrence: absence of prophylactic treatment [EL1a, RG A], smoking, disease location, and extent [EL2b, RG B]

ECCO Statement 8B

Perforating behaviour has been considered a risk factor; nevertheless the data from the literature do not support this [EL2b, RG D]

Several studies have looked for potential risk factors for recurrence after surgery for CD. Only colonic location and extent of the disease >100 cm before surgery and the smoking status seem to be independent risk factors for increased risk of recurrence. Prophylactic medical therapy (below) has been shown to be effective in randomised controlled trials, confirmed by meta-analysis [EL1a]. The age at onset of the disease, sex, duration of the disease, resection margins, or number of previous resections seem

Abbreviations: 5-ASA, mesalazine; AZA, azathioprine; CD, Crohn’s disease; CDAI, Crohn’s disease activity index; CDAI, cyclosporin; ECCO, European Crohn’s and Colitis Organisation; IBD, inflammatory bowel disease; IFX, infliximab; 6-MP, 6-mercaptopurine; UC, ulcerative colitis
8.3 Diagnosis of postoperative recurrence

**ECCO Statement 8C**

Global physician assessment and acute phase reactants are used in clinical practice during follow up, but their accuracy has not been investigated [EL5, RG D]. The CDAI is an unreliable indicator of recurrence [EL2a, RGC].

**ECCO Statement 8D**

Ileocolonoscopy defines the presence and severity of morphologic recurrence and predicts the clinical course, so is recommended in all patients where recurrence is suspected [EL2a, RG B].

Diagnosis of POR may be based on clinical symptoms or endoscopic findings. Symptoms are not always easily distinguishable from other postoperative conditions (such as pain attributable to adhesional obstruction, calculi or dysmotility, and diarrhoea attributable to bile salt malabsorption or bacterial overgrowth). The CDAI has not been specifically validated in the postoperative setting, although a sensitivity of 30% and a specificity of 89% have been reported.69 Several studies have shown that colonoscopy is the most sensitive tool to report morphological recurrence.1 5 6 Endoscopic recurrence precedes clinical recurrence and severe endoscopic recurrence predicts a poor prognosis.1 5 6 Radiology and imaging (US, MR, CT) are used as surrogates for endoscopy.70 71

8.4 Medical prophylaxis

Available data do not show a robust protective effect for any medical therapy. This remains a contentious area and it is important that all consensus statements are read in the context of the qualifying comments.

**ECCO Statement 8E**

All patients should be encouraged to quit smoking after surgery for Crohn’s disease [EL1b, RG B]

**ECCO Statement 8F**

Prophylactic treatment is recommended after small intestinal resection. The drug of choice is mesalazine > 2 g daily [EL1a, RG B]. Imidazole antibiotics have been shown to be effective after ileocolic resection [EL1a, RG A]. Other drugs including azathioprine/6-mercaptopurine should be considered as first line therapy in high risk patients [EL2b, RG C]

**ECCO Statement 8G**

The start of prophylaxis is recommended within two weeks of surgery on the basis of pathophysiological considerations, although an early start has not been proved superior to later treatment [EL5, RG D]

8.4.1 Mesalazine (5-ASA)

Prophylactic treatment to reduce the rate of POR remains controversial.51 54 In the 1990s, several randomised controlled trials showed that oral 5-ASA, given early after surgery, was able to reduce the frequency of recurrence and to attenuate its severity.5 56 It may be argued that the data are flawed and that one of the original studies57 would have been negative had a two tailed test been used more appropriately for statistical analysis. Furthermore, the other early study5 had endoscopic end points and was not blinded. In 1997 a meta-analysis from Camma et al58 showed that 5-ASA was superior to placebo for the prevention of clinical POR. This meta-analysis has been updated twice, the first59 after the publication in 2000 of a large European cooperative study, and then60 after the publication of a second study by the Gruppo Italiano per lo Studio del Colon e del Retto (GISC61). The GISC study compared 5-ASA 2.4 g with 4.0 g did not include a placebo control group and failed to show a benefit for either clinical or endoscopic recurrence. The European cooperative study62 showed that 5-ASA 4.0 g/day did not significantly affect clinical overall POR. It included, however, a substantial subgroup of 124 patients who had had isolated resection of small bowel CD who did benefit from treatment with 5-ASA 4.0 g/day compared with placebo. The updated meta-analysis63 included this large European trial and remained in favour of treatment with 5-ASA. Subsequently, the 206 patients in the negative GiSC study64 permitted a further updated meta-analysis65 of six studies61-64-67-68 in a total of 1141 patients. The results showed that 5-ASA reduced the rate of endoscopic recurrence by 18%, which is a clinically relevant result (NNT = 5.5). For clinical recurrence the data still remain in favour of 5-ASA, with an overall risk difference of 15% (NNT = 6.6), which is also clinically relevant, although the meta-analysis has not yet been fully published. Nevertheless, given 5-ASA’s limited effect, no prophylactic treatment may be an option in some asymptomatic or low risk patients.

**ECCO Statement 8H**

The duration of prophylaxis should be at least two years [EL1a, RG B]
8.4.3 Azathioprine/6-mercaptopurine

The thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP) are widely recommended for reducing the risk of POR after surgery for complex CD. The data are, however, open to interpretation. There was a trend for 6-MP 50 mg/daily to be more effective than placebo and 5-ASA in preventing clinical POR.17 The results of this study had originally been presented as an abstract six years previously.18 Observed rates of endoscopic recurrence (defined as Rutgeerts endoscopy score >1) at two years for placebo, 5-ASA, and 6-MP were 64%, 63%, and 43%, respectively, but the study had two main drawbacks. Firstly, the clinical recurrence rate (based on physician global assessment) in the placebo group at two years was higher than the endoscopic recurrence, which is unique. Secondly, of 131 patients enrolled only 57 completed the trial. The final analysis was therefore conducted on 57 patients, divided into three groups. Although the results of this study do not provide robust data in favour of 6-MP over placebo or 5-ASA, a further prospective study randomised 142 patients to receive AZA 2 mg/kg/day or 5-ASA 3 g/day for 24 months. This showed comparable rates of clinical (OR 2.04, CI 0.89 to 4.67) and surgical recurrence. Subgroup analysis showed a favourable effect of AZA for patients who had had a previous resection (OR 4.83, 95%CI 1.47 to 15.8).24

8.4.4 Other therapy

In controlled trials there is no evidence that probiotics,66 fishoil,67 or interleukin 10 therapy68 are effective at preventing POR after surgery for CD.

8.5 Management

**ECCO Statement 8I**

In asymptomatic patients, if colonoscopy is performed and mild lesions are found no change of therapy is recommended [EL1b, RG D]. Severe lesions are associated with high risk of clinical recurrence. Starting therapy with AZA/6MP may be considered, although its efficacy has not been firmly established in this setting [EL2b, RG D].

Management to reduce the risk of POR differs whether symptoms or endoscopic lesions are present. Not all gastroenterologists routinely perform colonoscopy after ileocaecal resection of CD. In asymptomatic patients with mild endoscopic lesions, there are no data showing the need to change therapy. In asymptomatic patients with severe endoscopic lesions, AZA therapy has been reported to be effective at healing the lesions and improving outcome.22 25

**ECCO Statement 8J**

Symptomatic patients should have a colonoscopy and be treated as any other patient with active disease [EL5, RG D].

Symptomatic patients are usually treated in the same way as those with active disease who have not had surgery.

**ECCO Statement 8K**

The risk of relapse does not seem to correlate with the type of operation, so patients undergoing conservative surgery should be treated in the same way as those who have an extensive resection [EL1b, RG B].

The extent of resection has not been shown to influence the risk of recurrence, but the decision on postoperative prophylaxis is best governed by what is at stake (proctectomy, short bowel syndrome) in the event of a further relapse. For patients who have had conservative surgery for CD, the risk of clinical relapse is comparable whether patients are treated by AZA or 5-ASA.24 26 However, in a subgroup analysis, AZA was significantly better than 5-ASA at preventing clinical relapse in patients who had had previous intestinal resections.26

9.0 DIAGNOSIS AND MANAGEMENT OF FISTULATING CD

9.1 Introduction

Fistulating CD includes fistulas 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 fistulas are:

- Locate the origin of the fistula and its anatomy
- Evaluate the originating intestinal loop (inflammation or stenosis)
- Identify or exclude local sepsis (abscesses)
- Determine which organs are affected and their contribution to systemic symptoms or impairment of the quality of life
- Assess the nutritional status of the patient

Most emphasis is placed on perianal fistulas complicating CD, as these are most common and supported by the largest body of literature. Nevertheless, the greatest limiting factor for this consensus was the scarce number of controlled data regarding combined medical and surgical management. Consequently this section includes more details on expert opinion (consensus views) quantified by the pre-consensus questionnaire, as this may help define current practice.

9.1.1 Perianal fistulas

In a series of 202 consecutive patients with CD at a teaching hospital up to 54% had suffered perianal complications.75 In population based studies,76 77 the occurrence varies between 21% and 23%. The cumulative frequency was 12% at 1 year, 15% at 5 years, 21% at 10 years and 26% at 20 years. The prevalence varies according to disease location. Perianal fistulas 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.77 Perianal disease often precedes or appears simultaneously with intestinal symptoms.75 77

9.1.2 Non-perianal fistulas

This includes fistulas communicating with other viscera (urinary bladder, vagina), loops of intestine (enteroenteral fistulae), or the abdominal wall (enterocutaneous fistulas). There is a notable lack of controlled data in this field.

9.2 Diagnosis of perianal fistulas

9.2.1 Initial diagnostic approach

The diagnostic approach is a crucial aspect in the management of fistulating perianal CD, as the findings influence the
therapeutic strategy. Various tools have been described, including examination under anaesthetic (EUA), fistulography, and imaging by endoscopic ultrasonography or magnetic resonance. As 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.

EUA is reported to be the most sensitive, with an accuracy of 90%,[1,2,3] It has the advantage of permitting 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, a prompt EUA is the procedure of choice to prevent the destructive effective of pus under pressure. It should not be delayed until an MR has been performed, unless the MR scan is immediately available. Nevertheless, MRI has an accuracy of 76%–100% compared with EUA[3,4,5] for fistulas and may provide additional information. Anorectal ultrasound has an accuracy of 56%–100%, especially when performed by experts in conjunction with hydrogen peroxide enhancement.[6,7,8] Any of these methods can be combined with the endoscopy to assess the presence or absence of inflammation in the rectosigmoid colon. Anecdototal experience indicates that treatment of fistulas is unsuccessful without treatment of underlying, active disease.

Consensus views
The preferred initial diagnostic approach was MRI (82% always or usually), plus proctosigmoidoscopy (75% always or usually). Depending on the circumstances and availability, 44% expressed a preference for EUA and 38% for endoanal ultrasonography for initial diagnosis.

9.2.2 Classification of perianal fistulas
Various classifications have been proposed, either relating fistulas to the anorectal ring (high or low), or in more precise anatomical terms where the external sphincter is the reference point, described by Parks.[9] A more empiric and easier classification into simple and complex fistulas has been proposed.[10] This includes the physical inspection of the area to detect fistulous connections, strictures, and abscesses, together with the endoscopic evaluation of the rectosigmoid area for the presence or absence of macroscopic inflammation.

Consensus views
Classification into simple and complex perianal fistulas based upon clinical and endoscopic features[11] was recommended by 75% and the Parks classification[12] by 25% who expressed an opinion. Other systems were not often used, although the perianal disease activity index (PDAI)[13] was used for overall assessment of perianal disease by 34% in some circumstances.

9.2.3 Influence of the treatment strategy on the diagnostic approach
Consensus views
Most (66%) consider that the medical or surgical treatment strategy should not influence the diagnostic approach. When surgery or medical therapy are planned, techniques designed to define the anatomical distribution of the fistulas are considered mandatory.

9.2.4 Progression from simple to complex disease in the short to mid-term
There are no objective data.

Consensus views
Most (72%) consider that simple fistulas rarely progress to complex fistulas in the short to mid-term (two years), although were this possible it would influence the therapeutic approach. Data are needed.

9.3 Treatment of fistulating disease
9.3.1 Simple perianal fistulas

Consensus views
Almost all used antibiotics as the first medical therapy option, AZA/6-MP as the second option, and infliximab as the third option (evidence below). However, when a simple perianal fistula is symptomatic in CD, opinion favours a combined medical and surgical strategy. Neither cyclosporin (CsA) nor tacrolimus were favoured as a fourth option.
9.3.2 Complex perianal disease

**ECCO Statement 9G**

Antibiotics and/or azathioprine/6-mercaptopurine should be used as the first choice of therapy for complex perianal Crohn’s disease in combination with surgical therapy despite a lack of clinical trials. The presence of a perianal abscess should be ruled out and, if present, it should be drained. Infliximab should be used as a second line treatment.

**ECCO Statement 9H**

Seton placement should be recommended. A diverting ostomy can rapidly restore the quality of life in highly symptomatic patients.

**Consensus views**

Most initially used the same type of medical treatment options as for simple perianal disease. However, there was less agreement on the sequence, especially for antibiotics as the first option, as earlier use of infliximab was generally recommended. Abscesses should be sought and surgical drainage must be performed if present.

9.3.3 Medical therapy

**Metronidazole and/or ciprofloxacin**

There are no randomised controlled trials (RCTs) on the effect of metronidazole and/or ciprofloxacin in perianal CD. Uncontrolled case series are the only basis for using these agents in these patients. Antibiotics are effective for improving symptoms of the disease, but rarely induce complete healing. Exacerbation is the rule when these drugs are withdrawn.

**AZA/6-MP**

There are also no RCTs assessing the effect of AZA or 6-MP on the closure of perianal fistulas as 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, in addition to uncontrolled case series. In this context, AZA and 6-MP seem to be effective in both closing and maintaining closure of perianal fistulas.

**Infliximab**

Infliximab was the first agent shown to be effective in an RCT for inducing closure of perianal fistulas and for maintaining this response for one year. For treatment of simple or complex perianal fistulas, 5 mg/kg infusions at weeks 0, 2, and 6 induced complete closure (cessation of all drainage on two visits one month apart) in 17 of 31 (55%) of cases. The ACCENT II trial confirmed this initial response (69%, or 195 of 306 at 14 weeks), and randomised responders to receive 5 mg/kg every eight weeks, or placebo. At week 54, 33 of 91 (36%) on infliximab had complete closure compared with 19 of 98 (19%) receiving placebo (p = 0.009). Response, defined as >50% closure on clinical assessment, was seen in 46% receiving infliximab (23% placebo, p = 0.01). Maintenance infliximab reduces hospitalisation and surgery. These effects have been confirmed in clinical practice by several uncontrolled case series. There are no data on the effect of infliximab on simple Crohn’s perianal fistulas.

CsA

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

**Tacrolimus**

Uncontrolled case series showed that tacrolimus may be effective for perianal CD. A subsequent small, placebo controlled trial showed that oral tacrolimus 0.2 mg/kg/day was better than placebo at improving (closure of at least 50% of fistulas), but not at inducing remission (closure of 100% of fistulas), in perianal CD after four weeks.

**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.

9.3.4 Surgical procedures for perianal CD

Surgical treatment is sometimes necessary for simple fistulas, but is always necessary for complex perianal disease. It includes abscess drainage, fistulotomy, and seton placement, according to the symptoms caused by the location and complexity of the fistulas. A diverting ostomy or proctectomy may be necessary for severe disease refractory to medical therapy. Fistulotomy and fistulotomy should not be performed, because of the risk of incontinence and later need of proctectomy.

9.3.5 Monitoring the therapeutic response

**ECCO Statement 9I**

In evaluating the response to medical or surgical treatment, or MRI were preferred by 59 and 53% respectively. Other treatments

**ECCO Statement 9J**

AZA/6-MP, with or without long term Seton drainage, should be used as maintenance therapy. If this fails, infliximab should be added for induction and maintenance for at least one year.
infliximab maintenance therapy. Around 75% of patients in the ACCENT II trial were already taking AZA/6-MP before 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 AZA/6-MP as background therapy in some cases. An additional reason for thiopurine therapy is to reduce the development of anti-infliximab antibodies. Nevertheless for perianal disease, it is only maintenance therapy with infliximab that has been shown to reduce hospitalisation and surgery.

Consensus views
More than 90% believe that maintenance therapy after successful infliximab induction is mandatory. The preferred drugs were AZA/6-MP or infliximab (in this order), with infliximab either as scheduled re-treatment every eight weeks, or as required in conjunction with thiopurines.

9.4.1 Therapeutic approach in the event of infliximab failure

**ECCO Statement 9K**

In the event of infliximab failure, the use of azathioprine/6-mercaptopurine or methotrexate, with antibiotics as adjunctive treatment, is the first therapeutic choice [ELS, RG D]. Depending on the severity of the disease, a diverting ostomy can be performed later, or proctectomy as the last resort [ELS, RG D].

Consensus views
In this event, surgical treatment (alone or combined with medical therapy) was suggested by about 50%. Among medical treatments, the preferred drugs were AZA/6-MP and MTX although some favoured a higher dose of infliximab.

9.4.2 Surgical intervention in conjunction with infliximab treatment

There is concern about infliximab treatment in the presence of undetected perianal sepsis. Surgery (by EUA) for perianal disease includes abscess drainage, fistulotomy, and Seton placement, and may be important to optimise therapeutic results as well as avoiding septic complications.

Consensus views
Most (78%) thought that it was only necessary in the presence of an abscess and 25% considered it mandatory (with the overlap representing those who felt an abscess could only be reliably excluded by EUA; note diagnosis section above). None thought that it should not be done. When asked if the surgical “toilette” should be performed before or after infliximab most (78%) believed that it should be done before.

9.5 Management of non-perianal fistulating CD

There are no RCT on the effect of medical treatment for non-perianal fistulating CD, other than the subgroups of the ACCENT II trial. Less than 10% of the patients in the ACCENT II trial receiving infliximab therapy had abdominal enterocutaneous fistulas. For the 25 (of 282) patients with rectovaginal fistulae in the ACCENT II trial, infliximab was only modestly effective (45% closure at week 14).
may be of more importance in paediatric CD, compared with adults.114

10.2 Diagnosis

**ECCO Statement 10A**

Initial investigation of a child suspected of CD should consist of colonoscopy (including terminal ileal intubation) with multiple biopsies [EL2b, RG B], and upper GI endoscopy with multiple biopsies [EL2b, RG B]. In addition to endoscopy, small bowel radiology (follow through or enteroclysis) should be performed [EL2b, RG B].

The IBD working group of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has reached a consensus on the diagnosis of IBD in children, which have been summarised as the “Porto Criteria”.117 This group feels it is essential to establish a diagnosis of the type of disease, as well as to determine severity, localisation, and extent of the disease, before treatment is started. The ECCO Consensus agrees that all children suspected of CD should have a complete examination at the time of diagnosis. Evidence from the literature supporting the colonoscopy with ileal intubation, and not simply sigmoidoscopy, is provided by retrospective cohort studies.118–122 Additional upper endoscopy is advised on the basis of both retrospective and prospective studies showing that histology of the upper GI tract may confirm a diagnosis of CD that would otherwise have been missed in 11% to 29% of cases.125–128 Small bowel radiology should be part of the initial investigation for the following reasons: firstly, the small bowel may be abnormal even though the terminal ileum is normal.129 In addition, small bowel follow through (SBFT) or enteroclysis with intubation of the duodenum with barium contrast will give information on extent and possible complications of small bowel CD including strictures or internal fistulas. The presence of small bowel strictures will affect therapeutic management, as inactive short segment stenosis may need resection. Transabdominal ultrasound is not a substitute, but may be used as for initial assessment of symptoms or to look for complications. Endoscopy in children is best carried out under general anaesthesia: it is safe and preferred for ethical reasons.131

10.3 Treatment

10.3.1 General

The medical treatment of CD in children is shifting towards a more aggressive approach at presentation of the disease. Immunosuppressants such as AZA are being introduced early. Evidence from clinical trials in children with CD is scarce, and treatment decisions are often based on extrapolation from clinical trials in adults. However, some good quality clinical trials have been performed during the past five years, providing the basis for these guidelines. Initial treatment of CD in children depends on disease severity and localisation. In mild disease, 5-ASA is often started although there is not one randomised clinical trial of 5-ASA in children. In moderate to severe disease, corticosteroids or nutritional treatment are primary treatment.

10.3.2 Induction therapy

Evidence from a meta-analysis of trials comparing efficacy of corticosteroids and nutritional treatment133 show that both options are effective (80% remission induction), but nutritional treatment is preferred because of lack of side effects and a beneficial effect on growth in children. Nutritional treatment is probably more effective in new onset disease than in recurrent disease, independent of disease severity or localisation. There is insufficient evidence to suggest that elemental (or oligomeric) formula is better than non-elemental (polymeric) formula feed.

**ECCO Statement 10B**

Both enteral nutrition (EN) and corticosteroids are effective for induction of remission (although EN lacks side effects), irrespective of disease activity or location [EL1a, RG A]. Enteral nutrition seems to be more effective in newly diagnosed CD patients. Elemental enteral formula is not more effective compared to polymeric formula feeds [EL3, RG C].

**ECCO Statement 10C**

Budesonide is effective and favoured over prednisolone in mild to moderate active ileocaecal CD because of significantly fewer side effects [EL1b, RG A].

In children with mild to moderately active ileocaecal CD, two randomised controlled trials supported the use of budesonide (controlled ileal release), which was less effective than prednisolone, but with significantly fewer side effects.134

**ECCO Statement 10D**

The role of mesalazine for inducing remission in children with active CD is unclear [EL2b, RG B].

10.3.3 Maintenance therapy

**ECCO Statement 10E**

Corticosteroids are not to be used as maintenance treatment [EL5, RG D].

In the maintenance treatment of paediatric CD, corticosteroids are not to be used because of their negative effect on growth and bone mineralisation. In addition, studies in adults have shown that long term treatment with corticosteroids does not maintain remission of disease.

**ECCO Statement 10F**

The role of mesalazine in maintaining remission in paediatric CD is unclear [EL2b, RG B].

The role of 5-ASA as maintenance treatment is unclear, as no studies are available in children. Extrapolation from the adult literature suggests that 5-ASA has no advantage over placebo. However, mainly because of its perceived lack of side effects, 5-ASA is still often used in children who present with mild disease.
The most effective drugs used to maintain remission seem to be the thiopurines AZA and 6-MP. Early introduction at the time of remission-induction has been shown to result in a valuable corticosteroid sparing effect, in addition to significant prolongation of the duration of remission. Methotrexate is an alternative to AZA or 6-MP if these drugs are not tolerated or are ineffective.

**10.3.4 Refractory disease**

**ECCO Statement 10I**

Infliximab is effective for induction of remission in refractory paediatric Crohn’s disease, including refractory fistulating disease [EL4, RG C]

In children with refractory CD (unresponsive to corticosteroids, corticosteroid dependent, or complicated by corticosteroid toxicity despite AZA or 6-MP treatment), infliximab has been shown to induce clinical remission effectively and safely in several open label studies and retrospective series. At this moment, the results of a multicentre RCT comparing two regimens of infliximab maintenance treatment (every eight weeks compared with every 12 weeks) are awaited.

**ECCO Statement 10J**

Elective surgery is indicated in pre-pubertal children with growth failure, especially when disease is limited to the terminal ileum [EL4, RG C]

Surgical treatment is indicated in localised (stricturing), treatment-resistant ileocaecal disease and should be considered at an early stage in the presence of growth failure, as the “moment of opportunity” might have lapsed once puberty has started.

**10.4 Supportive management**

**ECCO Statement 10K**

Psychosocial support should be given to patients and their families [EL4, RG C]

Special consideration should be given to the psychosocial support of children and adolescents with CD for several reasons: psychiatric problems such as depression occur more frequently in this population and quality of life may improve when adequate coping skills are taught.

Lastly, growth failure is a unique complication of paediatric inflammatory bowel disease (IBD) and needs to be addressed separately. Growth failure is caused by a combination of insufficient intake of calories, increased losses, and ongoing inflammation. When a child fails to grow, treatment is inadequate. In these paediatric patients, treatment should be intensified and adequate intake of calories ensured.

**10.5 Conclusions**

In summary, CD in children should be diagnosed by ileocolonoscopy and upper endoscopy (both with multiple biopsies) and small bowel follow through. For treatment of active disease, nutritional treatment is a good alternative to corticosteroids. Maintenance treatment is aimed at avoidance of corticosteroids, by early introduction of AZA or 6-MP. At the present time infliximab is reserved for induction of remission of refractory CD, including fistulating disease.

**11.0 THE MANAGEMENT OF PREGNANCY IN CD**

**11.1 Introduction**

CD often occurs in young adults, and therefore caring for patients who are also pregnant is not uncommon. It has been estimated that around 25% of female patients conceive after the diagnosis of CD. Maintaining adequate disease control is crucial for both maternal and fetal health, and should be performed in a multidisciplinary way, involving both gastroenterologists and obstetricians.

**11.2 Fertility in CD**

**ECCO Statement 11A**

Crohn’s disease does not seem to affect fertility when the disease is inactive [EL3b, RG B]; however active disease leads to reduced fertility [EL3b, RG B]. Female patients who undergo surgery are at risk for impaired tubal function [EL3b, RG B]. In male patients rectal excision may lead to impotence or ejaculatory problems; however there is no comparison with the general population [EL4, RG C]. Sulfasalazine therapy causes infertility (reversible) in male patients because of changes in semen quality [EL3b, RG B]

Patients with quiescent CD are as fertile as the general population. Patients with IBD have fewer children than the general population, but this is partly because of voluntary childlessness. Active CD reduces fertility by several mechanisms, including inflammation involving the fallopian tubes and ovaries, perianal disease causing dyspareunia and previous surgical intervention. Sulfasalazine therapy (but neither other 5-ASA compounds nor AZA) causes a reversible decrease in sperm motility and count in male patients. The effect is dose related and it is unaffected by supplemental folic acid.
11.3 Influence of disease activity on the course and outcome of pregnancy

**ECCO Statement 11B**

It is advisable to strive for clinical remission before conception. Flares are best treated aggressively to prevent complications [EL3a, RG B]. Active disease is a risk for preterm delivery and low birth weight [EL3a, RG B]. Insufficient data exist about maternal morbidity and fetal mortality at surgery.

Quiescent CD has minimal effects on the course and outcome of pregnancy. Active CD, either at the time of conception or during pregnancy, has been shown to increase the incidence of foetal loss, stillbirths, preterm delivery, low birth weight, and developmental defects. Importantly, it should be emphasised that this seems to be related to disease activity rather than medications used during pregnancy. Fetal mortality is very high if surgery is required, where abortion-stillbirth rates are as high as 18%–40%. Careful obstetric and medical follow up during pregnancy is prudent, especially in the third trimester.

11.4 The influence of pregnancy on the course of CD

**ECCO Statement 11C**

If conception occurs at a time of quiescent disease the risk of relapse is the same as in non-pregnant women [EL5, RG D]. If conception occurs at a time of active disease, two thirds have persistent activity and of these, two thirds deteriorate [EL3b, RG B]. There is a negative association between the number of pregnancies and surgical interventions [EL4, RG C]. Both clinical activity and surgical interventions decline with pregnancy and parity. Nutritional status also influences parity [EL4, RG C].

When conception occurs during a period of remission, about a third of patients relapse during pregnancy, which is similar to that expected in non-pregnant CD patients over a period of nine months. On the other hand, if conception occurs at a time of active disease, two thirds have persistent activity and of these, two thirds will deteriorate. This underscores the importance of advising patients to conceive at a time when disease is in remission. Two studies have suggested that pregnancy influences the overall course of IBD, because as parity increases, the need for surgical intervention decreases. Patients with a previous pregnancy require fewer resections and the interval between operations tends to be longer when compared with nulliparous women with CD. Mothers with CD also have a lower relapse rate in the year after pregnancy, compared with the year before pregnancy. Pregnancy has an effect on the immune system, which may contribute to these findings.

11.5 Mode of delivery

The mode of delivery should primarily be dictated by obstetric necessity, but the decision should be combined with the gastroenterologist to avoid perianal complications. The standard practice is vaginal delivery for women with quiescent or mild disease. Caesarean section is recommended in active perianal disease. Ileo-pouch-anal anastomosis in CD patients is also regarded as an indication for caesarean section, because of a theoretically increased risk of damage to the anal sphincter despite a lack of evidence. Patients with a colostomy or ileostomy can deliver vaginally, but if the obstetric risk is increased for other reasons, there should be a low threshold for caesarean section. Episiotomy should be avoided if possible, because a high rate of perianal involvement has been reported, but is better than an uncontrolled laceration.

11.6 Surgery during pregnancy

**ECCO Statement 11E**

The mode of delivery should primarily be governed by obstetric necessity and indication, but also in conjunction with the gastroenterologist. Uncomplicated CD patients without perianal disease should deliver vaginally, after obstetric evaluation has been performed [EL4, RG C]. Caesarean section should be preferred in active perianal disease [EL4, RG C]. For inactive perianal disease, caesarean section may be considered [EL5, RG D]. An ileoanal pouch in CD patients is regarded as an indication for caesarean section [EL4, RG C]. Caesarean section in this setting carries an increased risk of complications [EL4, RG C]. Episiotomy should probably be avoided, but is better than a spontaneous uncontrolled laceration. However there are discrepancies in the literature.

**ECCO Statement 11F**

Indications for surgery in pregnant CD women are the same as for non-pregnant patients: obstruction, perforation, haemorrhage, and abscess. In the severely ill patient, continued illness is a greater risk to the foetus than surgical intervention [EL5, RG D]. Indications for surgery in pregnant CD women are obstruction, perforation, haemorrhage, or abscess and are no different to those for non-pregnant women. In severely ill patients, continued illness is a greater risk to the fetus than surgical intervention. There are only few case reports of surgery in CD. Procedures have included proctocolectomy, hemicolecotomy, segmental resection, and ileostomy. A temporary ileostomy is generally preferred, to reduce the risk of postoperative complications after primary anastomosis.

11.7 Medical treatment during pregnancy

Proactive maintenance of quiescent disease is preferred. Benefit ratio of medication should be considered when counselling pregnant CD patients. In active disease during pregnancy the Food and Drug Administration (FDA) pregnancy categories, ABCDX, reflect this cautious approach (tables 11.1, 11.2). The drug description notice always emphasises risks and side effects.

The greatest risk to mother and fetus during pregnancy is active disease, and not the medication used to treat it. In general, pharmacological treatment for active disease during pregnancy is the same as for non-pregnant women.
11.7.1 Aminosalicylates (FDA B)
Sulfasalazine is the medication with the longest track record available for CD. It is safe during pregnancy and nursing213 214 215 (grade B,C). Kermiterus has been postulated as a potential consequence because of binding of the drug to plasma proteins, but it creates no clinical problems206 [EL4, RG C]. Folate is important for neural tube development during pregnancy, and as sulfasalazine treatment interferes with absorption, folate supplementation (about 2 mg/day) is recommended. 5-ASA has also proved safe during pregnancy203 204 for doses up to 3 g/day, but the safety of higher doses is uncertain [EL4, RG C]. Epidemiological database research has identified an increased risk of stillbirth or preterm birth in CD treated with 5-ASA, but could not determine whether this risk was secondary to active disease or medication.205 [EL3b, RG B]

11.7.2 Antibiotics (FDA B-C)
Antibiotics may be used as first line therapy for perianal CD.208 most often metronidazole and ciprofloxacin. Although metronidazole is mutagenic in some bacteria and carcinogenic in mice after long term use, this has never been reported in humans207 [EL1a, RG A]. Metronidazole is considered safe by most obstetricians after the first trimester.172 [EL5, RG D] Two studies on fluoroquinolones, in which the majority of patients had treatment in the first trimester, failed to show any increased risk of malformation, spontaneous abortion, prematurity, or low birth weight.209 210 [EL3b, RG B]

Tetracyclines and sulphonamides should be avoided during pregnancy. Tetracyclines can cause retardation of fetal skeletal development. Sulphonamides interfere with folic acid metabolism and are teratogenic in animals, which develop cleft palate and have high mortality.211 [EL4, RG C]

11.7.3 Corticosteroids (FDA C)
Corticosteroids cross the placental barrier but are rapidly converted to less active metabolites by placental 11-hydroxysteroidase, resulting in low fetal blood concentrations. Prednisone and prednisolone are more rapidly metabolised than alternative compounds. Nevertheless, risks of prematurity, spontaneous abortion, or cleft palate211 [EL4, RG C] are often cited, which have only been seen in animals. In humans no increase in congenital malformations has been found.209 210 [EL3b, RG B] Enemases and suppositories are considered acceptable until the third trimester.211 [EL5, RG D]

11.7.4 Budesonide (FDA C)
No studies are available in humans with IBD, although studies with inhaled budesonide suggest that the drug is safe during pregnancy.216 217 [EL3b, RG B] In animals, toxic doses of budesonide have shown both teratogenic and embryocidal effects.216 [EL4, RG C]

11.7.5 AZA and 6-MP (FDA D)
Most of the experience on AZA and 6-MP in pregnancy comes from the transplant and rheumatology literature. AZA is considered safe in these populations, with no consistent reports of abnormalities in fertility, prematurity, or congenital defects.217–219 [EL3b, RG B] The FDA rating is, however, based on human reports of high abortion rates.220 221 [EL4, RG C] Studies on animals given doses equivalent to 1.5 mg/kg for 6-MP and 2.5 mg/kg for AZA, report only low birth weights, but higher doses have been associated with increased incidences of congenital malformations, prematurity, low birth weight, and chromosomal abnormalities.222 223 [EL3b, RG B] In IBD there have been follow up studies on 341 pregnancies during treatment with AZA or 6-MP. All resulted in normal deliveries and no excess rates of prematurity, spontaneous abortion, congenital abnormalities, or neonatal/childhood infections.224 225 [EL3b, RG D] The only prospective randomised study confirms that outcome in pregnant patients treated with thiopurines is similar to the general population.226 When fathers used 6-MP within three months of conception a study of 50 pregnancies reported a higher incidence of pregnancy related complications.227 [EL3b, RG B] Consequently, although AZA and 6-MP have FDA rating D, available data suggest that these drugs are safe and well tolerated during pregnancy.

11.7.6 CsA (FDA C)
As for other immunosuppressants, most data in pregnancy come from transplant and rheumatology literature.227–229 [EL4,1a,3b, RG C,A,B] There is a higher rate of prematurity and low birth weight, but a high survival rate. Cyclosporin was used in two UC pregnancies without influence on fetal outcome.230 [EL4, RG C] There are no data available on the use of cyclosporin in pregnant CD patients; but the drug seems to be safe if clinically indicated.

11.7.7 Tacrolimus (FDA C)
The transplant literature reports apparent safety.231 [EL3b, RG B] Prematurity is more common, but no excess congenital malformations, low birth weight, or neonatal complications have been found.

11.7.8 Methotrexate (FDA X)
Animal studies have shown methotrexate to be both teratogenic and embryotoxic, resulting in chromosomal damage and miscarriage.231 232 [EL4, RG C] Although normal pregnancies have occurred, MTX is contraindicated in pregnancy.233 234 [EL4,3b, RG C,B] If conception should accidentally occur, therapeutic abortion should be discussed, but not necessarily performed.235 [EL5, RG D] Prospective mothers should be instructed to stop methotrexate immediately and start high dose folate replacement.236 [EL5, RG D]

### Table 11.1 Food and drug administration (FDA) categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Controlled studies show no risk</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out, animal studies showed adverse effects on fetus</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk in humans, risk/benefit ratio should be considered</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

### Table 11.2 Prescribing in pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Considered safe</th>
<th>Probably safe</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA (FDA B)</td>
<td>Budesonide (FDA C)</td>
<td>Methotrexate (FDA X)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics (FDA B)</td>
<td>Thiopurines (FDA D)</td>
<td>Thalidomide (FDA X)</td>
<td></td>
</tr>
<tr>
<td>Anti-TNFa (FDA B)</td>
<td>Ciclosporin (FDA C)</td>
<td>Sulphonamides (FDA C)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (no rating)</td>
<td>Tacrolimus (FDA C)</td>
<td>Tetracycline (FDA D)</td>
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</table>
The intracellular metabolites of MTX, methotrexate polyglutamates, have a long half life and take about six weeks to reach steady state or to completely wash out. Thus, women should stop MTX for at least six weeks and probably longer. The same applies to prospective fathers, to allow spermatogenesis return to normal. [EL5, RG D]

11.7.9 Infliximab (FDA B)
Anti-TNF antibodies are species specific. Murine models have failed to show any teratogenicity or embryotoxicity. Post-marketing data from Centocor of more than 280 pregnancies, of which a third had IFX during the first trimester showed that 75% had live births, 14% had a miscarriage, and 11% had therapeutic terminations ([EL4, RG C], personal communication, Troels Sørensen, Centocor). There is, however, a risk of transmission of infliximab (high serum concentrations have been detected in the baby of a mother who received IFX 10 mg/kg every eight weeks during pregnancy), although it is not yet known whether this induced antibody formation in the baby. IFX could not be detected in breast milk (below). The implications of exposure to IFX on the newborn are unknown, but patients and physicians should be aware of in utero exposure and treatment may best be avoided in the last trimester of pregnancy if circulating IFX in the neonate is to be avoided [EL3, RG D].

11.7.10 Thalidomide (FDA X)
Thalidomide is contraindicated in pregnancy. Use of this agent has been associated with major human fetal abnormalities involving not only limbs (phocomelia), but also ears and eyes. Neural tube abnormalities, duodenal fistulas, and haemangioma have been reported [EL4, RG C]. Neonatal mortality rates of 40% have been reported [EL4, RG C].

11.7.11 Non-specific symptomatic agents
Antiemetic (FDA B)
Metoclopramide is safe and no fetal abnormalities have been reported [EL4, RG C]. Vitamin B6 used as an antiemetic decreased nausea during pregnancy without teratogenic effect [EL2b, RG B]. Ondansetron has also been reported to be safe [EL3b, RG B].

Antacids and proton pump inhibitors (PPI) (FDA B, C)
Antacids are safe during pregnancy, as is sucralfate. H₂ receptor antagonists (FDA B) are considered safe [EL2b, RG B]. Omeprazole is in FDA category C, because although PPIs have not been found teratogenic in humans, they have in animal studies. [EL3b, RG B]

Pain relief (FDA C, D)
Aspirin (FDA D) has shown to cause prolonged gestations, prematurity, longer labour, and greater blood loss during labour and delivery. [EL4, RG C] NSAIDS (FDA C) have not been studied adequately and are not recommended. Codeine (FDA C) is considered safe [EL5, RG D]

### Table 11.3 Prescribing during breast feeding

<table>
<thead>
<tr>
<th>Considered safe</th>
<th>Probably safe</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Budesonide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Topical or oral mesalazine</td>
<td>Thiopurines</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Infliximab</td>
<td>Cyclosporin</td>
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<tr>
<td></td>
<td>Olalazine</td>
<td>Diphenoxylate</td>
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<td></td>
<td></td>
<td>Clofazamine</td>
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<tr>
<td></td>
<td></td>
<td>Metronidazole</td>
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<td></td>
<td></td>
<td>Loperamide</td>
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</table>

Antidiarrhoeals (FDA B)
Cholestyramine (FDA B) has anion binding capacity and is effective in controlling diarrhoea especially in patients with ileal disease or after resection and in those with cholestasis of pregnancy. Loperamide (FDA B) should be considered probably safe, although reports of congenital malformations have been reported in a selected group of patients. [EL4, RG C] Diphenoxylate should be used with caution.

11.8 Medical treatment when breast feeding (Table 11.3)
Sulfasalazine is safe for breast feeding. The sulfapyridine moiety is absorbed in minimal amounts and is excreted in milk, however the milk:serum ratio is acceptable. [EL4, RG C] The safety of aminosalicylates has been confirmed in prospective trials. [EL4,3b, RG C,B] Prednisone and prednisolone result in low human breast milk concentrations. To minimise exposure, a four hour delay after oral dosing could be recommended. [EL3b,4, RG B,C] Very small amounts of AZA/6-MP metabolites (nanomolar concentrations of 6-methyl mercaptopurine and thiouric acid) appear in breast milk, so their use should be discussed on an individual basis. There are no data to support the use of cyclosporin in breastfeeding. Infliximab could not be detected in milk in the one published case that it has been measured, although like other maternally acquired antibodies, the half life of infliximab appears prolonged in newborns after uterine exposure. The implications are unknown and breast feeding is probably best avoided while receiving infliximab. It is not known whether thalidomide is excreted in breast milk.

12.0 CD AND PSYCHOSOMATICS

12.1 Introduction
While psychosocial factors are considered important in CD, controversy still exists about their role. This may lead to inconsistencies in clinical practice. The biopsychosocial model represents an advantage over the biomedical model, as it embodies the complex biological and psychosocial interactions that explain human illness or its effects. Attention to the psychosocial factors associated with CD may have consequences not only on psychosocial wellbeing and quality of life, but also on the activity of the disease itself.

12.2 Psychosocial factors
Patients with CD seem to have slightly higher frequencies (up to 50%) of psychological disturbances and a lower quality of life. Patients with severe disease have higher rates of psychological disturbance compared to other groups. The degree of psychological distress correlates with the disease severity, predicts health related quality of life and influences the course of disease [EL11b, 2b and 3b, RG B].

#### ECCO Statement 12A
Psychological disturbances seem to be a consequence of the illness rather than the cause or specific to Crohn’s disease. The degree of psychological distress correlates with the disease severity, predicts health related quality of life and influences the course of disease [EL11b, 2b and 3b, RG B].
An association between psychological factors and the aetiology of Crohn’s disease is unproven [EL3b, 4, RG D], but there is a moderate influence on the course of the disease [EL1b, 2b, RG B].

Prospective studies suggest that patients with depressive mood and associated anxiety are at a higher risk of further disease activity.263–266 For CD, in contrast with UC, prospective studies have yielded contradictory results about the influence of stress or (single) major life events on disease activity.262 267–269 Patients themselves and most European experts at the consensus conference consider psychosocial distress as having a moderate influence on the course of the disease, which is consistent with evidence in the recent literature about the influence of psychological distress on CD activity.264 266

12.3 Psychological factors influencing the course of CD

There is evidence of an interaction between psychological factors and CD activity: Depression and perceived chronic distress seem to represent further risk factors for relapse of the disease. It remains unclear whether acute life events trigger relapses [EL1b,2b, RG B]. Most patients consider stress to have an influence on their illness [EL2c,3, RG C].

12.4 Doctor-patient relationship, information, and clinical care

The psychosocial consequences and health related quality of life of patients should be taken into account in clinical practice at regular visits. Individual information and explanation about the disease should be provided through a personal interview. The course of the disease can be improved by combining self management and patient centred consultations [EL1b,3b, RG B].

Health perceptions impact on the experience of the illness.255 Increased physician awareness of the fact that psychologically distressed patients have difficulty in processing clinically relevant information272 may lead to improved doctor-patient communication.273 It is important to inform patients about their condition through an individual interview in conjunction with emotional support.274 This is because a lower information level is associated with greater concern.275 Self management guidebooks and patient centred consultations improve patients’ disease control,276 277 but the addition of educational booklets on their own does not seem to be helpful and may even worsen the health related quality of life of patients attending tertiary centres.278 Patient education programmes seem to have very limited or even no influence on the course of the illness or the psychological affect of patients.279 280 Almost all experts at the consensus conference are convinced that a good doctor-patient relationship is helpful psychologically and take psychosocial factors into account in diagnosis and therapy.281 Most experts at tertiary centres have the opportunity for an integrative somatic and psychological care of patients in their area of work.

12.5 Assessment of health related quality of life, psychological distress, and provision of integrated psychological support

Physicians should assess the patient’s psychosocial status and demand for additional psychological care and recommend psychotherapy if indicated. Integrated psychosomatic care should be provided in IBD centres [EL2b, RG B].

For assessment of quality of life, two IBD specific questionnaires have been shown to have sensitive reliability, responsiveness, and validity for use in clinical trials: the inflammatory bowel disease questionnaire (IBDQ)282 283 and the rating form of inflammatory bowel disease patient concerns (RFIPC).255 284 Detection and treatment of psychological distress has the potential to improve health related quality of life.285

To assess the demand for psychological care in chronic diseases, a validated questionnaire is now available, developed and based on IBD.285 Most experts feel themselves able to recommend psychotherapy in a discussion with the patients. There is no study on this competence, although this clinical experience is consistent with that of the participants of the Consensus Conference of the German Society of Digestive and Metabolic Diseases on diagnosis and therapy of CD,286 as well as that of UC.287 As strategies aimed at improving social support can have a favourable impact on psychological distress,288 training of gastroenterologists to integrate psychosocial factors in clinical practice should be taken into consideration.

12.6 Psychotherapeutic interventions

12.6.1 Psychotherapy

Psychotherapy has a positive effect mainly on the psychological dimensions of the illness such as psychological well-being, coping strategies, and psychological distress.289–291 The psychotherapeutic interventions are indicated for psychological disorders, such as depression, anxiety, reduced quality of life with psychological distress, as well as maladaptive coping with the illness [EL1b,2b,3b, RG B].
diagnosis of “CD” alone is not sufficient to recommend psychotherapy. Studies of psychotherapy on patients without psychological disturbance show little or no benefit.\textsuperscript{292–295} One study combining patients with CD and UC has shown an influence of psychotherapy on the disease activity.\textsuperscript{296} However, this study shows inhomogeneity in randomisation of the treatment and control groups, so the results are not included in the evidence based recommendation.

### 12.6.2 Choice of psychotherapeutic methods and psycho-pharmaceuticals

**ECCO Statement 12H**

The choice of psychotherapeutic method depends on the psychological disturbance and should best be made by specialists (psychotherapist, specialist for psychosomatic medicine, psychiatrist). Psycho-pharmaceuticals should be prescribed for defined indications [EL5, RG D].

There is no evidence that preference should be given to one psychotherapeutic method in particular. Relaxation exercises are useful, as they are easy to learn and perform on the one hand, and because of their proved effectiveness on the other.\textsuperscript{296–298} There is an advantage if the psychotherapist has experience in the treatment of patients with chronic IBD and works closely with the patient’s gastroenterologist.

There are also no specific studies for the use of individual psycho-pharmaceuticals in CD. Despite this, most experts believe there are clinical situations in which psycho-pharmaceuticals should be recommended for treatment of psychological distress associated with CD, rather than disease activity.

### 13.0 EXTRAINTESTINAL MANIFESTATIONS OF CD

#### 13.1 Introduction

Extraintestinal manifestations (EIMs) are comparatively common in CD, and reports show that up to 30% of patients are affected.\textsuperscript{296–298} However EIMs are likely to be over-represented in studies from tertiary referral centres and community studies suggest that their prevalence may be much lower.

The occurrence of one EIM seems to predispose to others. Some EIMs are related temporarily to CD activity, while others more usually run an independent course, unrelated to disease activity. Some forms of peripheral arthritis, erythema nodosum, oral aphthous ulcers, and episcleritis belong in the former group, while pyoderma gangrenosum ulcers, spondylarthropathy and primary sclerosing cholangitis (PSC) are characteristic of the latter. Joint manifestations in CD may be peripheral, axial, or both. Most gastroenterologists will be comfortable diagnosing and treating extraintestinal manifestations, with the exception of eye involvement for which the advice of an ophthalmologist is selected in a great majority of cases.

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. Specific therapy for EIMs is strongly influenced by current IBD treatment, and may include increasing dose of existing drugs or the addition of new agents. This contribution concentrates on the more frequently encountered EIMs, for which at least some quantifiable data exist, and does not include systemic consequences of severe CD such as iron deficiency or malnutrition.

#### 13.2 Articular manifestations

**ECCO Statement 13A**

Diagnosis of non-axial arthritis and arthropathy associated with IBD is made on clinical grounds based on characteristic features and exclusion of other specific forms of arthritides [EL3b, RG C]. Type I is pauci-articular 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 [EL 2b, RG B]. Axial arthritis, including sacroiliitis and ankylosing spondylitis, is diagnosed on conventional rheumatological grounds, and is supported by characteristic radiological changes, magnetic resonance imaging being the most sensitive [EL2b, RG B]. Although HLA B-27 is overrepresented in axial arthritis related to Crohn’s disease and without diagnostic value [EL2b, RG B].

#### 13.2.1 Peripheral arthropathy

Peripheral arthritis is now sub-classified to types I and II.\textsuperscript{299} Type I is pauci-articular and affects large (predominantly weight bearing) joints including the ankles, knees, hips, wrists, elbows, and shoulders. By convention fewer than five joints are affected. The arthritis is usually acute and self limiting (weeks rather then months) and leaves no permanent joint damage. Type II is a polyarticular arthritis mainly affecting the small joints of the hand, it persists longer (months or years) and may recur independently of CD activity. The diagnosis of peripheral arthritis is made clinically from the finding of painful swollen joints. The differential diagnosis includes osteoarthritis, septic arthritis, or coincidental sero-positive rheumatoid arthritis, or treatment side effects (which may include the effects of corticosteroid withdrawal, osteonecrosis, AZA induced arthropathy and infliximab related lupus-like syndrome).\textsuperscript{300}

#### 13.2.2 Axial arthritis

Axial arthritis includes spondylitis and sacroiliitis.\textsuperscript{300} Asymptomatic sacroiliitis is common, with up to 50% of Crohn’s patients having abnormal radiography. Symptomatic sacroiliitis is characterised by pain in the buttocks after rest, which improves with movement. The leading symptom of ankylosing spondylitis is chronic low back pain, usually of onset before the age of 30. The diagnosis is made clinically by physical examination showing limited spinal flexion and, in the later stages, reduced chest expansion. Conventional radiographs are often normal in the early stages of disease. While computed tomography and technetium bone scans are more sensitive than simple radiographs, the current gold standard is now magnetic resonance imaging.\textsuperscript{301, 302} In more advanced cases there may be squaring of the vertebral bodies, marginal syndesmophytes, and bony proliferation, with ankylosis producing the classical “bamboo spine”. HLA B-27 associations are found in 50%–75% of patients with axial arthritis but HLA typing has no role in the management of an individual patient.\textsuperscript{302, 303}

In type I peripheral arthritis the emphasis should be on the treatment of the underlying CD, including corticosteroids, immunomodulation, and anti-TNF agents as appropriate; this may be expected to result in improvement of joint symptoms. The joint specific drug of first choice for all forms of IBD related arthritis seems to be sulfasalazine, but reliable evidence to support this choice is lacking. Symptomatic relief may be obtained from simple analgesics, rest and physiotherapy.\textsuperscript{303–305} Although there is concern that non-steroidal anti-inflammatory agents (conventional and COX II
inhibitors) may aggravate the underlying CD, they have been used by many gastroenterologists to apparently good effect. Injection of corticosteroid into the worst affected joints may also be useful.

Treatment of axial arthritis in CD is based on a comparatively good evidence base for axial arthritis in general. It should therefore include intensive physiotherapy, together with rheumatological disease modifying drugs such as sulfasalazine, and methotrexate. The safety and efficacy of infliximab in ankylosing spondylitis is now established, but is not routinely used as a first line treatment. The use of corticosteroids is poorly reported, but intra-articular injections can be appropriate in selected cases.

13.3 Metabolic bone disease

Diagnosis of osteoporosis is best made from a T score of less than –2.5 on radiographic bone densitometry [EL1a, RG A], all other diagnostic methods having current limitations [EL2b, RG B]. The presence of osteoporosis identifies patients at above average risk for fracture and who should receive treatment [EL2b, RG B]. Osteopenia may be a prognostic marker for future osteoporosis, but presents little direct risk [EL2b, RG C].

Osteoporosis and osteopenia are common in both male and female patients with CD (20%–50%). Contributing factors include age, corticosteroid treatment, smoking, low physical activity (including that from hospitalisation), inflammatory cytokines, extensive small bowel disease or resection, and nutritional deficiencies. Screening is appropriate in all patients with Crohn’s in whom there has been evidence of severe disease and in those repeatedly exposed to corticosteroids. Diagnosis is conventionally based on bone densitometry (DEXA scanning), osteoporosis being defined from a T score of less than –2.5. Ultrasound has been suggested as a method of screening but is not yet reliable. The presence of osteoporosis increases the risk of fracture of long bones and of the spine, although probably a great deal less in young patients than was once thought. It is conventional to take a diagnosis of osteoporosis as an indication for specific therapy.

Osteopenia (T score <–1.0) is thought by some to be an important risk factor for fracture in its own right, but this is increasingly questioned. It is probable that it is a marker of increased risk of later osteoporosis. Therapeutic intervention is probably not justified on present knowledge, but continued surveillance for bone loss is appropriate.

Data on the treatment of osteoporosis in Crohn’s disease depend on studies that are not specific to IBD. The evidence levels and recommendation grades are accordingly marked down. Weight bearing, isotonic exercise [EL2b, RG B], avoiding alcohol excess [EL4, RG D], and maintaining adequate dietary calcium (>1 g/day) [EL2b, RG B] are beneficial. Hormone replacement treatment is no longer generally advised in postmenopausal women with osteoporosis [EL2b, RG B], but regular use of bisphosphonates, calcitonin and its derivatives, and raloxifene may reduce or prevent further bone loss [EL2b, RG C]. Data in men with osteoporosis are less secure but bisphosphonates are probably of value, [EL3b, RG C], and those with low testosterone may benefit from its therapeutic administration [EL3b, RG C]. Routine administration of vitamin D is not warranted [EL3b, RG C].

The risks of osteoporosis (and the potential risks from osteopenia) should be explained. General advice should include recommendations on exercise (particularly when weight bearing and isotonic), the cessation of smoking, and avoidance of alcohol excess. Evidence exists to recommend a dietary calcium intake of 1000–1500 mg per day. Postmenopausal women with osteoporosis have been offered treatment with hormone replacement therapy, but recent studies showing that this invokes an increased risk of breast cancer and of cardiovascular event have lead to a substantial restriction in its use. Data also exist to warrant treatment with bisphosphonates, calcitonin and its derivatives, and raloxifene. One of these should be selected for osteoporotic women with Crohn’s. Men over the age of 50 with osteoporosis also deserve treatment, and seem to benefit from testosterone if their serum levels are low. Osteomalacia is also seen in CD but is comparatively rare in the absence of other risk factors. Routine administration of vitamin D is not warranted.

The diagnosis of erythema nodosum is made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy is rarely appropriate or necessary.

Pyoderma gangrenosum lesions are often preceded by trauma at the same site (which may have been many years earlier) in a phenomenon known as pathergy. They 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 infection has occurred.

### ECCO Statement 13F
Treatment of erythema nodosum is usually based on that of the underlying Crohn’s disease. Systemic corticosteroids are usually required [EL4, RG D]. Treatment of pyoderma gangrenosum has relied on topical and systemic corticosteroids [EL4, RG D], with the more toxic ciclosporin and tacrolimus reserved for resistant cases [EL4, RG D]. Newer data support the use of infliximab [EL1b, RG B].

The treatment of erythema nodosum will be mainly directed toward the underlying disease. Usually systemic corticosteroids will be required. In resistant cases and when there are frequent relapses immunomodulation with AZA and/or infliximab may be added, but it is most unusual to need such measures purely because of the erythema nodosum.

Corticosteroids have been considered the most effective treatment for pyoderma gangrenosum, and in resistant cases high intravenous doses have been thought required. Intravenous cyclosporin or tacrolimus are considered effective in refractory cases, but there are no reliable trials to support their use, and these drugs have significant side effects. Infliximab, reported to be effective in small case studies, has now shown its value in a small placebo controlled trial. The side effect profile and efficacy of IFX compared with high doses of corticosteroids, cyclosporin or tacrolimus are such that many now consider it the preferred treatment for established pyoderma gangrenosum.

### 13.5 Ocular manifestations

#### ECCO Statement 13G
Diagnosis of simple episcleritis depends on the exclusion of the more sinister features of uveitis. When this is not possible referral to an ophthalmologist for expert opinion and slit lamp examination is wise [EL4, RG D]. Episcleritis may not require specific treatment, but will usually respond to topical corticosteroids [EL4, RG D]. Uveitis is treated with corticosteroids, and it may be necessary to use both topical and systemic routes [EL3b, RG C]. Immunomodulatory therapy has been thought helpful in resistant cases [EL4, RG D].

Episcleritis may be self-limiting but will usually respond to topical corticosteroids, simple analgesics alongside the treatment of the underlying CD. Uveitis prompts urgent ophthalmological referral and treatment as vision loss may occur. The treatment will usually consist of both topical and systemic corticosteroids. AZA, methotrexate, and infliximab have each been reported to be valuable in resistant cases.

### 13.6 Hepatobiliary disease

#### ECCO Statement 13H
Diagnosis of hepatobiliary disorders in association with Crohn’s disease follows the standard investigatory pathways prompted by abnormal liver function tests, with ultrasound scanning, and serology to identify specific auto-immune and infective causes [EL2a, RG B]. Magnetic resonance cholangiography is now established as the first line diagnostic test for primary sclerosing cholangitis [EL2a, RG B]. Primary sclerosing cholangitis substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma [EL1a, RG A].

Hepatobiliary disease is not unusual in CD. PSC is less common than in UC but constitutes the most important condition relatively specific to the underlying IBD. Pericholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation are also over-represented, however, and many of the drugs used for Crohn’s have the potential to cause hepatotoxicity. In most cases attention will be drawn to the condition by the finding of abnormal liver function tests rather than symptoms or signs of liver disease. A predominantly obstructive pattern of liver enzymes or the presence of biliary symptoms will prompt ultrasonographic assessment, which may show gallstone disease, steatosis, or frank cirrhosis; less often it will show an abnormal duct pattern suggestive of PSC. If ultrasound scanning is normal, 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 usual diagnostic test now is magnetic resonance cholangiography (MRCP), which will show the characteristic pattern of irregular bile ducts, bearing zones of both narrowing and dilatation. If MRCP is normal it is safer and probably more effective (given probable predominant small duct disease) to perform a liver biopsy than diagnostic endoscopic retrograde cholangiography (ERC) to confirm a suspected diagnosis. PSC is a major risk factor for cholangiocarcinoma and colon cancer.

#### ECCO Statement 13I
PSC seems to respond to ursodeoxycholic acid (ursodiol), which improves abnormal liver function tests [EL1b, RG B] but it has taken some time for

Ursodeoxycholic acid (ursodiol), was promptly adopted as a treatment for PSC once it was shown reproducibly to improve liver enzymes, but it has taken some time for
reasonably convincing evidence to emerge supporting true benefit from a 20 mg/kg daily dose in respect of histological progression.\textsuperscript{329} The addition of corticosteroids has been examined with conflicting results. Ursodiol may however reduce colon cancer risk.\textsuperscript{328} Tacrolimus has yielded a rapid decrease in liver enzymes but no histological improvement.\textsuperscript{330} ERCP may still be needed to confirm the diagnosis of PSC in a few cases, but it retains a place in the management of dominant biliary strictures.\textsuperscript{327} In advanced disease with liver failure there is no alternative to liver transplantation.\textsuperscript{327}

14.0 ALTERNATIVE THERAPIES FOR CD

14.1 Introduction

The use of complementary and alternative medicine among IBD patients is common,\textsuperscript{312 313} and physicians are frequently confronted with questions about their use. However, evidence of efficacy and safety is often lacking, because there are only a few controlled trials that have assessed these therapies in IBD. As most of the reported studies contain methodological problems, it is often difficult for physicians to inform their patients adequately.

14.2 Confounding factors

Several factors can lead both doctors and patients to think that an alternative therapy has worked, when in fact it has not. This is as true for new treatments in scientific medicine, as it is for fringe practices in “complementary or alternative medicine” (CAM). The only way to control for this is to conduct properly powered, RCTs. For IBD, confounding factors include:

- the natural history runs a cyclical course, so alternative therapies will have repeated opportunities to coincide with periods of remission that would have happened anyway
- placebo does work: through suggestion, belief, expectancy, cognitive reinterpretation, or diversion of attention, patients given biologically useless treatments often experience measurable relief. In recent IBD trials, placebo rates as high as 50% have been reported.
- if improvement occurs after IBD patients have had both “alternative” and science based treatment, the alternative strategy sometimes gets a disproportionate share of the credit from patients, IBD groups, or organisations with vested interests.

In general, complementary and alternative therapies remain largely unregulated, although adverse drug reactions to CAM have more than doubled over the past three years (World Health Organisation). It is for this reason that the WHO have recently published a new set of guidelines (http://www.who.int/medicines/library/trm/Consumer.pdf) for national health authorities to develop context specific and reliable information for use of complementary and alternative medicines by consumers.

14.3 Definitions

Complementary and alternative medicine is a group of diverse medical and health care systems, practices, and products that are not presently considered part of conventional medicine. While some evidence exists regarding some therapies, for most there are key questions that have yet to be answered through well designed scientific studies. Complementary and alternative therapies are different entities: complementary therapy is used together with conventional medicine, while alternative therapy is used in place of conventional medicine. Distinctions ought to be made between beneficial alternative therapies, strategies complementary to routine practice and health frauds.

14.4 Use and prevalence

An appreciable number of IBD patients use complementary therapies to manage their disease. A survey in 2003 among 150 IBD patients from a tertiary centre revealed that up to 60% of patients used CAM.\textsuperscript{331} No differences were detected with regard to disease diagnosis, education level, employment status, use of IBD medications, number of hospitalisations, doctor visits, or GI specific doctor visits. The most commonly used therapies were diet (45%), herbal (17%), exercise (15%), prayer (11%), and relaxation (10%). Reasons for turning to CAM were abdominal pain/cramps (64%), diarrhoea (60%), and gas/bloating (21%). This is in contrast with a national German study that found that the cumulative dose of corticosteroids was associated with use of CAM.\textsuperscript{332} A study in children and young adults found that 40% used CAM in addition to conventional therapies.\textsuperscript{333} The most common CAMs were megavitamin therapy (19%), dietary supplements (17%), and herbal medicine (14%). As most patients using CAM attribute “significant” benefits to their CAM use, physicians should inquire about their use.

14.5 Choice and evidence

All alternative therapies for CD should be supported by scientific evidence of efficacy, so they should be evaluated using the same general approach about effectiveness and safety as conventional therapy. Otherwise the agents may be no better than placebo (which, it should be realised, is not the same as no therapy). Although measures of patient satisfaction are an important part of the evaluation process, they need to be accompanied by more objective measures of quality of life improvement. Furthermore, the lay literature is a very poor source of reliable information for patients. One area of particular concern is the use of unlicensed herbal remedies that may contain harmful substances.
Only a few studies are reported where the outcome supports the use of CAM. Gerhardt et al\textsuperscript{336} reported the efficacy and safety of the Boswellia serrata extract H15 with 5-ASA for the treatment of active CD. In this randomised, double blind, verum controlled, parallel group study, 102 patients were randomised to either H15 or 5-ASA. No significant differences were detected, and the authors conclude that H15 is not inferior to 5-ASA. Gupta et al\textsuperscript{337} studied the gum resin of Boswellia serrata for the treatment of UC. Twenty patients received a preparation of the gum resin of Boswellia serrata (900 mg daily divided in three doses for six weeks) and 10 patients were given sulfasalazine (3 g daily divided in three doses for six weeks) and served as controls. Although no validated scoring system was used and the study was small, the authors saw improvement in 18 of 20 patients treated with Boswellia gum resin compared with 6 of 10 given sulfasalazine. Aloe vera gel was evaluated in UC patients in a double blind, randomised, placebo controlled trial.\textsuperscript{190} Forty four patients with active UC were randomly given oral aloe vera gel or placebo, 100 ml twice daily for four weeks, in a 2:1 ratio. The primary end point was clinical remission (simple clinical colitis activity index \(<2\), sigmoidoscopic remission (Baron score \(<1\) and histological remission (Saverymuttu score \(<1\)). Clinical remission, improvement, and response occurred in nine (30%), 11 (37%), and 14 (47%), respectively, of 30 patients given aloe vera gel. This compared with one (7%) (\(p = 0.09; OR 5.6 (0.6 to 49)\)), one (7%) (\(p = 0.06; OR 7.5 (0.9 to 66)\)), and two (14%) (\(p <0.05; OR 5.3 (1.0 to 27)\)), respectively, of 14 patients given placebo. The simple clinical colitis activity index and histological scores decreased significantly during treatment with aloe vera (\(p = 0.01\) and \(p = 0.03\), respectively), but not with placebo. Sigmoidoscopic scores and laboratory variables showed no significant differences between aloe vera and placebo. Adverse events were minor and similar in both groups of patients. The authors concluded that oral aloe vera gel taken for four weeks was safe and more effective than placebo. A prospective, randomised, controlled, single blind clinical trial of acupuncture for active CD has also been conducted. The CDAI declined significantly after treatment, but did not reach the 100 point threshold of benefit.\textsuperscript{336}

ECCO Statement 14D

While physicians may permit use of complementary medicines, they should discourage use of those for which there is evidence for toxicity. It is plausible that dietary supplements could have a biological effect and there is some evidence for a number of specific supplements, which is strongest in the case of fish oil. [EL2a, RG C]

As malnutrition is prevalent both in active IBD as well as in quiescent disease, nutrition is an essential, complementary component of conventional medicine in CD. However, nutritional therapy does not qualify for primary therapy (that is, alternative therapy) in adults, in contrast with paediatric IBD (see chapter on treatment of active disease). Supplementation of fish oil preparations in CD has been reported beneficial in IBD patients. For maintaining remission, a double blind, placebo controlled study in 78 patients with CD evaluated the effects of a fish oil preparation. This demonstrated a significant reduction in relapse rate.\textsuperscript{140}

14.6 Conclusions

A distinction should be drawn between alternative and complementary medicines. Their widespread use should be recognised. Some of these agents exert plausible biological effects and warrant further investigation.

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