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SPECIAL ARTICLE

The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations

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8.1. Epidemiology of post-operative Crohn's disease

In the natural history of CD, intestinal resection is almost unavoidable since about 80% of patients require surgery at some stage. Surgery is unfortunately not curative as the disease inexorably recurs in many patients. The post-operative recurrence rate varies according to the definition used: 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 employed as the diagnostic tool.[1–10]

Data from endoscopic follow-up of patients after resection of ileo-caecal disease have shown that in the absence of treatment, the post-operative recurrence rate is around 65–90% within 12 months and 80–100% within 3 years of the operation. The clinical recurrence without therapy is about 20–25%/year.[1,10] It has been demonstrated that the post-operative clinical course of CD is best predicted by the severity of endoscopic lesions. Symptoms, in fact, appear only when severe lesions are present and it is not uncommon to observe patients with fairly advanced recurrent lesions at endoscopy who remain asymptomatic.[1] For these reasons, clinical indices such as the CDAI have low sensitivity at discriminating between patients with or without post-operative recurrence.[11]

These data mandate strategies aimed at interrupting or delaying the natural course of post-operative recurrence. Several medications have been tried in an attempt to prevent post-operative recurrence, mostly with disappointing results. The aim of this Consensus was therefore critically to evaluate the optimal strategies for the management of post-operative

recurrence in CD. Most, if not all, of the evidence available deals with recurrence at the site of the ileocolonic anastomosis. Therefore the recommendations specifically apply to this situation more than to segmental ileal or colonic resections without a new ileocolonic anastomosis. In common with other sections in the Consensus, the working party agreed a list of questions on post-operative recurrence that was circulated to ECCO members to quantify opinion on management. A systematic literature search was performed and evidence graded according to the Oxford Centre for Evidence-based Medicine.

8.2. Predicting post-operative recurrence

ECCO Statement 8A
The following are considered predictors of early post-operative recurrence after ileocolonic resection: smoking, prior intestinal surgery [EL 1 and RG A], penetrating disease behaviour, perianal location and extensive small bowel resection [EL2b, RG B]. Absence of prophylactic treatment [EL1a, RG A] is associated with a higher risk of relapse.

Several studies have looked for potential risk factors for recurrence after surgery for CD. Smoking,[1] prior intestinal surgery (including appendicectomy),[2] penetrating disease behaviour,[3] perianal location,[4] and extensive small bowel resection have been shown to predict early post-operative recurrence in the majority of studies.[5,6]

Prophylactic medical therapy has been shown to be effective in randomised-controlled trials, confirmed by meta-analysis [EL1a].[28–30]

Conflicting data exist for the age at onset of the disease, sex,[7] duration of the disease,[8] resection margins,[9,10] or type of surgery.[11–13]

A validated predictive index is desirable, but has not yet been developed.

8.3. Diagnosis of post-operative recurrence

ECCO Statement 8B
Clinical assessment, including measurements of disease activity and acute phase reactants are used during follow up, but their value remains to be determined [EL5, RG D].

Diagnosis of post-operative recurrence may be based on clinical symptoms or 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). The CDAI has not been specifically validated in the post-operative setting, but, a sensitivity of 30% and a specificity of 89% have been reported.[14] Serum and faecal markers such as lactoferrin and calprotectin have been evaluated.[15]

ECCO Statement 8C
Ileocolonoscopy is the gold standard in the diagnosis of post-operative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course [EL2a, RG B]. Ileocolonoscopy is recommended within the first year after surgery where treatment decisions may be affected [EL2a, RG B].

Several studies have shown that colonoscopy is the most sensitive tool to document morphologic recurrence. Histologic or endoscopic recurrence may occur within a few weeks to months after surgery.[16–21] Endoscopic recurrence precedes clinical recurrence and severe endoscopic recurrence predicts a poor prognosis.[19]

ECCO Statement 8D
Trans-abdominal ultrasound, MR enterography, small bowel capsule endoscopy (SBCE) are less invasive diagnostic methods emerging as alternative tools for identifying post-operative recurrence [EL2b RG C].

Radiology and imaging (US, MR, and CT) are being evaluated as independent diagnostic methods for post-operative recurrence,[22–24] SBCE performed 6 or 12 months after surgery appears of comparable sensitivity, specificity and positive and negative predictive values as ileocolonoscopy in diagnosing post-operative recurrence.[25] The value of MR or CT enterography, or SBCE to diagnose post-operative recurrence in the ileum or jejunum has not been systematically studied.[26]

8.4. Medical prophylaxis

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 [EL1, RG A]. Thiopurines are more effective than mesalazine or imidazole antibiotics alone for preventing both clinical and endoscopic recurrence [EL1, RG A]. In patients with a risk factor for early post-operative recurrence the drug of choice is azathioprine/mercaptopurine [EL3, RG C]. High dose mesalazine is an option for patients with an isolated ileal resection [EL1b, RG B]. Imidazole antibiotics have been shown to be effective after ileocolic resection but are less well tolerated [EL1a, RG A].

ECCO Statement 8G
Prophylaxis is best started within two weeks of surgery, although an early start has not been proven superior to later treatment [EL5, RG D].

ECCO Statement 8H
The duration of prophylaxis should be at least 2 years [EL1a, RG B].

8.4.1. Mesalazine

Prophylactic treatment to reduce the rate of post-operative recurrence remains controversial.[27–29] In the 1990s, several randomised-controlled trials demonstrated that oral mesalazine, administered early after surgery reduced the frequency of recurrence and attenuated its severity.[21,31,32] In 1997 a meta-analysis showed that mesalazine was superior to placebo for the prevention of clinical POR.[35] This meta-analysis has been updated twice, the first after the publication in 2000 of a large European cooperative study,[33,32] and then after the publication of a second study by the Gruppo Italiano per lo Studio del Colon e del Retto (GISC).[34] The European cooperative study showed that mesalazine 4.0 g/day did not significantly affect clinical overall post-operative recurrence.[32] It included, however, a substantial subgroup of 124 patients who had had isolated resection of small bowel CD who did benefit from treatment with mesalazine 4.0 g/day compared to placebo. The updated meta-analysis included this large European trial and remained in favour of treatment with mesalazine.[33] Subsequently, the large number of patients in the GISC study allowed a second updated meta-analysis of six studies in a total of 1141 patients.[34,35,7,30–32,34,36] The results showed that mesalazine 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 mesalazine, with an overall risk difference of 15% (NNT = 6.6), which is also clinically relevant, although the meta-analysis has not been published in full. Nevertheless, given mesalazine's limited effect, no prophylactic treatment is an option in some asymptomatic low risk patients.

8.4.2. Antibiotics

8.4.2.1. Metronidazole. Metronidazole (20 mg/kg d) administered for 3 months after surgery significantly reduced the incidence of severe endoscopic recurrence at 1-year follow-up, although the effect was not sustained beyond 12 months.[37] Clinical recurrence was also delayed, which was the most important effect. The risk difference (18%) on intention-to-treat analysis in this study of 60 patients was comparable to the overall risk difference (15%) in the meta-analysis of mesalazine including 1141 patients.[35] In the controlled trial, the one year clinical recurrence rate was decreased compared to placebo, when imidazoles were stopped after 3 months, but was no longer lower than in the placebo group after 2 and 3 years.

Another nitroimidazole antibiotic, ornidazole 1 g/day administered for one year, has also shown efficacy in the prevention of POR in 80 patients with CD at 1-year follow-up. Clinical recurrence was again only decreased at 1 year and not at 2 or 3 years. — As with metronidazole, this strategy was not welltolerated,[38] and beneficial effects did not persist after the interruption of the therapy. This study confirmed a close relationship between the development of severe endoscopic lesions in the neoterminal ileum after surgery and subsequent development of clinical recurrence.

On the basis of this finding, imidazoles are clearly effective for the prevention of post-operative recurrence, but in clinical practice are rarely used due to side effects during long-term treatment.

8.4.3. Thiopurines

8.4.3.1. Azathioprine/mercaptopurine. The thiopurines azathioprine (AZA) and mercaptopurine (MP) are widely recommended for reducing the risk of post-operative recurrence after surgery, in particular for high-risk CD. In the first trial, there was a trend for MP 50 mg/daily to be more effective than placebo and mesalazine in preventing clinical post-operative recurrence.[39] Observed rates of endoscopic recurrence (defined as Rutgeerts' endoscopy score >1) at two years for placebo, mesalazine and MP were 64%, 63% and 43%, respectively, but the study had two main drawbacks. First, the clinical recurrence rate (based on physician global assessment) in the placebo group at two years was higher than the rate of endoscopic recurrence. Second, out of 131 patients enrolled only 57 completed the trial. The final analysis was therefore conducted on 57 patients, divided into 3 groups. A second prospective study in 142 patients randomised to receive AZA 2 mg/kg/day or mesalazine 3 g/day for 24 months showed comparable rates of clinical (OR 2.04, 95%CI 0.89–4.67) and surgical recurrence. However, subgroup analysis showed a favourable effect of AZA for patients who had had a previous resection (OR 4.83, 95%CI 1.47–15.8).[40] Herfarth et al. performed a double-blind, double-dummy, randomised, prospective, multicentre study comparing the efficacy and safety of AZA (2.0–2.5 mg/kg/day) with those of mesalazine (4 g/day) for the prevention of post-operative recurrence of endoscopic lesions in CD patients.[41] However, the study was stopped

prematurely after the inclusion of 79 patients. Treatment failure was found to be equally high in each group (AZA 9/18, mesalazine 9/19; $p=1.00$). However, 6/18 patients on AZA and 2/19 patients on mesalazine were withdrawn because of adverse drug reactions (33% vs 11%; $p=0.12$). More recently, D'Haens et al. compared the association of AZA for 12 months with metronidazole for 3 months to metronidazole alone to reduce recurrence of post-operative recurrence in 81 "high-risk" patients. Significant endoscopic recurrence was observed in 14 of 32 (43.7%) patients in the AZA group and in 20 of 29 (69.0%) patients in the placebo group at 12 months post-surgery ($p=0.048$). Intention-to-treat analysis revealed endoscopic recurrence in 22 of 40 (55%) in the AZA group and 32 of 41 (78%) in the placebo group at month 12 ($p=0.035$).[42]

A meta-analysis of the four controlled trials with AZA (433 patients in total) has been published.[43] In the overall analysis, thiopurines were more effective than control arms in preventing clinical post-operative recurrence at 1 year (mean difference, 95%CI): 8%, 1–15%, $p=0.021$, number needed to treat (NNT) = 13) and 2 years (mean difference, 95%CI: 13%, 2–24%, $p=0.018$, NNT = 8). In sensitivity analyses, the efficacy of thiopurines was superior to that of placebo for the prevention of clinical and endoscopic post-operative recurrence at 1 year (mean differences, 95%CI: 13%, 2–25%, $p=0.025$, NNT = 7, and 23%, 9–37%, $p=0.0016$, NNT = 4, respectively). At 1 year, in the overall analysis, thiopurines were more effective than control arms in preventing severe (score i2–4) endoscopic recurrence (mean difference, CI 95%: 15%, 1.8–29%, $p=0.026$, NNT = 7), but they were not effective in the prevention of very severe (score i3–4) recurrence. The rate of adverse events leading to drug withdrawal was higher in thiopurine-treated patients than in control arms (17% vs. 10%, respectively, $p=0.021$).[44]

In a one-year, double-blind, double-dummy, randomised study comparing AZA at 2.0–2.5 mg/kg/day versus mesalazine 4 g/day for the prevention of post-operative clinical relapse in patients with moderate or severe endoscopic recurrence, superiority for AZA versus mesalazine could *not* be demonstrated for therapeutic failure.[45] Therapy failure occurred in 22% (9/41) of AZA patients and 11% (4/37) of mesalazine patients, a difference of 11% (95%CI −5.0% to 27.3%, $p=0.19$). Clinical relapse was significantly less frequent with AZA versus mesalazine (0/41 [0%] versus 4/37 [11%], $p=0.031$), whereas study drug discontinuation due to adverse drug reactions only occurred in AZA-treated patients (9/41 [22%] versus 0%, $p=0.002$). The proportion of patients showing ≥ 1 point reduction in Rutgeerts' score between baseline and month 12 was 63% (19/30) and 34% (11/32) in the AZA and mesalazine groups, respectively ($p=0.023$).

8.4.4. Anti-TNF agents

One pilot randomised-controlled trial has shown efficacy of infliximab (IFX) in the prevention of post-operative recurrence.[46] Twenty four patients with CD who had undergone ileocolonic resection were randomised to receive intravenous IFX (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 IFX group (1/11 patients; 9%) compared with the placebo group (11/13 patients; 85%) ($p=0.0006$). There was a non-significant higher proportion of patients in clinical remission in the IFX group (8/10; 80%) compared with the placebo group (7/13; 54%) ($p=0.38$). The histological recurrence rate at 1 year was significantly lower in the IFX group (3/11 patients; 27%) compared with the placebo group (11/13 patients; 85%) ($p=0.01$). There are as yet no data on prevention of post-operative recurrence by other anti-TNF therapies.

8.4.5. Other therapies

In controlled trials, there is no evidence that probiotics,[47–49] synbiotics,[50,51] or interleukin-10 therapy are effective at preventing post-operative recurrence after surgery for CD.[52]

9. Diagnosis and management of fistulating Crohn's disease

Principal changes with respect to the 2004 ECCO guidelines

Seton placement should be recommended for complex fistulae and active luminal Crohn's disease should be treated in conjunction with surgical therapy for fistulating disease [Statement 9H and 9I].

Anti-TNF agents should be used as a second line medical treatment [Statement 9K].

9.1. Introduction

Fistulating Crohn's disease (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 the origin of the fistula and its anatomy
2. Evaluate the originating intestinal loop (inflammation or stenosis)
3. Identify or exclude local sepsis (abscess)
4. Determine which organs are affected and their contribution to systemic symptoms or impairment of the quality of life
5. Assess the 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. 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, since this may help define current practice.

9.2. Perianal fistulae

In a series of 202 consecutive patients with CD at a Teaching Hospital, up to 54% had suffered perianal complications.[53] In population-based studies,[54–56] 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. The 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.[54] Perianal disease may precede or appear simultaneously with intestinal symptoms.[55,57]

9.3. Non-perianal fistulae

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

9.4. Diagnosis of perianal fistulae

9.4.1. Initial diagnostic approach

ECCO Statement 9A
Pelvic MRI should be the initial procedure because it is accurate and non-invasive, although it is not needed routinely in simple fistulae [EL2b, RG B].

ECCO Statement 9B
Examination under anaesthetic is considered the gold standard only in the hands of an experienced surgeon. It may allow concomitant surgery, but care should be taken to obtain appropriate informed consent of the patient, since unexpected findings may preclude this [EL5, RG D].

ECCO Statement 9C
Anorectal ultrasound requires expertise, but can be equivalent to pelvic MRI in completing examination under anaesthesia if rectal stenosis has been excluded. [EL2b, RG B]. Fistulography is not recommended [EL3, RG C].

ECCO Statement 9D
Since the presence of concomitant rectosigmoid inflammation has prognostic and therapeutic relevance, proctosigmoidoscopy should be used routinely in the initial evaluation [EL2b, RG B].

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

EUA is reported to be the most sensitive, with an accuracy of 90%.[55,57] 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, a 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 has been performed, unless the MR scan is immediately available. Nevertheless, MRI has an accuracy of 76–100% compared to EUA for fistulae and may provide additional information.[55–59] Anorectal ultrasound has an accuracy of 56–100%, especially when performed by experts in conjunction with hydrogen peroxide enhancement.[60–62] Any of these methods can be combined with the 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.[63,64]

9.4.2. Classification of perianal fistulae

ECCO Statement 9E
There is no consensus for classifying perianal fistulae in CD. In clinical practice most experts use a classification of simple or complex. From the surgical point of view Parks' classification is more descriptive and can influence surgical decisions, but it is complicated to use in routine practice [EL5, RG D].

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, described by Parks et al.[65] A more empiric and easier classification into simple and complex fistulae has been proposed.[66] 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.

9.5. Treatment of fistulating disease

9.5.1. Simple perianal fistulae

ECCO Statement 9F
The presence of a perianal abscess should be ruled out and if present should be drained as a matter of urgency [EL5, RGD].
ECCO Statement 9G
For simple perianal fistulae it is important to know if they are symptomatic. If they are not, nothing has to be done. Only when simple fistulae are symptomatic are the options of non-cutting Seton or fistulotomy recommended [EL3, RG D]. Antibiotics, metronidazole (750–1500 mg/day) or ciprofloxacin (1000 mg/day), should be added [EL3, RG D].

9.5.1.1. Consensus views. Almost all used antibiotics as the first medical therapeutic option, azathioprine/6-mercaptopurineas the second option, and infliximab as the third option (evidence below). However, when a simple perianal fistula is symptomatic in Crohn's disease, opinion favours a combined medical and surgical strategy. Neither ciclosporin (CsA) nor tacrolimus were favoured as a fourth option. Pain in patients with a simple fistula is most often caused by an underlying abscess and most agreed that this must be ruled out by EUA complemented with pelvic MRI or anorectal ultrasound when indicated. Surgical drainage of the abscess was considered an important first step in therapy.

9.5.2. Complex perianal disease

ECCO Statement 9H
Seton placement should be recommended [EL4, RGD] for complex fistulae. The timing of removal depends on subsequent therapy.
ECCO Statement 9I
Active luminal Crohn's disease should be treated if present, in conjunction with appropriate surgical management of fistulae [EL5, RGD].
ECCO Statement 9J
Antibiotics and azathioprine/mercaptopurine should be used as the first choice of therapy for complex perianal Crohn's disease in combination with surgical therapy, in spite of a lack of clinical trials [EL4, RG D].
ECCO Statement 9K
Infliximab [EL1b, RGA] or adalimumab [EL1b, RGB] should be used as a second line medical treatment [EL1b, RGB].

9.5.2.1. Consensus views. Most initially used the same type of medical treatment options as for simple perianal disease. However, the identification and drainage of related abscesses is even more important in complex disease. All agreed that despite the lack of controlled trials, antibiotics should be started as first line therapy, but always accompanied by appropriate surgical drainage and AZA as a maintenance strategy (assuming no thiopurine intolerance) despite limited controlled data. The threshold for using biological therapy varies. Some advocate first-line use in complex perianal disease, but most advocate combining anti-TNF and surgical therapy. Although the data for anti-TNF therapy in the management of fistulating CD are more robust than for any other medical treatment, it has to be recognised that anti-TNF therapy only heals fistulae in a small minority: MRI shows that tracks persist and drainage usually recurs if treatment is stopped. There is 'Grade A evidence' for the use of IFX since placebo-controlled trials with improvement of drainage from perianal fistulae as a primary endpoint have shown efficacy for induction and one year maintenance. For ADA no specific randomised trial has been performed in patients with perianal fistulating disease and controlled evidence has only shown efficacy after maintenance therapy in a single trial where fistula remission was a secondary endpoint (grade B evidence). Consequently the Consensus was that anti-TNF therapy should not be used as first-line therapy, but in conjunction with surgical drainage, antibiotics, or thiopurine therapy, although the sequence and timing of each treatment was not agreed.

9.5.3. Medical therapy

9.5.3.1. Metronidazole and/or ciprofloxacin. Uncontrolled case series are the only real evidence for using these agents in these patients.[67–70] on the effect of metronidazole and/or ciprofloxacin in perianal Crohn's disease. A recent small RCT comparing metronidazole 500 mg ($n=8$) and ciprofloxacine 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.[71] 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.

9.5.3.2. Azathioprine/mercaptopurine. There are also no RCTs assessing the effect of AZA or MP on the closure of perianal fistulae as the primary end point in Crohn's disease. 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,[72] in addition to uncontrolled case series. In this context, AZA and MP appear to be effective in both closing and maintaining closure of perianal fistulas.[73]

9.5.3.3. Anti-TNF agents

9.5.3.3.1. Infliximab. IFX was the first agent shown to be effective in a RCT for inducing closure of perianal fistulae and for maintaining this response over one 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 on 2 visits 1 month apart) in 17/31 (55%) of cases.[74] The ACCENT II trial confirmed this initial response (69%, or 195/306 at 14 weeks), and randomised responders to receive 5 mg/kg every 8 weeks, or placebo).[75,76] At week 54, 33/91 (36%) on IFX 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% on infliximab (23% placebo, $p=0.01$). Maintenance IFX reduces hospitalisation and surgery.[77] These effects have been confirmed in clinical practice by several uncontrolled case series.[78,79] There are no data on the effect of infliximab on simple Crohn's perianal fistulas.

9.5.3.3.2. Adalimumab. Despite the lack of a RCT 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 weeks) clinical trials comparing ADA to placebo. In CLASSIC-1 (Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's disease) ADA at 80/40 mg, 160/80 mg or placebo was administered and 32/299 patients had draining perianal fistulae.[80] In GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) a high dose induction regimen (160/80 mg) or

placebo was administered to 325 patients, who had lost of response to or were intolerant of IFX.[81] Of the 325 patients, 45 had perianal fistulae. In both trials no difference was found between placebo and any of the ADA induction strategies for fistula response or remission (same criteria as for IFX). In the CHARM trial (Crohn's trial of the fully Human Antibody Adalimumab for Remission Maintenance) 117 of the 778 patients had actively draining perianal fistulae.[82,83] All patients received open label induction of 80 mg/40 mg ADA and at week 4 they were randomised to receive either 40 mg weekly, 40 mg every other week or placebo injections for one year. Fistula response and fistula remission (cessation of drainage from all orifices) at week 26 and 56 were secondary endpoints. Fistula remission was more often observed in ADA-treated patients at week 26 (30% vs 13%, $p<0.04$) and at week 56 (33% vs 13%, ($p<0.02$).[83] In an open label trial (22 patients, treated with ADA 160/80 mg induction) efficacy (fistula remission 23%, 5/22) was suggested at 4 weeks.[84]

9.5.3.3.3. Certolizumab pegol. One 20 week trial with open label induction (PRECiSE-2) and one induction and maintenance trial (PRECiSE-1) compared CZP 400 mg 0–2–4 weeks (or placebo in PRECiSE-1) and then 400 mg or placebo every month.[85,86] In PRECiSE-1 107 patients had draining fistulae at baseline at week 26, 30% of CZP and 31% of placebo patients achieved fistula remission (secondary endpoint, criterion see IFX). In PRECiSE-2, 58% of patients had perianal fistulae draining and at week 20, 54% (CZP) vs. 43% (placebo, not significant) of patients had achieved fistula remission. The studies were not powered to show a difference for remission of fistula draining at the end of trial, but at present there is no controlled evidence indicating a beneficial role of CZP in patients with perianal fistulae related to CD.

9.5.3.3.4. Ciclosporin (CsA). The only data on intravenous CsA in perianal Crohn's disease come from several uncontrolled case series which, as a whole, include fewer than 100 patients.[87] Patients who responded were converted to oral CsA, but response was rapidly lost on drug withdrawal.

9.5.3.3.5. Tacrolimus. Uncontrolled case series indicated that tacrolimus may be effective for perianal CD.[88–92] 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 fistulae), but not at inducing remission (closure of 100% of fistulae), in perianal Crohn's disease after 4 weeks.[93]

9.5.3.3.6. 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.[94]

9.5.4. Surgical procedures for perianal Crohn's disease

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 caused by the location and complexity of the fistulae. Fistulectomy and fistulotomy should 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.[95,96]

During the last 5 years, several small cohort studies have shown that the combination of seton placement *and* IFX is superior to either strategy alone, probably because of better drainage of abscesses and fistulae.[97] This combination gives better response,[98] longer effect duration and lower recurrence rate.[99,100] Moreover, reparative surgery (e.g. mucosal flap or fistula plug) during IFX therapy may improve long-term healing rates.[100] 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.

9.5.5. Monitoring the therapeutic response

> ECCO Statement 9L
> In evaluating the response to medical or surgical treatment in routine practice, clinical assessment (decreased drainage) is usually sufficient [EL2b, RG D]. To quantify treatment efficacy the Perianal Crohn's Disease Activity Index (PCDAI) should be used [EL5, RGD]. In the setting of clinical trials, MRI in combination with clinical assessment is now considered mandatory [EL2b, RG D].

9.5.5.1. Consensus views. Most participants report using more than one method to assess the therapeutic response. Clinical assessment, as described by Present,[74] 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, P(C)DAI alone or in combination with other techniques.[88,94] 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.

9.6. Continuing therapy for perianal Crohn's disease

> ECCO Statement 9M
> Azathioprine/6-mercaptopurine [EL2B, RG C], infliximab [EL1b, RG A] or adalimumab [EL1b, RG B] or seton drainage, or a combination of drainage and medical therapy [EL3 RG C] should be used as maintenance therapy. All maintenance therapies should be used for at least one year [EL1b, RG A].

There are no data on the effect of AZA/MP as maintenance therapy for fistulae after induction with IFX, or during IFX maintenance therapy. Around 75% of patients in the

ACCENT II trial were already on AZA/MP prior to recruitment,[75,76] but this medication was continued together with IFX in only 30%. This implies that although IFX maintained longer fistula closure than placebo in this trial, it occurred with AZA/MP as background therapy in some cases.[75] Nevertheless for perianal disease, only maintenance therapy with IFX has been shown to reduce hospitalization and surgery.[77] For ADA, controlled maintenance data with perianal fistulating disease as a primary endpoint, indicate efficacy but data on reduction of hospitalization and surgery for patients with fistulating disease are not available.

9.6.1. Consensus views

More than 90% believe that maintenance therapy after successful cessation of fistula drainage is mandatory. The preferred drugs were AZA/MP, IFX or ADA as scheduled retreatment for at least one year, depending on the agent needed to induce remission.

9.6.2. Therapeutic approach in the event of infliximab failure

ECCO Statement 9N
In the event of anti-TNF failure, the use of azathioprine/mercaptopurine or methotrexate, with antibiotics as adjunctive treatment, is the first therapeutic choice [EL5, RG D]. Depending on the severity of the disease, a diverting ostomy can be performed and can rapidly restore quality of life, or proctectomy as the last resort [EL5, RG D].

9.6.3. Surgical intervention in conjunction with infliximab treatment

There is real concern about the use of anti-TNF treatment in the presence of undetected perianal sepsis. It is, therefore, important to perform surgery (by EUA) for perianal disease including abscess drainage and seton placement before, or at the start of IFX therapy, to avoid septic complications and optimise therapeutic results.

9.7. Management of non-perianal fistulating Crohn's disease

9.7.1. Enterocutaneous fistulae

There are no randomised-controlled trials 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 on IFX had abdominal enterocutaneous fistulae.[96] For the 25 patients (out of 282) with rectovaginal fistulae in the ACCENT II trial, IFX was only modestly effective (45% closure at week 14).[76] The management of enterocutaneous fistulae in CD is a complex, multidisciplinary challenge, and referral to a specialist centre is recommended. Gastroenterologists and colorectal surgeons should particularly beware early re-operation to close a fistulous track, because this is often associated with recurrence or further complications, unless the nutritional state is optimised.

9.7.2. Enterogynaecological fistulae

ECCO Statement 9O
Low anal-introital fistula may not need surgical treatment [EL5, RG D] if asymptomatic.

ECCO Statement 9P
If the patient has a symptomatic fistula, surgery is usually necessary (including diverting ostomy) [EL5, RG D]. Active Crohn's disease especially with rectal inflammation should be treated medically prior to surgery [EL5, RG D].

Intestinal small bowel or sigmoid-gynaecological fistulae can usually be treated with resection of the diseased bowel segment [EL5, RG D]. Surgical therapy for enterogynaecological fistulae should be precisely tailored to the individual patient. Rectovaginal fistulae failing conservative treatment should have surgery with an advancement flap and/or diverting -ostomy if associated with unacceptable symptoms. Most in the Consensus believed that interventional techniques such as fistula plugs or glues need to be evaluated in controlled trials [EL5, RGD]. Other techniques for recurrent fistulation, such as gracilis muscle interposition, have been reported to be successful,[101,102] but specialist assessment and management is essential.

Systemic corticosteroid therapy (>20 mg prednisolone equivalent for more than 2 weeks) increases the risk of septic post-operative complications and should be tapered prior to surgery if possible. Purine analogues and anti-TNF agents do not appear to confer a significant risk of septic complications in proctological surgery (see Section 7 in Current management).

10. Crohn's disease in children and adolescents: diagnosis and treatment

Principal changes with respect to the 2004 ECCO guidelines

Both exclusive enteral nutrition (EEN) and corticosteroids (CS) are effective for induction of remission of Crohn's disease in children but EEN has fewer side effects and promotes growth [Statement 10C].

Infliximab is effective for induction and maintenance of remission in paediatric Crohn's disease [Statement 10 I].

Multidisciplinary teams in paediatric gastroenterology centres are recommended for the care of children with CD [Statement 10M].

10.1. Introduction

According to recent literature, the incidence of CD in children and adolescents is approximately 3 (range 1–8)/100,000, and has risen across Europe in the past decade.[102–111] In up to 20% of all patients, the disease presents before the age of 18 years, and even in very young children (age <2 years) CD may occur.[112] There are specific differential diagnoses that

are particularly relevant to children presenting with suspected CD, including primary immunodeficiency disorders.[113,114] In addition, there are clear differences between adult and paediatric/adolescent onset CD in terms of natural history, the impact on the patient and appropriate therapeutic strategy.[115,116] For example, recent studies have demonstrated that the phenotype of CD presenting in the young differs from adult onset disease, with more extensive distribution at presentation and extension of disease during the first 2 years of diagnosis in approximately one third of patients.[116] Other features which are relevant to paediatric CD include growth failure, which is present at diagnosis in 10–40% of affected children.[117–119] Finally, chronic disease presenting in childhood and adolescence may be associated with marked psychological morbidity which impacts on education, relationships, psychosexual development and adherence to therapy.[120–123] These features mandate distinct guidelines on disease management for this patient group. The original ECCO consensus guidelines for the management of children and adolescents with CD have recently been revised based upon advances in the literature since 2004 and are presented below.[124]

10.2. Diagnosis

ECCO Statement 10A
Children and adolescents with suspected IBD require a thorough history and examination, including assessment of growth velocity and pubertal stage [EL4, RGC]. Normal laboratory investigations do not exclude a diagnosis of IBD [EL 2b, RG B]. Normal levels of faecal surrogate markers for intestinal inflammation, such as calprotectin or lactoferrin, make active disease in the lower gastrointestinal tract unlikely and may guide the need for invasive investigation [EL 3b, RG B].
ECCO Statement 10B
Initial investigation should consist of colonoscopy (including terminal ileal intubation) with multiple biopsies [EL2b, RG B], upper GI endoscopy with multiple biopsies [EL2b, RGB], and small bowel imaging [EL2b, RGB]. The technique used to examine the small bowel will depend on local expertise; but dynamic contrast-enhanced magnetic resonance imaging can reliably show most lesions of Crohn's disease without exposure to ionizing radiation [EL 2b, RG C].

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".[125] This group felt it is essential to establish a diagnosis of the type of disease, as well as to determine severity, localization and extent of the disease, *before* treatment is started. The ECCO Consensus agrees that all children suspected of Crohn's disease should have a complete work-up at the time of diagnosis.

Therefore all patients with suspected IBD should have a full medical history including abdominal and extra-intestinal symptoms, fever, stool pattern, growth velocity over the last year(s) and family history of IBD.[126] Physical examination must include oral and perianal inspection, anthropometric measurements and evaluation of the pubertal stage. Laboratory investigations should include signs of acute and/or chronic inflammation (ESR, CRP, and platelet count), anemia, hypoproteinaemia and signs of malnutrition. Faecal culture for infections, including *C. difficile* toxin assay, is recommended with microscopy to exclude parasites if there is a relevant travel history. It is important to note that the absence of the typical symptoms of abdominal pain and diarrhoea or signs of inflammation do not exclude a diagnosis of CD. Thus, data of 392 prospectively enrolled children with newly diagnosed CD in 18 US/Canadian centres showed that 21% with mild CD had normal values for the four most commonly used markers, haemoglobin level, platelet count, albumin level, and erythrocyte sedimentation rate.[127] Growth retardation may be the only symptom at diagnosis,[118,119] therefore it is essential to assess not only length, weight, and BMI according to sex and age matched percentiles, but also the growth velocity over the last year, if available.

Faecal surrogate markers for intestinal inflammation may be more helpful than serological markers in deciding whether an endoscopy is required.[128–135] However, most studies rely on the presence of colonic inflammation and the performance of these markers in CD presenting in the small intestine has not been systematically explored. If the level of faecal surrogate marker is constantly elevated but colonoscopy is normal, a site of inflammation should be sought in the small intestine. However, it is important to stress that these markers are non-specific and not sufficient to confirm *or exclude* a diagnosis. Faecal calprotectin and faecal lactoferrin have been studied most and seem to have equal performance in paediatric and adult patients.

Evidence from the literature supporting colonoscopy with ileal intubation, and not simply sigmoidoscopy, is provided by retrospective cohort studies.[136–140] 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.[141–144] Endoscopy in children should be performed by a gastroenterologist with training and experience in paediatric endoscopy. For safety reasons and to avoid psychological trauma from endoscopy, deep sedation or anaesthesia performed by an anaesthetist/paediatrician experienced with these methods in children and adolescents should be applied during upper and lower endoscopies in this age group.[145,146]

Small bowel investigation is indicated in all patients at diagnosis to guide therapeutic management and detect strictures that may need surgical resection even though the terminal ileum may appear normal at colonoscopy.[147,148] In the "Porto criteria" small bowel follow-through was the recommended imaging modality in children.[125] However, concern about the proven increased risk of high radiation exposure in this patient group mandates the use of alternative techniques where possible.[149,150] Contrast enhanced MRI with ingestion of a hyper-osmotic solution to aid resolution of small

bowel loops either orally or via MRI enteroclysis is the preferred imaging technique if available.[151–153] As in the adult population, MRI is also the method of choice for imaging pelvic fistulae and abscesses in paediatric patients.[154] Neither high resolution trans-abdominal ultrasound or dynamic Doppler sonography are sufficient for the initial work up of the small bowel, but may be used as an initial assessment of symptoms or to look for complications during follow up.[155,156]

Small bowel capsule endoscopy may be considered as a *diagnostic* investigation in children with suspected small bowel Crohn's disease when endoscopy of the terminal ileum was normal or technically not possible and other imaging techniques have not provided the diagnosis.[157–159] Although not evaluated in large numbers of children, small bowel capsule endoscopy is considered safe with low risk of impaction beyond infancy.[160–162] In patients with IBD the risk for capsule impaction is higher than in other indications (bleeding, protein loosing enteropathy etc.). In young children, problems in swallowing the capsule may require endoscopic replacement of the capsule in the duodenum.[160,163,164]

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. Immunomodulators such as AZA should be introduced early to prevent disease progression in selected patients. Evidence from clinical trials in children with CD is scarce, and treatment decisions are often based on extrapolation from the adult literature. However, some good quality clinical trials have been performed during the past 5 years, providing the basis for these guidelines. The initial treatment of CD in children depends on disease severity and distribution.

10.3.2. Induction therapy

ECCO Statement 10C
Both exclusive enteral nutrition (EEN) and corticosteroids are effective for induction of remission irrespective of disease activity or location [EL1a, RGA]. However, EEN has fewer side effects and promotes growth [EL2b RGB]. Elemental enteral formula is not more effective compared to polymeric formula feeds [EL3, RG C].

A meta-analysis of 11 trials comparing efficacy of corticosteroids versus exclusive enteral nutritional (EEN) therapy in 394 children with active CD demonstrated that both options are equally effective (OR 0.96, 95%CI 0.6 to 1.14).[165] This finding is not supported by the recent Cochrane review including both adult and paediatric patients, which concluded that steroids were significantly more effective.[166] However, in children, EEN has significant advantages over steroids, due to its beneficial effect on increasing growth velocity and reducing mucosal inflammation.[167–169] The marked differences in the efficacy of EEN between adult and paediatric studies may be explained by increased compliance in children with a lower dropout rate in the EEN group, resulting in enhanced results in 'intention-to-treat' analyses. EEN is effective at inducing remission irrespective of disease location, although there is evidence that children with colonic disease show a better response if there is also ileal involvement.[170] There is insufficient evidence to suggest that elemental (or oligomeric) formula has greater therapeutic efficacy than non-elemental (polymeric) formula feed.[171] However, the supplementation of only part of the daily energy intake is less effective in inducing remission and should not be recommended for this purpose.[172]

ECCO Statement 10D
Budesonide is effective and favoured over prednisolone in mild to moderate active ileo-caecal CD because of significantly fewer side effects [EL1b, RG A]. The role of budesonide in the treatment of severe or extensive Crohn's disease is uncertain.

Although most paediatric patients with CD initially respond to corticosteroids, the proportion of those entering histological remission is unknown.[173] Initial steroid resistance occurs in 11–17% and after one year from diagnosis, 30% of the paediatric patients are steroid dependent.[174,175] In prospective randomised-controlled trials the effect of budesonide was comparable to prednisolone in patients with mild to moderate active ileocolonic CD.[177–179] Although budesonide induces less glucocorticoid bioactivity than prednisolone,[176] steroid-related side effects cannot be avoided. However, the frequency of adverse events reported in clinical trials is lower with budesonide than with prednisone.[179] Adrenal suppression with budesonide may occur as early as one week after starting therapy, particularly in children younger than 12 years of age.[180]

ECCO Statement 10E
The role of mesalazine [EL2b, RG B], antibiotics [EL4 RGD] and probiotics [EL4, RGC] for inducing remission in children with active CD is unclear.

There are no studies that demonstrate a therapeutic benefit for mesalazine, antibiotics or probiotics to induce remission in paediatric/adolescent patients with active CD. However, there is a role for antibiotics in treating Crohn's related sepsis, draining fistulae, abscesses or bacterial overgrowth.

10.3.3. Maintenance therapy

ECCO Statement 10F
Neither prednisolone/prednisone [EL5, RG D] nor budesonide [EL1a, RG B] should be used as maintenance treatment in paediatric Crohn's disease.

A recent Cochrane review and meta-analysis has reported no benefit for budesonide in the maintenance of

remission of paediatric CD.[181] There are no studies in the paediatric population investigating the maintenance role of prednisolone/prednisone; however, studies in adults have shown that long-term treatment with corticosteroids does not maintain remission. Therefore, prednisolone and budesonide should not be used as maintenance treatment in view of their negative effect on growth and bone mineralization.

ECCO Statement 10G
The role of mesalazine in maintaining remission in paediatric Crohn's disease is unclear [EL2b, RG B].

The role of mesalazine as maintenance treatment is unclear, because no studies are available in children. Extrapolation from the adult literature suggests that mesalazine has no advantage over placebo. However, mainly due to its perceived lack of side effects, mesalazine is still often used in children who present with mild disease. The role of mesalazine as prophylaxis against colorectal cancer in patients with long-term extensive active colonic CD is covered in the adult statements as there are no studies relevant to the paediatric/adolescent age group. A single study investigating the maintenance effect of the probiotic *Lactobacillus rhamnosus* strain GG in children with CD showed no benefit compared to placebo in delaying disease recurrence.[182]

ECCO Statement 10H
Azathioprine or mercaptopurine is effective for the maintenance of remission [EL1b, RG A]. Early introduction should be considered at the time of remission induction with either corticosteroids or exclusive enteral nutrition as a part of the treatment regimen in newly diagnosed paediatric patients with severe or extensive Crohn's disease [EL1b, RG A].

ECCO Statement 10I
Methotrexate is effective in maintaining remission in patients resistant or intolerant to azathioprine/mercaptopurine [EL2b, RG B].

The most effective drugs used to maintain remission appear to be the thiopurines, azathioprine (AZA) and mercaptopurine (MP). Early introduction at the time of remission induction has been shown to result in significant prolongation of the duration of remission as well as a valuable steroid-sparing effect.[183] Methotrexate is an alternative to AZA or MP if these drugs are not tolerated or are ineffective, and has shown steroid-sparing effects in retrospective cohort series.[184–187] There is one retrospective single centre cohort study suggesting benefit for thalidomide in thiopurine refractory patients of this age group, however the development of neuropathy limited use in 25% patients.[188]

10.3.4. Refractory disease

ECCO Statement 10J
Infliximab is effective for induction of remission in paediatric Crohn's disease patients with moderate to severe disease who are refractory to or intolerant of standard induction therapy [EL2b, RGB]. Regular infliximab infusions can maintain remission for patients with an initial response [EL1b, RGA] and may be effective at closing fistulae [EL4, RGC], although a significant proportion will require dose modification [EL4, RG C].

There have been no randomised placebo controlled trials assessing the efficacy of IFX as an induction regime in children/adolescents with CD. However, evidence of benefit comes from a randomised, dose-blind, open-label trial,[189] the open-label induction arm of the REACH study,[190] as well as retrospective case series.[191–198] The REACH study demonstrated the clinical efficacy of 8 weekly infliximab infusions as a maintenance therapy in children on concomitant immunosuppression who responded to IFX induction therapy.[190] Dose escalation or a reduction in dose interval may be required to maintain remission in the long term.[190,199,200] Maintenance IFX has a steroid-sparing effect,[175,190,195] as well as a benefit on growth.[190,201,202] Several case series suggest benefit in patients with fistulating disease.[193,197,203] There are case reports of benefit with alternative anti-TNF agents in paediatric CD,[204] and results from current controlled trials are awaited.

There is some evidence that concomitant immunosuppressive therapy reduces the immunogenicity of IFX and increases serum IFX concentrations in patients receiving episodic therapy.[205,206] There are, however, significant increased risks of opportunistic infections in patients taking multiple immunosuppressive therapies and case reports of fatal hepatosplenic T-cell lymphoma in patients receiving combination AZA and anti-TNF therapy.[207,208] Therefore, decisions about the role of concomitant immunosuppressives should discussed with the individual patient and family.

ECCO Statement 10K
Elective surgery should be considered in children with disease resistant to medical therapies, especially in pre-pubertal or early pubertal children with growth failure and localized Crohn's disease [EL4 RGC].

Surgical treatment is indicated in localized (stricturing) or treatment-resistant ileo-caecal disease and is associated with a significant increase in growth velocity.[209] Early intervention should be considered in the presence of

growth failure, because the "window of opportunity" might have lapsed once puberty has started.[119,210–214]

10.4. Supportive management

ECCO Statement 10L
Psychosocial support should be given to patients and their families [EL4, RG C].

The limited data available suggest that adolescents with IBD are more depressed and anxious with clinically significant social problems and have significantly worse health related quality of life scores than their healthy peers.[120–123] Therefore, special consideration should be given to the psychosocial support of children and adolescents with CD as their quality of life will improve when adequate coping skills are taught.[215]

ECCO Statement 10M
Nutritional status, growth and pubertal development should be recorded at diagnosis and during the course of disease. Nutritional deficiencies should be vigorously treated [EL3, RG B].

Growth failure is a unique complication of paediatric inflammatory bowel disease 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 for their Crohn's disease is likely to be inadequate. In these paediatric patients, treatment should be intensified and adequate intake of calories ensured.[119,172,216]

Low bone mineral density (BMD) is frequently detected in newly diagnosed children.[217–219] Risk factors for BMD are especially active inflammation, impaired nutritional status and corticosteroid therapy.[217,220–222] Studies that support regular monitoring of BMD have not been performed, but monitoring at the time of diagnosis should be considered.[117,118] The reference for normal BMD relates to adults aged 25 years, so paediatric reference ranges should be sought and results carefully interpreted to the individual and family; adjustment may need to be made for bone age. Interventions that lead to increased bone mineral content may be helpful including adequate nutrition, weight-bearing exercise and optimal disease control using immunosuppressants or biological therapies.[217,218,222,223] The role of routine vitamin D and calcium supplementation on BMD is not clear.[223,224]

ECCO Statement 10N
The care of children with CD should involve a multi-disciplinary team in a paediatric gastroenterology centre [EL5, RGD]. Transition clinics for adolescents with Crohn's disease represent optimal care and are highly recommended [EL5, RG D].

Although no studies have prospectively assessed the value of specialist clinics, there is evidence that children seen in a paediatric IBD centre are more likely to receive nutritional therapy and less likely to receive steroids than those seen in a non-specialist clinic.[225]

10.5. Conclusions

The full extent of CD in children should be assessed at diagnosis by ileocolonoscopy, upper endoscopy (both with multiple biopsies) *and* small bowel imaging. First line therapy for the induction of remission in patients with ileal/ileocolonic disease should be exclusive enteral nutrition rather than steroids, because the former has fewer side effects and a positive impact on growth velocity. Early introduction of immunosuppressive maintenance treatment reduces the relapse rate and may therefore have a significant steroid-sparing effect. IFX should be considered for patients refractory to initial induction therapies. Maintenance IFX is appropriate for patients in whom induction therapy is effective, although surgery should also be considered for patients with localized disease. It is important to assess and treat nutritional deficiencies and impaired growth aggressively and to consider the psychological morbidity associated with CD. The Consensus group considers that this is best achieved in the setting of multidisciplinary care in a paediatric gastroenterology clinic with defined adolescent transition clinics.

11. The management of pregnancy in Crohn's disease

Principal changes with respect to the 2004 ECCO guidelines

Medical therapy for Crohn's disease should generally continue during pregnancy as the benefits of controlled disease outweigh the risks of medication [Statement 11F].

11.1. Fertility in Crohn's disease

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.[226–228] Patients with IBD have fewer children than the general population, but this appears to reflect 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.[228–231,232–240] 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.[241–246]

IFX seems to affect semen quality by reducing motility *in vitro* in a small group of patients; however sperm concentration increased after infusion in one study.[247] IFX safety data in women impregnated by men on IFX have been published. In 10 pregnancies indirectly exposed to IFX through the male partner only one miscarriage and no congenital malformations were reported.[248]

11.2. 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]. Crohn's disease is a risk for preterm delivery and low birth weight [EL 1a, RG B]. Insufficient data exist about maternal morbidity and fetal mortality at surgery.

Clinical remission at conception is associated with better pregnancy outcome, although there are conflicting reports on the influence of disease activity.[229,230,249–254] In some studies, CD itself appeared to be associated with an increase in the incidence of fetal loss, stillbirths, preterm delivery, low birth weight, and developmental defects.[255,256] However, in a meta-analysis on the influence of inflammatory bowel disease on pregnancy, the incidence of low birth weight and premature birth was increased but the incidence of still birth and congenital abnormalities was not.[257] Therefore, in general Crohn's disease in the mother does not increase the risk of congenital abnormalities. Unfortunately, most studies do not report on disease activity in relation to adverse outcomes. Spontaneous abortion is not increased in patients with CD compared to the normal background population.[258] 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 indicated, especially in the third trimester.[226,259,260]

11.3. 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]. Both clinical activity and surgical interventions decline with pregnancy and parity [EL4, RG C]. Nutritional status also influences parity [EL4, RG C].

When conception occurs during a period of remission, about a third of patients relapse during pregnancy,[251] 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.[227,261,262] This underscores the importance of advising patients to conceive at a time when disease is in remission. It seems that pregnancy influences the overall course of IBD positively,[263,264] because as parity increases, the need for surgical intervention decreases. Furthermore 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 seem also to have a lower relapse rate in the years after pregnancy, compared with the years before pregnancy but specific confounders such as smoking have not been investigated or ruled out in multivariate analyses.[258] Pregnancy has an effect on the immune system, which may contribute to these findings.[265]

11.4. Mode of delivery

ECCO Statement 11E
The mode of delivery should primarily be governed by obstetric necessity and indication, but also in conjunction with the gastroenterologist and/or the colorectal surgeon. Patients with uncomplicated Crohn's disease without perianal disease or rectal involvement can deliver vaginally after obstetric evaluation has been performed [EL4, RG C]. Caesarean section should be preferred in perianal disease or rectal involvement [EL4, RG C]. An ileoanal pouch is regarded as an indication for caesarean section [EL4, RG C]. Colostomy or ileostomy patients can deliver vaginally [EL4, RG C].

The mode of delivery should primarily be dictated by obstetric necessity, but the decision should be combined with the gastroenterologist and/or the colorectal surgeon to avoid perianal complications. Caesarean section is recommended in patients with perineal disease or rectal involvement. Although some clinicians advocate caesarean section for all patients with CD, it seems reasonable to allow vaginal delivery for women with quiescent or mild disease, because no evidence can be found in the literature to support either approach.[266] Ileal pouch-anal anastomosis (IPAA) in patients with is exceptional, but is regarded as an indication for caesarean section.[236,267–271] The rationale for this is that a person with an IPAA has borderline continence and depends much more on intact, optimal sphincter function to maintain faecal continence than a patient with an intact rectum. This is extrapolated from our knowledge of patients with an IPAA for ulcerative colitis. Patients with a colostomy, ileostomy or continent 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 at all possible, because a high rate of perineal involvement has been reported, although it is better than an uncontrolled laceration.[272] A recent patient survey has indicated that patients with IBD have more problems with persisting faecal incontinence after vaginal delivery compared with controls.[273]

11.5. Surgery during pregnancy

ECCO Statement 11F
Indications for surgery in pregnant women with Crohn's disease 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 fetus than surgical intervention [EL5, RG D].

Indications for surgery in pregnant women with CD include obstruction, perforation, haemorrhage, or abscess and are no different to those for non-pregnant women.[274–277] In severely ill patients, continued illness is a greater risk to the fetus than surgical intervention.[274] There are only few case reports of surgery in CD.[275] Procedures have included proctocolectomy, hemicolectomy, segmental resection, and ileostomy. A temporary ileostomy is generally preferred, to reduce the risk of post-operative complications after primary anastomosis.[277]

11.6. Medical treatment during pregnancy

ECCO Statement 11G
Medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risk of medication.

Proactive maintenance of quiescent disease is preferred and the benefit of medication in comparison to the risk of a disease flare when stopping medication should carefully be considered when counselling pregnant patients with CD. It seems that 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. Special attention should be given to folic acid, vitamin B12 and iron deficiency and these should be corrected in women with CD wanting to conceive, since the need for these vitamins and micronutrients increases early in pregnancy.

11.6.1. Aminosalicylates in pregnancy

Sulfasalazine is the medication with the longest track record available for CD. It is safe during pregnancy and nursing.[261,278–280] Kernicterus has been postulated as a potential hazard because of binding of the drug to plasma proteins, but has not been reported to be relevant in clinical practice [EL4, RG C].[281] Folate is important for neural tube development during pregnancy, so because sulfasalazine treatment interferes with absorption, folate supplementation (about 2 mg/day) is recommended. Mesalazine has also proven to be safe during pregnancy for doses up to 3 g/day,[262,282–286] but the safety of higher doses is uncertain [EL4, RG C]. Meta-analyses have identified either no significant increase in congenital malformations,[287] or a slight increase in congenital abnormalities in CD treated with 5-ASA, but could not determine whether this risk was secondary to active disease or medication.[257] [EL1a, RG B].

11.6.2. Antibiotics in pregnancy

Antibiotics, most often metronidazole and ciprofloxacin, are used as first line therapy for perianal CD. Although metronidazole is mutagenic in some bacteria and carcinogenic in mice after long-term use, this has never been reported in humans [EL1a, RG A].[288] Metronidazole has generally been considered safe by most obstetricians after the first trimester, but recent evidence that it might be associated prematurity suggests that it should be used with caution and only if there is no alternative.[289] 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.[290,291] [EL3b, RG B] Amoxicillin ± clavulanic acid seem also to be safe.[292,293] To minimise risk during pregnancy, the shortest possible antibiotic treatment course should be prescribed.

Tetracyclines and sulphonamides should be avoided during pregnancy. Tetracyclines can cause retardation of fetal skeletal development and discoloured teeth. Sulphonamides interfere with folic acid metabolism and are teratogenic in animals, which develop cleft palate and have high mortality [EL4, RG C].[294]

11.6.3. Corticosteroids in pregnancy

Corticosteroids cross the placental barrier but are rapidly converted to less active metabolites by placental 11-hydroxygenase, resulting in low fetal blood concentrations. Prednisone and prednisolone are more rapidly metabolised than alternative compounds. Only a marginally increased risk (OR 3.0, 95%CI 1.08–8.54) of oral cleft malformations has been shown in a meta-analysis after exposure to corticosteroids during pregnancy.[295] Preterm birth has also been described.[296] In humans no other increase in congenital malformations has been found [EL3b, RG B].[261,297] Enemas and suppositories are considered acceptable until the third trimester [EL5, RG D].[298]

11.6.4. Budesonide in pregnancy

No studies have reported on the safety of budesonide in pregnant patients with IBD. The compound has marked first pass hepatic metabolism and studies with inhaled budesonide suggest that the drug is safe at the doses tested (much lower than the usual dose in IBD) [EL3b, RG B].[299,300] The outcome of pregnancies in 8 mothers who received budesonide 6 to 9 mg/day for CD was uneventful.[301] In animals, toxic doses of budesonide have shown both teratogenic and embryocidal effects [EL4, RG C].[302]

11.6.5. Thiopurines in pregnancy

Most of the experience with AZA and MP in pregnancy comes from the transplant and rheumatology literature. AZA is considered safe in these populations, with no consistent reports of abnormalities of fertility, prematurity, or congenital defects.[303–305] [EL3b, RG B] The FDA rating (D) is, however, based on anecdotal reports of high abortion rates.[306,307] [EL4, RG C] Studies in animals given doses equivalent to 1.5 mg/kg for MP and 2.5 mg/kg for AZA, report a risk of low birth weight, but up to 10-fold higher doses in animals have been associated with an increased incidence of congenital malformations, prematurity, low birth weight and chromosomal abnormalities [EL3b, RG C].[308,309] In IBD, follow up studies on pregnancies during treatment with AZA or MP reported normal deliveries and no excess rates of prematurity, spontaneous abortion, congenital abnormalities, or neonatal/childhood infections [EL3b, RG B].[310–313] One study using national Danish registries and databases suggested that in 20 pregnancies exposed to AZA or MP (9 in actively smoking women) the rate of preterm birth,[296] low birth weight and congenital abnormalities was higher compared to the reference group, although confounding factors such as disease activity may not have been adequately accounted for. A prospective randomised study, currently published as an abstract, showed that outcome in pregnant patients treated with thiopurines was similar to that of the general population.[314] In fathers using MP within three months of conception a study of 50 pregnancies reported a higher incidence of pregnancy-related complications [EL3b, RG C].[315] In conclusion, although AZA and MP have FDA rating D, this extrapolates from animal data and human studies suggest that thiopurines are safe and well tolerated during pregnancy.

11.6.6. Ciclosporin in pregnancy

As with other immunosuppressants, most data on CsA in pregnancy come from transplant and rheumatology literature [EL4, 1a, 3b, RG C, A,B].[303,316–318] A higher rate of prematurity and low birth weight has been reported in babies born to mothers taking CsA, although survival rate was high. In the nine reported CsA-exposed pregnancies in patients with ulcerative colitis, no influence on fetal outcome was demonstrated in 3 births, low birth weight was observed in 2, one spontaneous abortion occurred, placental insufficiency was suspected in another (the child developed intracerebral haemorrhage and respiratory distress syndrome) and no outcome data were available for two.[252,319] A recent report from the French GETAID group reported on the outcome of an additional 8 pregnancies in mothers treated with CsA for severe ulceative colitis. One stillbirth and 2 premature deliveries were noted, but no congenital malformations [EL4, RG C].[320] There are no data available on the use of CsA in pregnant patients with CD.

11.6.7. Tacrolimus in pregnancy

The transplant literature reports apparent safety [EL3b, RG B].[321] Prematurity is more common, but no excess congenital malformations, low birth weight, or neonatal complications have been found.

11.6.8. Methotrexate in pregnancy

Animal studies have shown MTX to be both teratogenic and embryotoxic, resulting in chromosomal damage and miscarriage [EL4, RG C].[303,304] Although normal pregnancies have occurred, MTX is contraindicated in pregnancy [EL4,3b, RG C,B].[304,322] If conception should accidentally occur, therapeutic abortion should be discussed, but not necessarily performed [EL5, RG D].[323] Prospective mothers should be instructed to stop MTX immediately and start high dose folate replacement.[323] [EL5, RG D] 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 prior to conception. The same applies to prospective fathers, to allow spermatogenesis to return to normal. [EL5, RG D].

11.6.9. Anti-TNF therapy in pregnancy

11.6.9.1. Infliximab. Placental transfer of IFX occurs during in pregnancy, although it is not yet known whether this induces antibody formation in the baby.[324] Two papers have reported the use of intentional infliximab in 92 pregnancies. No significant increase in the incidence of still births, ectopic pregnancies, spontaneous abortions and low birth weight was found. In 2 pregnancies a congenital abnormality occurred, although this may relate to the underlying increased risk for women with IBD [EL4, RGC].[325,326]

11.6.9.2. Adalimumab. ADA should have similar placental transfer rates to IFX. There are case reports documenting the successful use of ADA to treat CD during pregnancy, including one in which the patient received weekly dosing throughout pregnancy for a total of 38 doses.[327–329] The Organization for Teratology Information Specialists (OTIS) reports on 33 women enrolled in a prospective study of ADA in pregnancy and an additional 89 adalimumab exposed pregnant women in a registry. The rate of spontaneous abortion (4/33, 12.1%) and stillbirth (0/29) was similar to the disease control (3/54, 5.6%) and the general population (2/50, 4.0%). The rates of congenital malformation (2/29, 6.9%) and preterm delivery are also within the expected range in the non-disease controls (2/43, 4.7%).[330]

The implications of exposure to anti-TNF therapy on the newborn are unknown. Patients and physicians should be aware of in utero exposure and treatment may best be avoided in the last trimester of pregnancy in order to prevent circulating anti-TNF antibodies in the neonate, because IgG1 antibodies cross the placenta barrier in late second and third trimesters. Patients and partners need to be fully informed about potential risks.

No data have been published on the use of certolizumab pegol in pregnancy in humans although animal data and theoretical considerations suggest that the pegylated molecule (a Fab' fragment) is not be able to cross the placenta.

11.6.10. Thalidomide in pregnancy

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 fistulae, and haemangioma have been reported [EL4, RG C].[331] Neonatal mortality rates of 40% have been reported.[332] [EL4, RG C].

11.6.11. Agents for symptomatic relief of Crohn's disease in pregnancy

11.6.11.1. Antiemetics. Metoclopramide is safe and no fetal abnormalities have been reported [EL4, RG C].[333] Vitamin B6 used as antiemetic decreased nausea during pregnancy without teratogenic effect [EL2b, RG B].[334] Ondansetron has also been reported to be safe [EL3b, RG B].[335]

11.6.11.2. Antacids and proton pump inhibitors (PPI). Antacids are safe during pregnancy, as is sucralfate. H_2 receptor antagonists are considered safe [EL2b, RG B].[336] Although PPIs have not been found to be teratogenic in humans, they have been in animal studies [EL3b, RG B].[337] When indicated, they can be used in pregnancy with caution.

11.6.11.3. Pain relief. Aspirin has shown to cause prolonged gestation, prematurity, longer labour, and greater blood loss during labour and delivery [EL4, RG C].[338] NSAIDS have not been studied adequately and are not recommended. Codeine is considered safe [EL5, RG D].[339]

11.6.11.4. Antidiarrhoeal agents. Colestyramine 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 should probably be considered safe, although congenital malformations have been reported in a selected group of patients [EL4, RG C].[340] Diphenoxylate should be used with caution.

11.7. Medical treatment when breast feeding

Data are few and advice is based on anecdotes or small studies that have measured metabolite concentrations in breast milk or the neonate.[341] Sulfasalazine is safe for breast feeding. The sulfapyridine moiety is absorbed in minimal amounts and is excreted in milk, but the milk:serum ratio is low [EL4, RG C].[281] The safety of mesalazine has been confirmed in prospective trials [EL4,3b, RG C, B].[282,283,286]

Since metronidazole and ciprofloxacin are excreted into milk they are usually not considered appropriate during the breast feeding period.[342,343]

Prednisone and prednisolone appear in low concentrations in human breast milk. To minimise exposure, a 4-hour delay after oral dosing might be recommended [EL 4, RG C].[321,344] AZA/MP metabolites are undetectable or have been detected in tiny amounts (nanomolar concentrations of 6-methyl mercaptopurine and thiouric acid) in breast milk.[345–348] Metabolites are undetectable in the few neonates studied, so it is acceptable to advise breast feeding while continuing AZA/MP/. IFX cannot be detected in breast milk, so can be considered acceptable. As with all drugs, the advice has to be tailored to the individual and carefully discussed.

12. Crohn's disease 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,[348] since 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 well-being and quality of life, but also on the activity of the disease itself.

12.2. Psychosocial factors

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 and predicts health related quality of life. Its influence upon the course of disease remains controversial [EL1b, 2b and 3b, RG B].

ECCO Statement 12B
An association between psychological factors and the aetiology of Crohn's disease is unproven [EL3b, 4, RG D] and the role of psychological factors on the disease course is controversial [EL1b, 2b, RG B].

Patients with CD seem to have slightly higher frequencies (up to 50%) of psychological disturbances and a lower quality of life compared to patients with ulcerative colitis or those with other chronic diseases.[349–355] The psychosocial consequences of the illness become more significant with increasing severity of the disease.[354,356–361] Studies investigating the influence of psychological factors on the development of CD are very limited),[353,360,361] but there is evidence that children and adolescents with IBD comprise a population at high risk of developing a psychiatric disorder.[361] According to several authors, psychological factors are considered to have a moderate influence on the course of the disease.[362–364,366,368] However, other studies did not confirm any influence of psychological factors upon CD course.[365]

12.3. Psychological factors influencing the course of Crohn's disease

ECCO Statement 12C
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].

Prospective studies suggest that patients with depressive mood and associated anxiety are at higher risk of further disease activity.[361–364] For CD, in contrast to ulcerative colitis, prospective studies have yielded contradictory results about the influence of stress or (single) major life events on disease activity.[360,367–372] In the best study to date, 704 patients with IBD (62% with CD) in Manitoba were followed prospectively for a year. Almost half the patients relapsed and only perceived stress (as documented quarterly by a validated questionnaire) was associated with relapse in multivariate analysis.[361] Still, the precise impact of stress factors on the course of Crohn's disease has not been proven.

12.4. Doctor–patient relationship, information and clinical care

ECCO Statement 12D
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.[353] Increased physician awareness of the fact that psychologically distressed patients have difficulty in processing clinically relevant information may lead to improved doctor–patient communication.[372,373] It is important to inform patients about their condition through an individual interview in conjunction with emotional support.[374] This is because a lower information-level is associated with greater concern.[375] Self-management guidebooks and patient-centred consultations improve patients' disease control,[376,377] 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.[378] Patient education programmes seem to have very limited or even no influence on the course of the illness or the psychological affect of patients.[379,380] Almost all experts at the Consensus were convinced that a good doctor–patient relationship is helpful psychologically and take psychosocial factors into account in diagnosis and therapy.[381] 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

ECCO Statement 12E
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].

ECCO Statement 12F
Patients should be informed of the existence of patient associations [EL 5, RG D].

For assessment of quality of life, two IBD-specific questionnaires have been shown to have sensitivity, reliability, responsiveness and validity for use in clinical trials: the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC).[382,383,257,353,384] Detection and treatment of psychological distress has the potential to improve health-related quality of life.[350]

To assess the demand for psychological care in chronic diseases, a validated questionnaire is now available, developed and based on inflammatory bowel disease.[385] Most experts feel 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 Crohn's disease,[386,387] as well as that of ulcerative colitis. Since strategies aimed at improving social support can have a favourable impact on psychological distress,[388] training of gastroenterologists to integrate psychosocial factors in clinical practice should be taken into consideration.

12.6. Psychotherapeutic interventions

ECCO Statement 12G
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].

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,[389–391] but also on the number of hospital days and sick-leave days.[392] The diagnosis of "Crohn's disease" alone is not sufficient to recommend psychotherapy. Studies of

psychotherapy on patients without psychological disturbance show little or no benefit.[393–396] One study combining patients with CD and ulcerative colitis has shown an influence of psychotherapy on the disease activity.[391] However, this study showed heterogeneity 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, since they are easy to learn and perform on the one hand, and due to their proven effectiveness on the other.[388,389,395] There is an advantage if the psychotherapist has experience in the treatment of patients with chronic inflammatory bowel diseases and works closely with the patient's gastroenterologist.

There are also no specific studies for the use of individual psycho-pharmaceuticals in CD. In spite of 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. Extraintestinal manifestations of Crohn's disease

Principal changes with respect to the 2004 ECCO guidelines

Arthropathy associated with Crohn's disease belongs to the concept of spondylathrtitis. The efficacy of anti-TNF therapy for axial arthropathy resistant to NSAIDs or physiotherapy is well established [Statement 13 A and B].

Pyoderma gangrenosum is initially treated with systemic steroids or calcineurin inhibitors or infliximab [Statement 13E].

13.1. Introduction

Extraintestinal manifestations (EIMs) are common in CD affecting up to 35% of patients.[397,398] Detailed prospective studies using adequate criteria are rare. Most reports are retrospective and based on review of patients' files. The occurrence of one EIM seems to predispose to others. 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. 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.

ECCO Statement 13A
Arthropathy associated with CD belongs to the concept of spondylarthritis and includes axial arthropathy [EL2b, RG B]. 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 arthritis [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 over-represented in axial arthritis related to Crohn's disease it is without diagnostic value [EL2b, RG B].

13.2. Arthropathy

13.2.1. Peripheral arthropathy

The Oxford group subclassified peripheral arthropathy into type I and type II, but only type I is associated with intestinal disease activity.[399,400] 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 less 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.[399,400] Type II is a polyarticular arthritis mainly affecting the small joints of the hand but independent of CD activity and is observed is 2.5% of patients with CD.[399] The diagnosis of arthritis is made clinically from the finding of painful swollen joints (synovitis). The differential diagnosis includes osteoarthritis, rheumatoid arthritis and arthritis associated with connective tissue diseases as lupus. It has to be differentiated from arthralgia (which may complicate corticosteroid withdrawal), osteonecrosis related to corticosteroids, and infliximab related lupus-like syndrome.[401]

13.2.2. 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.[400,402–404] The diagnosis of ankylosing spondylitis (AS) according to the modified Rome criteria includes a chronic inflammatory back pain (at night and at rest, improving by exercise),[405] morning stiffness, limited spinal

flexion and, in later stages, reduced chest expansion. Radiographs demonstrate sacroiliits, syndesmophytes and bone proliferation evolving to ankylosis ('bamboo spine'). While computed tomography is more sensitive for detecting structural abnormalities than simple radiographs, the current gold standard is magnetic resonance imaging due to its ability to demonstrate inflammation before bone lesions occur.[406,407] The overall prevalence of AS in IBD ranges from 4 to 10%.[400,404] HLA-B27 is found in 25–75% of patients with CD and ankylosing spondylitis but only in 7–15% of patients with isolated sacroiliitis.[400,403,408,409] HLA-B27 positive IBD patients seem to be at risk for the development of AS.[409] Axial arthropathy is independent of CARD15 mutations.[404,410]

13.2.3. Treatment of arthropathy related to Crohn's disease

ECCO Statement 13B
In the case of peripheral arthritis there is general support for use of short term treatment with non-steroidal anti-inflammatory agents, local steroid injections, and physiotherapy [EL4, RG D]. The emphasis should be on that of the underlying Crohn's disease [EL2c, RG C]. Sulfasalazine has a role in persistent peripheral arthritis [EL1a, RG B]. In axial arthropathy arguments in favour of intensive physiotherapy [EL2a, RG B], associated with NSAIDs are stronger, but safety concerns mean that long-term treatment with NSAIDs is best avoided if possible [EL1b, RG C]. Sulfasalazine [EL1a], methotrexate [EL1b] and azathioprine are generally ineffective, or only marginally effective. The efficacy of anti-TNF therapy for patients with ankylosing spondylitis and Crohn's disease intolerant or refractory to NSAIDs is well established [EL1b, RG B].

Recommendations for the treatment of IBD-related arthropathy are based on studies in spondyloarthropathy, predominantly ankylosing spondylitis. No single prospective controlled trial in IBD patients is available in the literature. Only small open-label trials or case reports are published.[411–414]

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. Although there is concern that NSAIDs may aggravate the underlying CD,[415–417] this risk seems low, particularly if prescribed at low dose and for short duration.[418] The use of COX-2 inhibitors such as Etoricoxib and Celocoxib appear safer with a lower risk of disease flare than conventional NSAIDs.[419,420] A beneficial effect of sulfasalazine on large joint arthropathy has been reported.[421,422] Several open-label studies and some controlled trials have demonstrated an impressive effect of IFX on peripheral arthritis.[423]

Treatment of axial arthropathy in CD is based on evidence from ankylosing spondylitis. 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-doses NSAIDs is generally inadvisable in patients with CD. The effect of corticosteroids is poorly reported. Local corticosteroid injections can be considered. Sulfasalazine, methotrexate and azathioprine are considered to be ineffective or only marginally effective in AS with axial symptoms.[424] In patients with active AS refractory to or intolerant of NSAIDs, anti-TNF agents are recommended. The efficacy and safety of IFX and ADA in ankylosing spondylitis is now well established.[423,425–430] Etanercept is not recommended because of the lack of effect in CD and the association with a flare up of IBD,[430] possibly related to low dosing.

13.3. Metabolic bone disease

Low bone mass and osteoporosis are common in both male and female patients with CD (20%–50%). Contributing factors include chronic inflammation, corticosteroid treatment, extensive small bowel disease or resection, age, smoking, low physical activity and nutritional deficiencies.[431] Diagnosis of osteoporosis is best made by a T score <-2.5 on bone densitometry (DEXA scanning) in patients over 50 years old and in patients under 50 'low bone mass' is defined by a Z-score <2.0 [EL1a, RG A].

The precision and reproducibility of ultrasound and Q-CT is not sufficient for repeated clinical measurements.[432] DEXA scanning is best performed in all patients with persistently active Crohn's disease, in those repeatedly exposed to corticosteroids and patients with long disease duration. The presence of osteoporosis identifies patients at above average risk for fracture, who should receive treatment [EL2b, RG B]. 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.[433–435] 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 like the FRAX index for postmenopausal women.[436]

ECCO Statement 13C
Patients on steroid therapy or those with reduced bone density should receive calcium and vitamin D supplements [EL2b, RG B]. Isotonic exercise [EL2B, RG B] and cessation of smoking [EL2b, RG B] are beneficial. Patients with established fractures should be treated with bisphosphonates [EL2b, RGB]. The efficacy of primary prevention of fracture with bisphosphonates has not been demonstrated in patients with Crohn's disease. Routine hormone replacement in postmenopausal women in not warranted due to the risk of side effects. Men with low testosterone may benefit from its therapeutic administration [EL3b, RG C].

Treatment with calcium 500–100 mg/day and vitamin D (800–1000 IU/day) increases bone density in patients with IBD.[431] The value of calcium and vitamin D in preventing

fractures has not been demonstrated in patients with IBD, although there is value in postmenopausal or steroid-induced osteoporosis.[437] Various bisphosphonates increase bone density in patients with Crohn's disease (for review see).[431] Fracture prevention with bisphosphonates has been clearly established in postmenopausal women and steroid-induced osteoporosis but not in young, premenopausal patients with Crohn's disease. 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.

Patients with chronic active disease should be treated according to guidelines with immunosuppressive therapy (azathioprine, TNFa antibodies) to avoid prolonged steroid treatment and general inflammatory activity. It has been shown that a significant proportion of patients with Crohn's disease are able to normalise their bone density after 3 years in stable remission.[438] Newer drugs like teriparatide, strontium ranelate or recombinant OPG should be prospectively studied in patients with Crohn's disease before their use can be recommended.

13.4. Cutaneous manifestations

ECCO Statement 13D
Diagnosis of the cutaneous manifestations of IBD is 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 [EL3b, RG C].

ECCO Statement 13E
Treatment of erythema nodosum is usually based on that of the underlying Crohn's disease. Systemic steroids are usually required [EL4, RG D]. Pyoderma gangrenosum is initially treated with systemic steroids or calcineurin inhibitors [EL4, RG D] or infliximab [EL1b, RG C].

13.4.1. Erythema nodosum (EN)

EN is usually readily recognised. It is characterised by raised, tender, red or violet subcutaneous nodules of 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.[439,440] In recent publications the prevalence of EN in IBD and CD, respectively, ranged from 4.2 to 7.5% and seems to be higher in CD than in UC.[441–443,442] 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.[444] Because EN is closely related to disease activity despite a genetic link,[445] 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 may be added,[446] but it is exceptional to need such measures solely to treat EN.

13.4.2. Pyoderma gangrenosum (PG)

Lesions are often preceded by trauma at the site through a phenomenon known as pathergy.[447] 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.[441,442,448] 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.[449] Histopathological findings in PG are unspecific, but biopsy can be helpful to exclude other specific skin disorders.

Rapid healing should be the therapeutic goal, because PG can be 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. Corticosteroids have been considered first line treatment, with intravenous ciclosporin and tacrolimus reserved for refractory cases.[450–452] Infliximab has, however, changed the management of PG in patients with CD. Its effectiveness was first reported in small case studies.[453,454] The largest study on the treatment of PG with IFX was a multicentre, randomised, placebo-controlled trial of 30 patients, including 19 patients with IBD.[455] IFX 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the IFX group had improved compared to placebo (46% vs. 6%, $p=0.025$). At week 2, subjects in both arms were then offered open-label IFX. Overall, 29 patients received IFX with the majority of them demonstrating a beneficial clinical response: response 69%, remission 31% at week 6. The response rate was over 90% in patients with short duration of PG (<12 weeks) and less than 50% in those with disease present for more than 3 months. Until now, no trial has compared the efficacy of different immunosuppressive drugs. IFX should be considered if a rapid response to corticosteroids cannot be achieved. In patients with peristomal PG, closure of the stoma might lead to resolution of the PG lesions.[456] Topical tacrolimus is an alternative, but specialist advice is recommended.

13.4.3. Sweet's syndrome

Sweet's syndrome is characterised by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face or neck.[457] It has only been recognised as an extra-intestinal manifestation of IBD relatively recently.[458,459] It is part of the group of acute neutrophilic dermatoses that includes pyoderma gangrenosum, 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.

13.5. Ocular manifestations

ECCO Statement 13F
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 steroids [EL4, RG D]. Uveitis is treated with steroids, 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].

Uveitis and episcleritis are the most common ocular manifestations of IBD. Episcleritis may be painless, presenting simply with hyperaemic sclera and conjunctiva, but itching and a burning sensation may also occur.[460] Uveitis is less common but has potentially more severe consequences. When related to Crohn's disease it is frequently bilateral, insidious in onset and long-lasting [460]. Patients complain of eye pain, blurred vision, photophobia and headaches. The possibility of progression to loss of vision should prompt urgent referral to an ophthalmologist. Slit-lamp examination will confirm the diagnosis and permit the differentiation between anterior and posterior uveitis.

Episcleritis may be self-limiting but will usually respond to topical steroids, simple analgesics alongside the treatment of the underlying Crohn's disease.[460]

Uveitis prompts urgent ophthalmologic referral and treatment as visual loss may occur. The treatment will usually consist of both topical and systemic steroids.[460] Azathioprine, methotrexate and infliximab have each been reported to be valuable in resistant cases.

13.6. Hepatobiliary disease

ECCO Statement 13G
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].

Liver test abnormalities are common in IBD though more often associated with hepatobiliary disease in UC than in CD and are associated with a small but significant reduction in survival [EL2b, RG C]. Primary sclerosing cholangitis (PSC) is less common than in ulcerative colitis, but constitutes the most important condition relatively specific to the underlying IBD. 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, the condition will be detected by abnormal liver function tests on routine screening 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 reveal gall stone 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 is magnetic resonance cholangiography (MRCP), which will show the characteristic pattern of irregular bile ducts, bearing zones of both narrowing and dilatation.[461,462] 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 (ERCP) to confirm a suspected diagnosis.[462,463] PSC is a major risk factor for cholangiocarcinoma and colon cancer, but this complication is very much less common in patients with CD than ulcerative colitis.[463]

ECCO Statement 13H
PSC appears to respond to ursodeoxycholic acid (ursodiol), which improves abnormal liver function tests [EL1b, RG B] may, at 20 mg/kg, improve prognosis [EL2a, RG C], and will perhaps reduce the risk of colonic cancer in these patients [EL2a, RG C]. ERCP may be used to treat dominant strictures by dilatation and/or stenting [EL4, RG C]. Advanced liver disease may necessitate transplantation [EL2a, RG B].

Ursodeoxycholic acid (ursodiol), was promptly adopted as a treatment for PSC once it was shown reproducibly to improve liver enzymes,[464] 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.[465] The addition of steroids has been examined with conflicting results. Ursodiol may also reduce colon cancer risk.[466] Tacrolimus has yielded a rapid decrease in liver enzymes but no histological improvement.[467] 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.[463] In advanced disease with liver failure there is no alternative to liver transplantation.[463]

13.7. Venous thromboembolism

ECCO Statement 13I
Antithrombotic prophylaxis should be considered in all hospitalized patients with CD [EL5, RG D]. Treatment of venous thromboembolism in IBD should follow established antithrombotic therapy options [EL 1a, RG A] taking into account the potentially increased risk of bleeding [EL5, RG D].

Patients with IBD are at increased risk for venous thromboembolism (VTE), which represents an important cause of morbidity and mortality.[468–471] The prevalence of VTE in IBD ranges between 1.2 and 6.7% in clinical studies.[469–472] A population-based study and a case–control study revealed that IBD patients have a 3.5-fold greater risk than the general population and control subjects, respectively.[468,469] Deep venous thromboses (DVT) 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. 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.[472] Thus, the majority of VTE occurs during the active phase of IBD.[469] 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 based on appropriate imaging techniques.[473,474] The most widely used procedures are ultrasound and venography for diagnosis of DVT and ventilation–perfusion scan and multidetector helical computer axial tomography for diagnosis of PE.

The mainstay of therapy of acute DVT and PE is anticoagulation and should follow international guidelines.[475,476] 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 venous thromboembolism. The risk of bleeding complications of IBD patients under anticoagulant therapy compared to non-IBD patients is not known. Major gastrointestinal bleeding may occur, but is rare. A meta-analysis evaluated the use of heparin for the treatment of ulcerative colitis included in 8 randomised-controlled trials.[477] In 6 of 268 patients in the heparin groups an increase in rectal bleeding was reported: only 3 of them had to be withdrawn from the study, including one patient who required urgent surgery. No equivalent data for CD are available.

Hospitalisation for an acute medical illness is independently associated with an 8-fold-increased risk for VTE.[478] This risk can be reduced by anticoagulant prophylaxis with low-molecular-weight heparin, unfractioned heparin, or fondaparinux.[478,479] 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.[480,481] However, hospitalised IBD patients have a higher rate of VTE than non-IBD hospitalised patients, with an associated increased age- and comorbidity-related excess mortality from VTE.[470,471] Hospitalised patients with acute severe or fulminant disease, as well as those with active fistulating CD are most appropriately treated with anticoagulant prophylaxis with low-molecular-weight heparin, unfractioned heparin, or fondaparinux, especially in the event of prolonged immobilisation.[469,471,479–481] Anticoagulant prophylaxis after abdominal surgery should follow established guidelines.[478] Non-IBD specific risk factors for VTE might further increase the risk. Thus, CD patients should be informed about risk factors for VTE such as oral contraceptive use and long-distance travel.

13.8. Cardiopulmonary disease

Cardiac involvement should be considered not only rare, but also is usually subclinical [EL 2–3].The treatment of IBD-related cardiac involvement depends on the specific pattern of involvement and patients should be seen by a cardiologist. Pulmonary disease represents the least frequent extraintestinal manifestation of IBD, but it is likely that its true prevalence is unknown. Respiratory symptoms may be present in >50% of IBD patients [EL3], but these are often mild, attributed to smoking, or ignored. Drugs, including sulfasalazine, mesalazine and methotrexate may cause a pneumonitis. Respiratory symptoms in patients on anti-TNF therapy should never be ignored, because it may indicate the onset of serious opportunistic infection. The treatment of IBD-related respiratory disease depends on the specific pattern of involvement. Colonic surgery may aggravate prior airway disease [EL3].

14. Alternative therapies for CD

Principal changes with respect to the 2004 ECCO guidelines

None of the alternative medicines has shown efficacy in randomised-controlled trials for Crohn's disease. The initial positive results with omega-3 fatty acids have been offset by the negative results of two large placebo controlled trials.

14.1. Introduction

The use of complementary and alternative medicine among IBD patients is common, and physicians are frequently confronted with questions about their use.[482,483] 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. Nevertheless, experienced clinicians recognise that an enquiry about alternative or complementary therapy represents anxiety about continuing symptoms and actual or potential side-effects of conventional therapy, so such questions are best answered with empathy and explanation.

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. Confounding factors in trials of CAM for IBD include:

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

In general, complementary and alternative therapies remain unregulated, although adverse drug reactions to CAM have more than doubled over the past 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 CAM 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 of benefit 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 frank quackery or health frauds.

14.4. Use and prevalence of CAM

An appreciable number of patients with IBD use complementary therapies. A survey in 2003 among 150 patients with IBD from a tertiary centre revealed that up to 60% of patients used CAM.[484] 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 therapy (10%). Reasons for turning to CAM were generally inadequate symptom control: 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.[483] A study in children and young adults found that 40% used CAM in addition to conventional therapies.[485] The most common CAMs were megavitamin therapy (19%), dietary supplements (17%) and herbal medicine (14%). Since most patients using CAM attribute "significant" benefits to their CAM use, physicians should inquire about their use, if only to identify those patients who want more information about the therapeutic options and reasons for, or efficacy of conventional therapy.

14.5. Choice and evidence

All therapies for CD should be supported by scientific evidence of efficacy, so CAM should be evaluated using the same general approach to 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 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.

There are a number of uncontrolled observational reports on the use of CAM in IBD. The few controlled trials have been conducted mainly in ulcerative colitis and report on beneficial effects of traditional Chinese medicine, wheat grass juice, *Boswellia serrata*, aloe vera gel and bovine colostrum enemas.[486,487] These trials suffer from elementary and substantial methodological problems (related to the power, blinding, inclusion criteria and randomisation procedures) and lack sufficiently rigorous outcome measures. Almost all are uncontrolled, unblinded and underpowered, so the interpretation is difficult.

Only a few controlled studies are reported in CD where the outcome supports the use of CAM. Gerhardt et al. reported the efficacy and safety of the *B. serrata* extract H15 with 5-ASA for the treatment of active CD.[487] In this randomised, double-blind, 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. However, the beneficial effect of 5-ASA in active CD is only marginal (see chapter on treatment of active disease) and the study was not sufficiently powered for non-inferiority. In contrast to ulcerative colitis, no trial has been conducted with aloe vera in CD.

There are two prospective, randomised-controlled trials on the efficacy of acupuncture in IBD, one in ulcerative colitis and one in CD. Both compared the effect of acupuncture including a technique termed moxibustion versus penetrating sham acupuncture (p-SAC). In the UC trial, the colitis activity index fell significantly in the treatment group compared to the sham acupuncture group. However, recruitment did not reach its target and the

number of patients was small ($n=29$).[488] In the only controlled study on acupuncture for active CD, the CDAI declined significantly after treatment compared to p-SAC (−87 vs. −39 points) but did not reach the −100 point threshold of benefit.[489]

Malnutrition is prevalent both in active IBD as well as in quiescent disease, so nutrition is an essential, complementary component of conventional medicine in CD. However, nutritional therapy does not qualify for primary therapy in adults, in contrast to paediatric disease (see Section 3). Dietary supplementation with fish oil preparations in patients with CD has been reported to be beneficial for maintaining remission. A double-blind, placebo controlled study in 78 patients with CD demonstrated a significant reduction in relapse rate.[490] In contrast, two recent large trials (EPIC-1 and EPIC-2) including 753 patients have shown no differences in 1-year relapse rates between omega-3 free fatty acids and placebo (32% vs 36% and 48 vs 49%, respectively).[491] A recent Cochrane review concluded that there is no significant benefit for omega-3 free fatty acids in the treatment of CD.[492]

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, but in controlled trials in CD have so far failed to show any significant therapeutic benefit.

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