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CONSENSUS/GUIDELINES

Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease

F.M. Ruemmele[a,b,c,*,1], G. Veres[d,1], K.L. Kolho[e,1], A. Griffiths[f,1], A. Levine[g,1], J.C. Escher[h,1], J. Amil Dias[i,1], A. Barabino[j,1], C.P. Braegger[k,1], J. Bronsky[l,1], S. Buderus[m,1], J. Martín-de-Carpi[n,1], L. De Ridder[o,1], U.L. Fagerberg[p,1], J.P. Hugot[q,r,1], J. Kierkus[s,1], S. Kolacek[t,1], S. Koletzko[u,1], P. Lionetti[v,1], E. Miele[w,1], V.M. Navas López[x,1], A. Paerregaard[y,1], R.K. Russell[z,1], D.E. Serban[aa,1], R. Shaoul[ab,1], P. Van Rheenen[ac,1], G. Veereman[ad,1], B. Weiss[ae,1], D. Wilson[af,1], A. Dignass[ai,1], A. Eliakim[aj,1], H. Winter[ag,1], D. Turner[ah,1]

[a] *Department of Paediatric Gastroenterology, APHP Hôpital Necker Enfants Malades, 149 Rue de Sèvres 75015 Paris, France*
[b] *Université Paris Descartes, Sorbonne Paris Cité, 2 Rue de l'École de Médecine, 75006 Paris, France*
[c] *INSERM U989, Institut IMAGINE, 24 Bd Montparnasse, 75015 Paris, France*
[d] *Department of Paediatrics I, Semmelweis University, Bókay János str. 53, 1083 Budapest, Hungary*
[e] *Department of Gastroenterology, Helsinki University Hospital for Children and Adolescents, Stenbäckinkatu 11, P.O. Box 281, 00290 Helsinki, Finland*
[f] *Department of Paediatrics, Hospital for Sick Children, University of Toronto, 555 University Avenue, M5G 1X8 Toronto, ON, Canada*
[g] *Paediatric Gastroenterology and Nutrition Unit, Tel Aviv University, Edith Wolfson Medical Center, 62 HaLohamim Street, 58100 Holon, Israel*
[h] *Department of Paediatric Gastroenterology, Erasmus Medical Center, Wytemaweg 80, 3015 CN Rotterdam, Netherlands*
[i] *Unit of Paediatric Gastroenterology, Hospital S. João, A Hernani Monteiro, 4202-451, Porto, Portugal*
[j] *Gastroenterology and Endoscopy Unit, Istituto G. Gaslini, Via G. Gaslini 5, 16148 Genoa, Italy*
[k] *Division of Gastroenterology and Nutrition, and Children's Research Center, University Children's Hospital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland*
[l] *Department of Pediatrics, University Hospital Motol, Uvalu 84, 150 06 Prague, Czech Republic*
[m] *Department of Paediatrics, St. Marien Hospital, Robert-Koch-Str.1, 53115 Bonn, Germany*
[n] *Department of Paediatric Gastroenterolgoy, Hepatology and Nutrition, Hospital Sant Joan de Déu, Paseo Sant Joan de Déu 2, 08950 Barcelona, Spain*
[o] *Department of Paediatric Gastroenterology, Erasmus Medical Center, Wytemaweg 80, 3015 CN Rotterdam, Netherlands*
[p] *Department of Pediatrics, Centre for Clinical Research, Entrance 29, Västmanland Hospital, 72189 Västerås/Karolinska Institutet, Stockholm, Sweden*

* Corresponding author at: Pediatric Gastroenterology, Hôpital Necker-Enfants Malades INSERM U989, Université Paris Descartes, Sorbonne Paris Cité 149 Rue de Sèvres F-75015 PARIS, FRANCE. Tel. +33 1 44 49 25 16; fax. +33 1 44 49 25 01.
E-mail address: frank.ruemmele@nck.aphp.fr (F.M. Ruemmele).
[1] All authors contributed equally.

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[q] *Department of Gastroenterology and Nutrition, Hopital Robert Debré, 48 Bd Sérurier, APHP, 75019 Paris, France*
[r] *Université Paris-Diderot Sorbonne Paris-Cité, 75018 Paris France*
[s] *Department of Gastroenterology, Hepatology and Feeding Disorders, Instytut Pomnik Centrum Zdrowia Dziecka, Ul. Dzieci Polskich 20, 04-730 Warsaw, Poland*
[t] *Department of Paediatric Gastroenterology, Children's Hospital, University of Zagreb Medical School, Klaićeva 16, 10000 Zagreb, Croatia*
[u] *Department of Paediatric Gastroenterology, Dr. von Hauner Children's Hospital, Lindwurmstr. 4, 80337 Munich, Germany*
[v] *Department of Gastroenterology and Nutrition, Meyer Children's Hospital, Viale Gaetano Pieraccini 24, 50139 Florence, Italy*
[w] *Department of Translational Medical Science, Section of Paediatrics, University of Naples "Federico II", Via S. Pansini, 5, 80131 Naples, Italy*
[x] *Paediatric Gastroenterology and Nutrition Unit, Hospital Materno Infantil, Avda. Arroyo de los Ángeles s/n, 29009 Málaga, Spain*
[y] *Department of Paediatrics 460, Hvidovre University Hospital, Kettegård Allé 30, 2650 Hvidovre, Denmark*
[z] *Department of Paediatric Gastroenterology, Yorkhill Hospital, Dalnair Street, Glasgow G3 8SJ, United Kingdom*
[aa] *2nd Department of Paediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Children's Hospital, Crisan nr. 5, 400177 Cluj-Napoca, Romania*
[ab] *Department of Pediatric Gastroenterology and Nutrition, Rambam Health Care Campus Rappaport Faculty Of Medicine, 6 Ha'alya Street, P.O. Box 9602, 31096 Haifa, Israel*
[ac] *Department of Paediatric Gastroenterology, Hepatology and Nutrition, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, Netherlands*
[ad] *Department of Paediatric Gastroenterology and Nutrition, Children's University Hospital, Laarbeeklaan 101, 1090 Brussels, Belgium*
[ae] *Paediatric Gastroenterology and Nutrition Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, 52625 Tel Hashomer, Israel*
[af] *Child Life and Health, Paediatric Gastroenterology, Royal Hospital for Sick Children, 9 Sciennes Road, Edinburgh EH9 1LF, United Kingdom*
[ag] *Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Mass General Hospital for Children, 175 Cambridge Street, 02114 Boston, United States*
[ah] *Pediatric Gastroenterology Unit, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel*
[ai] *Department of Medicine I, Agaplesion Markus Hospital, Wilhelm-Epstein-Str. 4, 60431 Frankfurt/Main, Gemany*
[aj] *33-Gastroenterology, Sheba Medical Center, 52621 Tel Hashomer, Israel*

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Abstract

Children and adolescents with Crohn's disease (CD) present often with a more complicated disease course compared to adult patients. In addition, the potential impact of CD on growth, pubertal and emotional development of patients underlines the need for a specific management strategy of pediatric-onset CD. To develop the first evidenced based and consensus driven guidelines for pediatric-onset CD an expert panel of 33 IBD specialists was formed after an open call within the European Crohn's and Colitis Organisation and the European Society of Pediatric Gastroenterolog, Hepatology and Nutrition. The aim was to base on a thorough review of existing evidence a state of the art guidance on the medical treatment and long term management of children and adolescents with CD, with individualized treatment algorithms based on a benefit-risk analysis according to different clinical scenarios. In children and adolescents who did not have finished their growth, exclusive enteral nutrition (EEN) is the induction therapy of first choice due to its excellent safety profile, preferable over corticosteroids, which are equipotential to induce remission. The majority of patients with pediatric-onset CD require immunomodulator based maintenance therapy. The experts discuss several factors potentially predictive for poor disease outcome (such as severe perianal fistulizing disease, severe stricturing/penetrating disease, severe growth retardation, panenteric disease, persistent severe disease despite adequate induction therapy), which may incite to an anti-TNF-based top down approach. These guidelines are intended to give practical (whenever possible evidence-based) answers to (pediatric) gastroenterologists who take care of children and adolescents with CD; they are not meant to be a rule or legal standard, since many different clinical scenario exist requiring treatment strategies not covered by or different from these guidelines.

1. Introduction

The incidence of Crohn's Disease (CD) in children is increasing worldwide, ranging from 2.5 to 11.4 per 100,000,[1] with an estimated prevalence of 58/100,000.[2] In pediatric-onset CD the genetic component is more dominant and therefore recurrence within the family is more prevalent than in adults.[3,4] Childhood is a time of dynamic physical changes, bone accrual and growth along with emotional maturation. Pediatric inflammatory bowel disease (IBD) is also more often extensive and is associated with a more aggressive disease course, including a greater propensity for disease extension and early immunomodulation.[5–7]

The cumulative risk of progression to complicated CD (i.e. fistulizing or stricturing disease) is similar to adults, but by virtue of early onset of disease, children are more likely to have undergone surgery by young adulthood. By the age of 30 years, the risk of surgical resection was 48 ± 5% and 14 ± 2% in pediatric and adult onset CD, respectively.[7] The development of new medications in clinical trial settings may have the potential to change the natural history, but entail higher costs and additional toxicity. Evidence-based consensus statements can provide guidance for physicians who care for this vulnerable and complicated population.

The objective of these guidelines is to provide state of the art guidance for medical treatment and long term management of children and adolescents with CD, while individualizing therapy based on risk and benefit, based on a thorough review of the existing evidence. The guidelines are intended to help and support (pediatric) gastroenterologists who are experienced in the care of children and adolescents.

1.1. Consensus/guidelines strategy

The guidelines have been prepared by an international working group of specialists in pediatric IBD from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO), following an open call to the societies' members constituting the Guideline Development Group (GDG). A total of 25 topics were distributed between five working groups, as such each topic was addressed by at least 2 authors who also performed a systematic review of the relevant literature.

Databases used included Medline-PubMed, Pre medline, Embase and the Cochrane Library using appropriate search strategies relevant to the clinical questions (available upon request); last search date was June 30th, 2013. There was no formal quality appraisal of the included studies but the contents were discussed during the meetings. The level of evidence was scored according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. (http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf). Particular attention was given to short and long term outcome data for efficacy and safety.

All members interacted during two face-to-face meetings, by iterative e-mails in the form of a modified Delphi process and by means of an interactive e-platform.

Controversial recommendations or those with an absence of evidence were decided by consensus. All recommendations were voted on and accepted when at least 80% agreement was achieved. ECCO national representatives and members of ESPGHAN council acted as external reviewers and provided notable contributions to the final draft.

1.2. Dissemination and update procedure

The guidelines will be published in English and posted on the websites of both societies ESPGHAN and ECCO. Tools that facilitate the use of the guidelines are made available as treatment algorithms and with supplemental tables. Guideline members will present the guidelines to their respective national societies and provide translations whenever possible. An update of the current guidelines is planned every 3–4 years by the pediatric ECCO/ESPGHAN IBD working groups. The group will seek an evaluation of the applicability and impact of guidelines by the users in order to improve the update.

1.3. Treatment goals

The aims of therapy in pediatric CD traditionally have been to relieve symptoms, optimize growth, and improve quality of life while minimizing drug toxicity. The notion that achieving mucosal healing may potentially change the natural history of the disease and decrease the need for surgery has placed "deep remission" (meaning mucosal healing) in the center of interest as being the desired treatment target. Early treatment with biologics and immunomodulatory agents improve rates of mucosal healing and clinical remission in adults[8–10] and there is first evidence in pediatric CD patients.[11] In a French GETAID comparative study of 51 adult CD patients, mucosal healing was achieved in 2/18 (11%) with methotrexate (MTX), in 9/18 (50%) with azathioprine (AZA) and in 9/15 (60%) with infliximab IFX.[12] Induction of complete mucosal healing with IFX in early-stage CD predicted sustained clinical remission and steroid-free remission in adults.[13]

However, the risks and benefits of treat to target strategies when patients are in remission are still controversial and the evidence on which to base firm recommendations for escalating medical therapy to achieve this target in low risk patients as well as the selection of patients for early aggressive immunotherapy remains difficult to ascertain. Moreover, the necessary degree of mucosal healing and the necessary depth of transmural healing are still unclear. Pediatric magnetic resonance imaging (MRI)-based inflammatory and damage scores are under development, similar to the MaRIA and Lemann-scores developed for adult CD, and offer the opportunity to evaluate more than simply mucosal healing.[14,15]

Non-invasive biomarkers of mucosal healing such as fecal calprotectin are particularly useful for children as a way of monitoring resolution or recurrence of intestinal inflammation,[16] but the cutoff value in each scenario that should trigger change in management is still elusive.

Improved quality of life is another central outcome in the management of CD, especially in children, but usually quality of life (QoL) increases as the inflammatory disease is under control. Linear growth impairment is a unique feature of pre-pubertal pediatric patients with CD and is mainly a consequence of chronic inflammation.[17] Peak bone mass, reached by late adolescence, acts as the "bone bank" for life and is decreased in approximately half of children with CD, especially in those malnourished.[18] Growth and bone density restoration can be considered a marker of

disease control and successful therapy in children, but this is not always achieved despite early introduction of immunomodulators and biologics.[19] Failure to control inflammation and monitor linear growth and bone health may result in children not achieving their genetic growth potential and having an increased risk of fractures.

Although there are many arguments in favor of using early immunomodulatory and biologic therapies to induce mucosal healing,[20,21] the selection of ideal candidates who are at high-risk for poor disease outcome must depend on predictive factors. In adults, these predictive variables include age younger than 40 years, extensive disease, perianal disease, smoking and the use of corticosteroids[22] The presence of deep ulcerations at diagnosis or relapse may be a risk factor,[23] but this has not been replicated in other studies. The large GETAID cohort identified younger age, upper gastrointestinal tract and rectal involvement (but not colonic or ileal), or penetrating disease as bad prognostic factors over 15 years of disease, while high education was protective.[24] Most of the aforementioned factors are not relevant for children whose age alone places them in the high-risk group. Furthermore, smoking is not applicable to most young children and many have extensive and upper tract disease that is often treated with EEN.

Ongoing studies of the Porto IBD working group of ESPGHAN, and the Crohn's and Colitis Foundation of American sponsored RISK study are aimed to establish more precise predictive tools in children. Until these are available, the following factors can be considered as potentially predictive for poor outcome:

- deep colonic ulcerations on endoscopy
- persistent severe disease despite adequate induction therapy
- extensive (pan-enteric) disease
- marked growth retardation >-2.5 (minus 2.5) height Z scores),
- severe osteoporosis
- stricturing and penetrating disease (B2 and/or B3 disease behavior[25,26]) at onset
- severe perianal disease

These factors suggestive of poor outcome should lead to optimization of therapy with agents that have been shown to modify the natural history of disease including immunomodulators, biologics or when appropriate surgical resection. It is plausible that the more predictors exist and the greater their severity is, the likelihood increases for poor outcome. Significant diversity of predictors found in various studies makes it impossible to define so far clear criteria of number of predictors mandating treatment escalation. Nonetheless, the aforementioned predicting variables should be considered as a whole by the clinician on an individual basis considering the entire clinical scenario.

2. Induction of remission

2.1. Nutritional therapy

Statement 1

Exclusive Enteral Nutrition (EEN) is recommended as first line therapy to induce remission in children with active luminal CD [EL1] 96% agreement

Statement 2

Partial Enteral Nutrition should not be used for induction of remission [EL2] 100% agreement

Practice points:

1. To promote mucosal healing, restore bone mineral density and improve growth, EEN should be preferred over corticosteroids for all children with inflammatory intestinal luminal disease, including colonic involvement. However, there are no firm data on the effectiveness of EEN in severe isolated Crohn's pancolitis. There are also no data to support the use of EEN in isolated oral or perianal disease
2. Duration of EEN as induction therapy is usually 6–8 weeks
3. Feeds should be given orally using a whole protein formula. Elemental feeds should only be used when there is a specific medical indication for their use (i.e. cow's milk protein allergy). Nasogastric tubes may be used in case of failure to achieve adequate oral intake but quality of life and body image should be individually balanced against the alternative treatments in each case
4. If EEN does not induce clinical response within 2 weeks an alternative treatment should be considered
5. There is no evidence to guide reintroduction of normal food at the end of EEN. The consensus panel suggests gradual food re-introduction with concomitant decrease of formula volume every 2–3 days over a 2–3 week period

2.1.1. Efficacy of EEN

To date, no placebo-controlled randomized controlled trial (RCT) of exclusive enteral nutrition (EEN) with exclusive liquid formula feeds has been conducted in children with CD, but there have been several RCTs comparing EEN to standard treatment. These are summarized in three meta-analyses,[27–29] with an overall combined remission rate for EEN in pediatric CD of 73% (relative risk (RR) 0.95, 95% confidence interval (CI) 0.67–1.34[28] and RR 0.97, 95% CI 0.7–1.4[29]). In the most recent meta-analysis, seven RCTs (two non-peer-reviewed studies) were included with a total of 204 participants (100 in corticosteroid group, 104 in enteral nutrition group, age: 4 to 18.6 years) comparing elemental,[30–32] semielemental[33,34] or polymeric liquid diets[35,36] with corticosteroid therapy. There was considerable heterogeneity with regard to treatment duration (varying from 3 to 10 weeks), disease location and duration (new onset or relapsing disease), or associated treatment. However, the overall conclusion was that induction of remission was equipotent with EEN compared to corticosteroids for pediatric CD.[28,29] Since then, a further pediatric RCT was published,[37] as well as many heterogeneous open label studies.[38,39] The vast majority of published studies support EEN as treatment for induction of remission in CD with clinical and biochemical response seen within only a few days of starting EEN.[40,41] Two large single center cohort studies containing more than 100 subjects each confirmed a treatment effect of approximately 80%.[42,43] One RCT showed the superiority of EEN over partial enteral nutrition in remission rates using the pediatric Crohn's disease activity index (PCDAI) as outcome measures at 6 weeks (10/24 [42%] vs.4/26 [15%], respectively, p = 0.035).[44]

2.1.2. Treatment modalities

The dietary source of protein (i.e. polymeric versus elemental formulas) does not appear to effect efficacy in

RCT's,[37,45–47] open label studies in children,[48] and adult meta-analyses of adult trial data.[27] In addition, polymeric feedings are better tolerated, more cost effective, and less often require naso-gastric tube feeding.[43,48] Oral EEN seems to be as effective as continuous naso-gastric tube feedings.[43] In addition, although EEN has been shown to improve quality of life in children with CD,[49,50] the use of a nasogastric tube may decrease this improvement in some patients.[50] For these reasons patients initially should be offered oral feeds with a polymeric formula, and only treated with a naso-gastric tube if unable to achieve adequate caloric intake —approximately 120% of daily caloric need.[51] There are no contrasting studies to elucidate the preferred or optimal EEN treatment duration but the range in clinical studies varies from 2 to 12 weeks, with most using 6–8 weeks.[52]

2.1.3. Efficacy according to disease location and behavior

Historically EEN was thought to be more effective in patients with small bowel disease, as studies demonstrated differential healing rates between ileal and colonic mucosa[53,54]; however, many other studies and the Cochrane meta-analysis support the use of EEN for induction of remission for all patients with *luminal disease* regardless of the site of inflammation. In studies that have specifically evaluated patients with isolated colonic disease, no differences in remission rates were noted with regards to the site of disease.[27,42,43,55,56] Nonetheless, these studies included a variety of patients with colonic involvement and it is impossible to elucidate whether EEN is as effective as corticosteroids also in isolated severe Crohn's colitis. There are no data to date to support the use of EEN for active arthritis other extraintestinal manifestations, or penetrating disease.

2.1.4. EEN and mucosal healing

Mucosal healing rates in children treated with EEN are reported in six studies ranging from 19% to 75%.[36,43,49,53,57,58] Differences in the definition of mucosal healing in these studies limit the ability to summarize the results. The only RCT to include improvement in mucosal healing as an outcome of EEN compared with corticosteroids demonstrated a clear superiority after 10 weeks of EEN with rates of 74% vs. 33%, respectively.[36] Duration of remission after EEN is controversial in the literature with some studies showing shorter[30,32] and some longer intervals to relapse[57] as compared with corticosteroids. Ten months after EEN, 39% of patients relapsed.[53] In a recent series, after 6 weeks of EEN, one-third of patients maintained remission for 2 years[59] and mean days to relapse was 162 (range: 53–301 days) on polymeric diet.[37]

2.2. Corticosteroids

Statement 3

Oral corticosteroids are recommended for inducing remission in children with moderate to severe active luminal CD if EEN is not an option [EL2 (Pediatrics), EL1 (Adults)] 96% agreement

Statement 4

In children with mild to moderate ileo-cecal CD, budesonide may be used as alternative to systemic corticosteroids for induction of remission [EL2 (Pediatrics) EL2 (Adults)] 96% agreement

Statement 5

Corticosteroids should not be used as a maintenance therapy (EL4) 100% agreement

Practice points

1. The recommended dose of oral prednisone/prednisolone (or equivalent) for active pediatric CD is in most children 1 mg/kg (to a maximum of 40 mg/day) once daily. A dose increase to 1.5 mg/kg to a maximum of 60 mg/day may be considered if response is unsatisfactory
2. When oral corticosteroids have failed, intravenous corticosteroids may prove efficacious in some patients
3. The initial dose of budesonide is 9 mg, doses up to 12 mg have been used for the first 4 weeks for induction of remission in children. Budesonide can be tapered within 10–12 weeks
4. The steroid-tapering scheme presented in the pediatric UC guidelines[60] should be used also for CD (Table 1); the table is based on common practice and group consensus

2.2.1. Efficacy of corticosteroids

Since there are few studies reporting the use of corticosteroids in pediatric IBD, treatment strategies in children are mostly extrapolated from the experience in adults.[39,61] Two pediatric RCTs[62,63] compared prednisone to budesonide and one[64] compared prednisone to prednisone plus 6-mercapto purine (MP) in children with newly diagnosed CD. In addition, pediatric IBD-registries and population-based studies have contributed additional data. Thirty day remission rates for prednisone in pediatric studies ranged from 57%[63] to 79%[64] in the RCTs and 62% in a population-based study.[65] The studies used tapering time over eight[62] to 12 weeks.[64] In clinical practice, the introduction and tapering of corticosteroids is

Table 1 Steroid tapering during induction therapy.

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
40	40	30	30	25	25	20	15	10	5	0
35	35	30	30	25	20	15	15	10	5	0
30	30	30	25	20	15	15	10	10	5	0
25	25	25	20	20	15	15	10	5	5	0
20	20	20	15	15	12.5	10	7.5	5	2.5	0
15	15	15	12.5	10	10	7.5	7.5	5	2.5	0

not standardized and is determined by the experience of the clinician.[39,60,66] A single total oral dose in the morning reduces potential harmful suppression of growth.[67] Intravenous corticosteroid administration is limited for severe, active disease.[68,39,69]

2.2.2. Corticosteroids and mucosal healing

Clinical response does not correlate with endoscopic improvement[70] and endoscopic response to corticosteroids in pediatric CD patients has been assessed in only two studies: Berni Canani[57] showed endoscopic improvement in 4 of 10 patients but mucosal healing in none after eight weeks of treatment. In the study by Borrelli et al.[36] partial mucosal healing was seen in 6 of 18 patients (33%) on corticosteroids at week 10. Similarly in adults, mucosal healing was demonstrated in 25% and 29% of glucocorticoid treated CD patients who entered clinical remission at 7 and 9 weeks respectively.[70,71] In a 1-year maintenance study, complete or near-complete endoscopic healing was achieved with budesonide alone in 24% compared to 83% in those treated with azathioprine.[72]

2.2.3. Treatment modalities and efficacy according to disease location and behavior

As in adults, the disease phenotype or location does not appear to determine response to corticosteroids in pediatric patients.[65,73–75] However, in patients with moderately or mildly active ileal disease (or ascending colonic disease), budesonide may be an alternative treatment to prednisone.[63,76,62,77,78] The two formulations of oral budesonide, pH-dependent (Budenofalk®) and controlled ileal release (Entocort®) have high topical glucocorticoid activity with low systemic bioavailability (10%).[79,78] In the study by Levine,[63] patients with colonic inflammation proximal to the hepatic flexure were included. The efficacy for inducing remission at 8 weeks in the two pediatric studies ranged from 42%[63] to 55%,[62] considerably lower than prednisone but with fewer side effects. In a follow-up study, Levine et al.[80] reported a better 7-week remission and response with 12 mg dosing vs. the standard 9 mg dosing (66% and 74% vs 42% and 51%, respectively) at seven weeks. In distal colonic disease, steroid-based enemas may be used, as in adult patients.[81] Budesonide doses should be adapted according to the age and weight in small children.

There are no evidence-based guidelines for tapering oral corticosteroids, but common practice is to decrease the dose at 7–10 day intervals,[64,60] after an initial induction period of two to four weeks.[62,75] Maintaining remission with corticosteroids is not recommended and steroid-sparing strategies are mandatory in steroid-dependency cases.

2.2.4. Steroid safety and side effects

Regarding side effects, adrenal suppression may occur as early as one week after starting therapy.[82] The risks for adverse effects are related to the dose and the length of treatment,[83] but sensitivity among individuals may vary greatly. Side effects are less frequent, but may still occur in children receiving budesonide as compared to prednisone[63,62]. Unfortunately, no biomarkers are available as yet to predict the risk of developing adverse events.[84,85,66,86] One major issue when using corticosteroids to treat children with CD is growth retardation. Therefore, steroid-avoiding or sparing treatment strategies are preferred whenever possible.

2.3. Antibiotics

Statement 6

Antibiotics, such as metronidazole or ciprofloxacin, are recommended in the treatment of perianal fistulising disease (EL 3 (pediatrics) EL1 (adults)) 80% agreement

Statement 7

In more severe perianal fistulising disease, antibiotics should be used as adjuvant (EL3) 88% agreement

Practice points

1. In perianal disease, metronidazole/ciprofloxacin-based treatments have a good short-term response and may offer a bridge to immunosuppressive medications
2. Usual daily doses for metronidazole are 10–20 mg/kg, and for ciprofloxacin 20 mg/kg
3. Azithromycin and rifaximin may be useful for induction of remission in children with mild to moderate luminal inflammatory pediatric CD
4. There is no evidence to recommend the use of anti-mycobacterial antibiotics

2.3.1. Efficacy of antibiotics

2.3.1.1. Penetrating disease. The first placebo-controlled trial to evaluate the efficacy of antibiotics in active perianal CD showed that remission (closure of all fistulas) occurred in 3/10 patients treated with ciprofloxacin, 0/8 patient treated with metronidazole, and 1/7 patients treated with placebo at week 10 (P = 0.41).[87] A meta-analysis of three trials with 123 adult CD patients with perianal fistula[88] revealed a statistically significant effect in reducing fistula drainage using ciprofloxacin or metronidazole (RR = 0.8; 95% CI = 0.66–0.98); number needed to treat was 5 (95% CI = 3–20). No pediatric trial was conducted up to date.

Management of abdominal abscesses in CD with antibiotics alone seems to be a good option for small abscesses, especially those without associated fistula and appearing in immunomodulator-naïve patients. Surgery offers better results in the remaining cases, although percutaneous drainage can avoid operative treatment in some patients. Bermejo et al.[89] analyzed 128 adult CD patients with abdominal abscesses. The highest 1-year efficacy was related to surgery (91%) as compared with antibiotic therapy alone (63%) or antibiotics combined with percutaneous drainage (30%). Failure of initial antibiotic therapy was related to immunomodulators at diagnosis (OR: 8.45; 95% CI 1.16–61.5; P = 0.03), fistula (OR 5.43; 95% CI 1.18–24.8; P = 0.02), and abscess size (OR 1.65; 95% CI 1.07–2.54; P = 0.02).

2.3.1.2. Luminal disease. Unfortunately, there are no pediatric RCTs on the effect of antibiotics to control luminal inflammation in CD. In adults, a cross-over trial showed no clinical benefit of metronidazole in comparison to sulphasalazine[90] in 78 active luminal adult CD patients (25% remission rates in each arm). Similarly, ciprofloxacin was as effective (56% remission) as mesalazine (55%) in a 6-week RCT.[91] A placebo-controlled trial of anti

Mycobacterium avium paratuberculosis (MAP) cocktail (clarithromycin, rifabutin, clofazimine vs placebo in addition to tapering steroid protocol) in 213 adult CD patients showed a significant difference in the antibiotic arm (66%) compared with placebo (50%; P = .02). However, during maintenance therapy, relapse rates were 39 vs 56% at 1 year, 26 vs 43% at 2 years and 59 vs 50% at 3 years, for antibiotics versus placebo arm, respectively. A meta-analysis of six trials of anti-mycobacterial therapy showed that the 2 trials including corticosteroids for induction of remission influenced the disease course.[92] Although a meta-analysis showed that long-term treatment with nitroimidazoles or clofazimine has some benefit for maintenance of remission in CD,[93] the risk of *Clostridium difficile* infection, the development of bacterial resistance and the side effects limit their long-term use.

In a recent systematic review and meta-analysis for active CD 10 RCTs (1160 patients) were included.[88] There was a statistically significant effect of antibiotics being superior to placebo (RR of active CD not in remission = 0.85; 95% CI 0.73–0.99, P = 0.03). Different antibiotics were administered (anti-tuberculosis therapy, macrolides, fluroquinolones, 5-nitroimidazoles, and rifaximin) either alone or in combination. Rifamycin derivatives either alone or in combination with other antibiotics showed significant effect at inducing remission in active CD.[88]

In children, Levine and Turner[94] conducted a retrospective analysis of 32 active CD children treated with an identical 8 week course of combined azithromycin and metronidazole. Azithromycin based therapy was applied due to its effect in inducing apoptosis (down regulation of Bcl-xL) and efficacy against biofilms and intracellular bacteria. Azithromycin was given 7.5–10 mg/kg, once daily (maximal dose: 500 mg), for five consecutive days/week for 4 weeks, and 3 times a week for the following 4 weeks, in conjunction with metronidazole. After 8 weeks of treatment, 21/32 (66%) patients entered complete clinical remission, and 54% of these normalized C-reactive protein (CRP). The effect was better in milder disease. A retrospective report of 23 IBD children (12 with CD) showed that rifaximin at doses 10 to 30 mg/kg for 4 weeks improved symptoms in approximately 12 patients (60%).[95]

3. Maintenance therapy

3.1. Thiopurines

Statement 8

Thiopurines (azathioprine or 6-mercaptopurine) are recommended as one option for maintenance of steroid free remission in children at risk for poor disease outcome [EL2 (pediatrics), EL1 (adults)) 96% agreement

Statement 9

Thiopurines alone are not recommended as induction therapy (EL3) 100% agreement

Practice points

1. Maximum efficacy of thiopurines may require 8 to 14 weeks
2. In patients with normal metabolism the recommended azathioprine dose is 2.0–2.5 mg/kg, and for its prodrug, 6-mercaptopurine, 1.0–1.5 mg/kg once daily
3. Full thiopurine dose may be prescribed from the outset without the need for gradual dose increase. Dose reduction is usually necessary in patients who are heterozygous in the thiopurine methyltransferase (TPMT) gene or with intermediate enzymatic activity. Thiopurines are contraindicated in the rare homozygous patients or with extremely low enzymatic activity
4. Testing of TPMT activity (genotype or phenotype) helps in the identification of patients at risk of early profound myelosuppression and is recommended prior to treatment (when available); however cytopenia can still occur despite normal TPMT activity,

Table 2 Interpretation of thiopurine metabolite profiles in case of suspected dose-dependent adverse events or refractoriness.

6-TGN (pmol/8.10^8 RBC)[134]	6-MMP (pmol/8.10^8 RBC)	Dose-dependent adverse event	Interpretation	Recommendation
Low (<230)	Low–normal (<5700)	–	Under-dosing or low compliance	Increase compliance or thiopurine dose as appropriate
Low (<230)	High (≥5700)	Hepatotoxicity and others	TPMT hyper-metabolizers	Consider allopurinol co-treatment and dose reduction to 25–33% of standard dose; or change medication
Therapeutic (230–450)	Normal or high	Hepatotoxicity and others	Therapy failure	If clinically resistant, change drug category
High (>450)	Normal	Myelosuppression	Low TPMT activity (heterozygote or homozygote)	Switch type of immunomodulation if homozygote (or absent TPMT activity) or reduce dose to half if heterozygote (or moderately low TPMT activity)
High	High	Myelosuppression and hepatotoxicity	Overdosing	Reduce dose and if clinically resistant-change drug category

The cut-off values given in this table are based on the method according to Lennard[134]; higher cut-off values (therapeutic range of 6TGN from 600 to 1200 pmol/8.10^8 RBC) are necessary when analyses are based on the method of Dervieux and Boulieu.[135]

which also does not identify patients at risk for other toxic or allergic adverse events. The actual values for enzyme activity are not reliable if red blood cells have been transfused to the patients within the previous 3 months
5. Periodic monitoring of complete blood count (CBC) and liver enzymes is mandatory during the first month, initially every 1–2 weeks with decreasing frequency thereafter, but continuing for duration of therapy once every 3 months in all patients on thiopurines (regardless of the TPMT status
6. Pancreatitis may occur early (within the first six weeks) after introduction of thiopurines and is dose-independent and usually requires discontinuation of the drug. Thoughtful consideration should differentiate true thiopurine-related toxicity from extra-intestinal manifestation of IBD reflected as pancreatitis
7. A switch between azathioprine (AZA) and 6-mercaptopurine (6-MP) can be considered in patients who develop flu-like or acute gastrointestinal symptoms
8. Increased transaminases twice above the upper normal value can be transient or resolve after drug tapering or discontinuation
9. Determination of thiopurine metabolites (6TGN and 6MMP) should be considered in patients with elevated Alanine transaminase (ALAT), cytopenia, or in suboptimal response and to monitor compliance (Table 2)
10. If allopurinol is added, the thiopurine dose should be reduced to 25–33% of the original dose, and metabolites re-evaluated. The standard adult allopurinol dose is 100 mg/d, for children allopurinol doses should be reduced (to 50–75 mg according to body weight)
11. Lifelong sun protection and regular dermatological screening is recommended in all current or past users of thiopurines

3.1.1. Efficacy of thiopurines

There is one placebo-controlled trial and several observational studies in children evaluating thiopurines for maintaining remission in children with CD. In the Markowitz RCT[64] relapse rates were 4 and 9% in the 6-MP arm (n = 27 patients) and 26 and 47% in the placebo arm (n = 28 patients) at six and 18 months, respectively, after induction of remission by prednisone in newly diagnosed moderate-to-severe CD. In retrospective case studies, AZA has been associated with prolonged maintenance of remission, decreased rates of hospitalization, corticosteroids use, and surgery.[6,96–99] However, the ~90% remission rate through 18 months observed in the Markowitz study has not been replicated in neither retrospective pediatric studies that reported ~60% remission rates,[96–98] nor in adult RCT's (see below).

The recent Cochrane review in adults with quiescent CD concluded that thiopurines had a positive effect on maintaining remission,[100] including eight trials[101–108] and a total of 550 patients (208 with AZA, 47 with 6-MP and 295 with placebo). The overall 1-year remission rate was 71% (95%CI 64–77%) for AZA treatment and 51% (36–66%) for 6-MP (lower doses of 50 mg/day) compared to 55% (95%CI 49–61%) for placebo, with OR of 2.32 (1.55–3.49%) for AZA and 3.32 (1.4–7.87%) for 6-MP. Higher AZA doses of 2.5 mg/kg/day were more effective than lower doses of 1.0 or 2.0 mg/kg/day. Adult observational trials showed decrease in surgery, prevention of perianal disease, especially if therapy is started early,[109–111] but other more recent studies challenged the efficacy of thiopurines to maintain remission.[112,113]

Data on thiopurine and linear growth are sparse. AZA at a high dose of 3 mg/kg led to height z-scores which were maintained or improved in 36% of children with CD.[114] Markowitz et al.[64] did not find any difference in growth between the 6-MP and the placebo group after 18 months of treatment. Nonetheless, growth usually follows mucosal healing; D'Haens et al.[115] reported 70% complete colonic mucosal healing after 24.4 ± 13.7 months of AZA treatment while Mantzaris et al.[72] found mucosal healing in 58% of AZA treated patients compared to 15% with budesonide after one year. The SONIC study provided prospective mucosal healing concerning the largest number of adult CD patients; of 115 patients receiving azathioprine, mucosal healing (resolution of ulcers) was observed in 16.5%.[116]

3.1.2. Thiopurine safety and side effects

Adverse drug reactions (ADR) to thiopurines have been reported in 15–46% of treated patients.[117–119] In 8%–28% the ADR lead to dose reduction and in 18%–43% therapy was discontinued. AZA given at a higher dose of 3 mg/kg/day to IBD children caused a discontinuation rate of 30%.[114] Dose-dependent toxicities can manifest weeks to years after the initiation of therapy and include hepatotoxicity and myelosuppression. At conventional dosage hematologic toxicity occurs in 1.8%–13.7% of patients.[117–119] The risk of infections is ~8%[119] but in the recent large pediatric DEVELOP and adult TREAT registries, immunomodulators were not associated with an increased infectious risk whereas biologics more than doubled the risk.[120,121]

Dose-independent toxicities usually appear within the first weeks of treatment. Pancreatitis is most often a hypersensitivity reaction, occurring in 3–4% of patients. Other dose-independent adverse reactions include gastrointestinal intolerance (5–8%), fever, flu-like symptoms, myalgia, arthralgia and rash (occurring in ~9%). A shift to 6-MP may be successful in ~50% of AZA-intolerant patients, especially in myalgia or arthralgia but may also be effective in hepatotoxicity, gastrointestinal symptoms, flu-like illness, or rash.[118] Recent small case series suggested that it may be safe and successful in some children with AZA-induced pancreatitis to attempt 6MP, but this is still not a common practice.[122] Approximately 9% of IBD patients do not respond to thiopurines[123] and those patients with higher TPMT (>14 U/ml RBC) are less likely to benefit.[124] A recent North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) statement summarized that TPMT activity should be measured (if possible) prior to initiation of thiopurines and that measuring the biochemical enzymatic activity is superior to the genetic assay.[125] In addition, three studies in IBD determined that measuring TPMT is cost effective.[126–128] A significantly greater therapeutic effect was found in pediatric IBD patients when the level of the

thiopurine metabolite 6-TGN was >235 pmol/8 × 10^8 erythrocytes while hepatotoxicity correlated with elevated 6-methyl mercaptopurine (MMP) levels (>5700 pmol/8 × 10^8 erythrocytes).[129] A meta-analysis of six studies showed that 6-TGN levels were closely associated with clinical response to the drug with an OR of 3.27 (95%CI 1.7–6.3)[130]. Measuring metabolite levels can identify under-dosing or low adherence and those who are TPMT hypermetabolizers (i.e. having low 6-TGN and high 6MMP) (Table 2). In those, adding allopurinol together with a reduced thiopurine dose can successfully restore the desired 6-TGN/6-MMP balance and clinical effectiveness.[131,132] If allopurinol is added, the thiopurine dose should be reduced to 25–33% of the original dose, and metabolites re-evaluated if available. A recent retrospective study suggested that splitting the thiopurine dose may also restore the balance in some cases but this awaits further confirmation.[133]

With regards to side effects, the relative risk of lymphoma is calculated to increase by approximately fourfold in IBD patients taking thiopurines especially in males, but the absolute risk is smaller in children and adolescents.[136,137] In children, the risk was calculated to be 4.5 cases/10,000 patient years[138] and the risk has been documented also in the pediatric DEVELOP registry.[139] In addition, a fatal hepatosplenic T-cell lymphoma (HSTCL) has occurred in nearly 40 teenage and young adult patients with IBD, almost all male, and 50% less than age 20 years at the time of neoplasia development. About half of the patients had been treated with longterm thiopurines only and the other half with longterm thiopurines and highly varied duration of anti-tumor necrosis factor antibody therapy.[140] Thiopurines have also been associated with a 4–5 fold increased risk of non-melanoma skin cancers even before the age of 50 years.[141,142] Interestingly, thiopurines were recently shown to reduce the risk of colorectal neoplasia in both CD and UC and the chemopreventive effect seemed to be better than with 5-ASA therapy.[143] Care should be taken to avoid use of thiopurines during EBV infection due to the risk of EBV associated lymphomas.

3.2. Methotrexate

Statement 10

Methotrexate is recommended as one option for maintenance of steroid free remission in children at risk for poor disease outcome (EL4 (Pediatrics) EL1 (adults)) 96% agreement

Statement 11

Methotrexate can be used as a primary maintenance therapy or in thiopurine failure (EL 4 (Pediatrics), EL1 (Adults)) 92% agreement

Practice points:

1. Methotrexate (MTX) should be prescribed at a dose of 15 mg/m^2 (body surface area) once a week to a maximum dose of 25 mg
2. After a period of a few months in sustained complete remission with normal inflammatory markers, an attempt can be made to decrease dose to 10 mg/m^2 once a week to a maximum of 15 mg
3. Methotrexate is usually administered via subcutaneous injection which is likely as effective as intramuscular; bioavailability of oral methotrexate is highly variable and there are no comparative studies with the parenteral route
4. Oral administration of folate (5 mg 24–72 h after MTX once weekly or 1 mg once daily for 5 days per week) is advisable
5. Patients in stable remission should have a blood count and ALAT monitored periodically. Use of MTX does not require surveillance liver biopsies if ALAT and ASAT are consistently normal
6. MTX is strictly contraindicated in pregnancy, as well as in the male partners, and an effective birth control method must be applied when appropriate
7. Administration of ondansetron one hour prior to injection from the outset may reduce nausea and may improve tolerance

3.2.1. Efficacy of MTX

Seven pediatric retrospective cohort studies suggest that MTX is effective in 50 to 80% of children who had failed to respond or had been intolerant to thiopurines[144–150] with a remission rate of 37–62% and 25–33% at 6 and 12 months, respectively with remission rates of 16–35% beyond the first year. In adults, a Cochrane meta-analysis of RCT's report remission rates that range from 19% to 67% at 16 weeks.[151,152] The maintenance review included 3 studies (n = 98 patients) and concluded in the pooled analysis that intramuscular MTX at a lower dose than used for induction (15 mg/week) was more effective than placebo (OR 3.11; 95%CI 1.31–7.41; NNT = 4). A pooled analysis of two small studies (n = 50) showed no difference between MTX and 6-MP for maintenance of remission (OR 2.63; 95%CI 0.74–9.37; P = 0.14).

The potential of MTX to induce mucosal healing was not evaluated except in one adult study indicating mucosal healing in 2/18 (11%) with MTX, 9/18 (50%) with AZA (P = 0.011 vs. MTX) and 9 /15 (60%) with IFX (P = 0.008 vs. MTX).[12] No pediatric studies are available. Clinical response to MTX was associated with significantly improved linear growth among responders in one pediatric cohort study including catch up growth[144]; this might be an indirect testimony for an efficient control of mucosal inflammation.

3.2.2. Treatment modalities

The effective dose of MTX is 15 mg/m^2 (to 25 mg), administered intramuscularly or subcutaneously once weekly[151,152]; the subcutaneous route seems as effective while increasing adherence.[153] The few reports on oral administration route in pediatric CD patients most often included patients with a less severe disease activity (lower baseline PCDAI[144]) or patients who were switched from subcutaneous administration to oral, once they were stable and in remission.[149] Concurrent administration of folic acid may reduce adverse effects and is recommended in all patients; data to support either once weekly or daily administration are lacking.

MTX administration during pregnancy or within 3 months of planning pregnancy is contraindicated, in both females as

well as in the male partners, and contraceptive measures must be practiced. Unlike thiopurines, MTX is not clearly associated with malignancy but rare case reports of EBV-associated lymphoma have been reported with MTX treatment.[154]

3.2.3. MTX safety and side effects

Adverse events are currently the factor that has deterred widespread use of MTX. These include nausea/vomiting, flu-like symptoms, hepatocellular liver disease and, much less frequently, myelosuppression. The issue of nausea and vomiting, can be especially disturbing and commonly leads to MTX discontinuation[154]; in a study by Uhlen et al.[145] nausea/vomiting occurred in 7/61 (11%) and Turner et al.[144] observed this side effect in 4/17 (24%) of children treated orally and in 6/39 (15%) of the subcutaneous group. Nausea and vomiting may be prevented by pre-emptive use of a serotonin 5-hydroxytryptamine (HT)3 receptor antagonist drug (ondansetron).[155] Pulmonary toxicity is a very serious but exceedingly rare complication of MTX-treatment never ever reported in pediatric CD. Elevated liver enzymes may occur in up to 30% of patients and usually respond to temporary discontinuation of MTX and/or dose reduction. The development of significant fibrosis and cirrhosis in children is extremely rare and, thus, routine liver biopsies are unwarranted if liver enzymes are consistently normal.[154] A systematic review identified 12 high-quality studies examining hepatotoxicity after the administration of MTX in the treatment of pediatric IBD.[156] Hepatotoxicity, as diagnosed by abnormal liver biochemistry, was observed in 1 of 10 patients, 1 of 15 required dose reduction, and 1 in 22 required discontinuation of MTX.[156] At a median follow-up of 0.6 years (range, 0–4.1 years), 49% of patients experienced an adverse event, of whom 13 (14%) discontinued the drug. However, no serious adverse effects occurred and all events resolved with discontinuation of MTX or dose change. Folic acid supplementation did not prevent nausea or vomiting (with folic acid: 24% vs. 21%).[150]

3.3. Biological (anti-tumor necrosis factor (TNF)) therapy

Statement 12

Anti-TNF therapy is recommended for inducing and maintaining remission in children with chronically active luminal CD despite prior optimized immunomodulator therapy (EL2) 100% agreement

Statement 13

Anti-TNF therapy is recommended for inducing remission in children with active steroid-refractory disease (EL2) 100% agreement

Statement 14

Anti-TNF therapy is recommended as primary induction and maintenance therapy for children with active perianal fistulising disease in combination with appropriate surgical intervention [EL2] 84% agreement

Statement 15

Regularly scheduled and not episodic treatment should be used to maintain remission in patients responding to induction therapy with anti-TNF agents [EL2] 100% agreement

Practice points:

1. Anti-TNF therapy is the preferred strategy to treat active perianal fistulizing disease after appropriate medical (antibiotics) and surgical (e.g. fistula/abscess drainage, seton placement) management of the perianal lesions
2. Anti-TNF therapy as primary induction therapy may be considered for selected children with high risk for poor outcome (see list of predictors above)
3. Anti TNF-agents should be considered early in the treatment plan for severe extraintestinal manifestations (e.g. severe arthritis, pyoderma gangrenosum).
4. Primary efficacy of anti-TNF therapy should be evaluated after the second or third dose and should be discontinued if no significant response is observed (i.e. primary treatment failure)
5. Available data suggest that for patients previously naïve to anti-TNF therapy, both infliximab (IFX) and adalimumab (ADA) show comparable efficacy and adverse-events profile and could be offered to the patient according to availability, route of delivery, patient preference, cost, and local regulations
6. There is insufficient evidence to define the risk/benefit ratio for mono- or combo-therapy in all CD children; while it seems that combo therapy for the first 6 months may be associated with a lower rate of antibodies development and loss of response, this benefit should be weighed against the eventually increased lymphoma risk with thiopurines on an individual basis (also based on predictors of disease outcome). The use of concomitant low dose MTX may be safer but is less evidence-based
7. Pre-medication with acetaminophen, corticosteroids or anti-histamines are not routinely indicated prior to anti-TNF therapy
8. Testing for tuberculosis (chest radiograph, purified protein derivative (PPD) skin test and/or interferon-gamma release assay) prior to anti-TNF therapy is obligatory
9. IFX should be administered at 5 mg/kg with 3 induction doses over 6 weeks (week 0-2-6) followed by maintenance therapy of 5 mg/kg every 8 weeks. Higher doses up to 10 mg/kg and/or shorter intervals to every 4 weeks may be required in those losing response to the drug or when the drug level is low. Physicians should consider reducing IFX dose when trough levels are above 8–10 μg/ml and remission is achieved
10. ADA should be administered as induction therapy at 2.4 mg/kg (maximum 160 mg) at baseline, 1.2 mg/kg (maximum 80 mg) at week 2, followed by 0.6 mg/kg (maximum of 40 mg) every other week. Alternatively, for patients under 40 kg dosing regimens of 80-40-20 mg were proposed, and for patients over 40 kg dosing regimens of 160-80-40 mg. Weekly injections should be considered in patients losing response or with low trough levels

11. In case of partial response or loss of response, measurement of serum trough level and antibodies of both IFX and ADA may facilitate decision-making whether to optimize or stop therapy
12. A switch from one anti-TNF agent to another may be considered in patients who are intolerant or have lost response to one agent; however, response rates are lower than in anti-TNF naïve patients
13. Patients who achieved sustained remission should either continue scheduled anti-TNF therapy, or may step down to thiopurines or MTX, especially in those naïve to the drug and in those who are having longstanding sustained deep remission (confirmed by endoscopy, fecal calprotectin and/or imaging)
14. Biosimilars are subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent expiry on the innovator product. Biosimilars for both infliximab and adalimumab are rapidly emerging and starting to be approved for IBD by EMA (for children and adults) and Health Canada (for adults only). Currently, however, there are data only in rheumatology for judging the effectiveness of biosimilars and therefore the guidelines do not include specific recommendations. The issue is likely to be further clarified in the near future

3.3.1. Efficacy of anti-TNF therapy

3.3.1.1. Luminal disease. Several high quality studies confirmed the efficacy of IFX for induction and maintenance therapy for pediatric CD. In the randomized REACH trial,[157] children aged 6 to 17 years with active CD despite prior corticosteroid and immunomodulator therapy received IFX at weeks 0, 2 and 6. Ninety-nine (88%) of 112 patients achieved response, and 59% were in clinical remission at week 10. Week 10 responders were randomized to receive IFX (5 mg/kg) every 8 weeks or every 12 weeks in combination with continuation of the immunomodulator (usually a thiopurine). Dosing at 8-weekly intervals was more effective than 12-weekly intervals, with 56% and 24% of responders being in remission at 54 weeks without the need for dose escalation.[157] The French pediatric randomized GFHGNP Trial,[158] showed a comparable response of 85% (34/40 patients) remission rate at week 10. Remission rates at week 60 after randomization were 61% vs 23% in the scheduled versus on demand IFX infusion arms. Other evidence supporting benefit of IFX in treating moderate to severe CD comes from nonrandomized cohort studies (Supplementary Table 1).[11,159–166] Use of IFX early in the course of the disease may result in a better outcome in selected high-risk patients,[160,163] but the results of these uncontrolled studies need to be confirmed in adequately powered clinical trials to determine the benefit/risk/cost ratio and to determine who are the most appropriate patients for early treatment. The pediatric IFX data are in keeping with numerous trials in adult patients with CD, summarized in a recent meta-analysis.[167]

The IMAgINE trial was the first double-blind randomized evaluation ADA in 192 children aged 6–17 years with moderate-to-severe CD (PCDAI > 30) despite concurrent treatment with oral corticosteroid and/or immunomodulator.[168] Previous IFX responders who lost response or who were intolerant to the drug were also eligible. Following an open-label induction phase, children were randomized to high or low dose ADA. At week 54, 31/93 children (33.3%) in the high dose arm were in clinical remission (compared with 22/95 children (23.2%) in the low dose arm; P = 0.1). Within the high dose group, the 54 week remission rate in the IFX naïve patients was 45.1% of 51 children (compared with 19% of 42 children who previously lost response or were intolerant to IFX). Similarly, the 1-year steroid-free remission in a retrospective multicenter study of 115 pediatric CD who received at least 1 dose of ADA (95% were previously exposed to IFX) was 42%.[169] British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) published a retrospective analysis of 70 CD children treated with ADA (94% had previously received IFX) with a 1, 6 and 12 months remission rates of 24%, 58% and 41%, respectively.[170]

The pediatric data are comparable to the reported adult ADA trials: the CLASSIC trial in adult CD was based on anti-TNF naïve patients; clinical remission was documented in 36%.[171] The GAIN trial showed that ADA induced remission at week 4 in 21% (34/159) compared to 7% (12/166) in the placebo group in patients with moderately to severely active CD, being intolerant or unresponsive to IFX.[172]

3.3.1.2. Penetrating disease. Supportive data on the efficacy of IFX in children with fistulizing CD are based on a small number of patients[158,162,163,173] (Supplementary Table 2). Post-hoc analyses on the effect of IFX on concurrent perianal disease in a subpopulation of 31 patients of the REACH study (28%) showed that two weeks after a single infusion, 41% of the patients attained partial or complete fistula response.[174] The recent series of the pediatric GETAID indicated a response rate to IFX therapy at 12 months of 75% 76/101 CD patients with 54% complete closure of perianal fistula (Dupont C et al. in revision). Regarding IFX for treatment of entero-vesicular fistulas in children, Teitelbaum[175] reported the absence of fistula closure in 5 treated patients, whereas Afzal[176] reported complete fistula closure in 3 out of 4 patients. Data on ADA for fistula closure in pediatric CD patients is scant. In a subgroup analyses of IMAgINE, 23.8% of patients (5/21) in the low-dose group achieved fistula remission (i.e. non draining fistula) and 28.6% (6/21) showed improvement (i.e. decrease of 50% in the number of draining fistulae) at week 52.[168] In the high-dose group, 40% of patients (6/15) achieved fistula remission (week 52). One adult trial was designed specifically to address fistula closure as the primary endpoint, demonstrating a clear benefit of IFX (55% of patients with closure of all fistulas over placebo 13%) (P = 0.002).[177] Median time to onset of IFX response was 14 days. Regarding ADA, 12-week fistula healing rates were 48% for anti-TNF-naive patients, and 26% for IFX-experienced patients.[178] At week 24, fistula healing rates were significantly greater for the anti-TNF-naive group (60% versus 28%; P < 0.01). The recent randomized, adult trial (ADAFI) showed that ADA combined with ciprofloxacin achieved higher perianal fistula closure rate than ADA plus placebo at week 12 (65% vs 33%).[179] Nevertheless, after discontinuation of ciprofloxacin therapy (week 12), the beneficial effect of initial coadministration was diminished.

3.3.2. Treatment effects

Several pediatric studies have demonstrated a strong corticosteroid-sparing effects of IFX, including the REACH study,[180] the French GFHGNP trial[158] and others.[164,162,181]

Evidence from adult studies suggests that IFX can be effective for the treatment of EIM.[182] The use of IFX for children with extraintestinal symptoms has been described in case reports for pyoderma gangrenosum, orofacial involvement, erythema nodosum, cutaneous metastatic CD of the penile and scrotal skin, uveitis, primary lung involvement, primary sclerosing cholangitis in combination with pancreatitis, and osteomyelitis.[183–187]

The Inflammatory Bowel Disease Questionnaire (IBDQ) for quality of life improved four weeks after a single infusion of IFX compared with subjects receiving placebo ($P < 0.001$).[188] Similarly in the REACH trial,[180] and in the study by De Boer et al.,[189] the mean IMPACT III score at week 10 had significantly improved from baseline.

3.3.3. Anti-TNF therapy and mucosal healing

Baldassano et al.[161] observed that endoscopic improvement four weeks following a single IFX infusion was dose dependent with only 7% of children receiving 1 mg/kg demonstrating improvement compared with 69%, and 52% in the groups receiving 5 mg/kg and 10 mg/kg, respectively. Borrelli[164] found a decrease in both endoscopic and histological scores in 66% of subjects after 3 infusions. A recent Polish study[11] demonstrated complete mucosal healing in 23% of 66 treated children at week 10. This mucosal healing rate is translated into improved growth and bone formation in REACH,[157] IMAgINE,[168] and the French GFHGNP trial.[158] Malik et al.[190] described a cohort with 42% of patients treated with ADA showing improved linear growth, especially in those entering remission regardless of the steroid sparing effect. Measurement of serum bone markers showed rapid improvement after anti-TNF therapy in both pediatric and adult CD.[191–194] Mucosal healing may be also translated into improved disease outcome and it seems that anti-TNF drugs may reduce the need for surgery.[110]

3.3.4. Treatment intensification

In clinical practice pediatric gastroenterologists will adjust dosing (from 5 mg/kg to 10 mg/kg for IFX) and/or intervals (from every 8 to every 4 weeks in IFX-treated patients and from every other week to weekly ADA administration) during scheduled maintenance therapy with the goal of sustaining continuous clinical remission. Most will consider this dose optimization rather than treatment failure or even loss of response. The importance of maintaining detectable serum trough levels of drug at trough has been recently demonstrated in the TAXIT trial in adults.[195] In TAXIT, patients on IFX treatment were randomized to dose optimization based on IFX levels (3–8 μg/ml) or based on clinical loss of response and elevated CRP. A benefit to the level-based optimization was noted in some of the endpoints, without increased cost. The superiority of the level-based optimization has been similarly reported in another recent trial.[196]

3.3.5. Combination therapy

Whether to use anti-TNF monotherapy or anti-TNF in combination with an immunomodulator has been particularly controversial in pediatrics. The SONIC trial conducted among adult patients naïve to both immunomodulators and IFX has demonstrated a modest increment in efficacy when infliximab was combined with azathioprine.[116] However, SONIC did not address whether combination therapy is superior in those previously failing AZA treatment. In both ACCENT I and II trials, there were no differences in the remission and response rate between those treated with concomitant immunomodulators and those on IFX monotherapy.[197] Similar results were obtained with ADA in the CHARM trial.[198] The continuation of AZA when starting IFX was not associated with improved clinical outcomes in a large retrospective cohort of 614 adult CD patients from Leuven.[199] On the other hand, two adult IBD cohorts showed a modest superiority of combination therapy, especially in the first 6 months of treatment.[200,201] A RCT of 80 adult CD who were randomized to stopping or continuing AZA after 6 months of combination treatment, did not show an added benefit to adding AZA to IFX after 2 years of treatment including clinical remission and mucosal healing.[202] However, most of the studies that failed to show clinical benefit to combination therapy, did report higher antibodies to IFX and lower trough levels in patients on monotherapy, which have been repeatedly associated with more infusion reaction and less favorable treatment outcome.

Indeed, in another recent study, combo therapy at IFX initiation and not at loss of response was associated with less infusion reactions and antibodies to IFX.[203] A recent meta-analysis of studies presented by Jones et al. at Digestive Disease Week (DDW) 2013[204] concluded that combination therapy with AZA is associated with improved clinical outcome compared to IFX monotherapy, even in those who failed AZA previously. However, patients on ADA or certolizumab did not profit from combo-therapy. Finally, a pediatric controlled trial from Poland randomized 78 children to stopping AZA after 6 months of IFX treatment or continuing to 1-year with comparable clinical outcomes and loss of response rate.[205]

The down side of combination therapy of anti-TNF agents with AZA is the increased risk of lymphoma, especially HSTCL.[206] Combination with MTX is attractive as there is no evidence to suggest increased lymphoma risk and there are supporting data from rheumatologic disorders on the advantage of combining MTX with IFX. In the COMMIT clinical trial, adults with CD who were treated with IFX and corticosteroids as induction therapy were randomized to receive concomitant MTX or placebo.[207] There was no difference in the clinical outcome but combination therapy was associated with high trough levels and lower antibodies to IFX. Taken together it is reasonable to allow concomitant AZA treatment in the first 6 months of IFX therapy and then consider stopping AZA, especially in boys, but individualization of the strategy is required based on prediction variables. To stop combo-therapy is only reasonable in patients in deep remission (mucosal healing). The place of MTX in combo-therapy has to be defined in pediatric CD.

Reenaers et al.[208] described that successful induction was achieved in 171/207 (83%) adult CD patients, with no significant difference between ADA combined with

immunomodulators and monotherapy (85% vs. 82%). This is in line with the aforementioned meta-analysis that did not show superiority of adding AZA to ADA.[204] On the other hand, in a BSPGHAN retrospective analysis of 70 CD children treated with ADA[170] remission rates were higher in those on concomitant immunosuppressants versus those who were not (34/46 (74%) vs. 9/24 (37%), p = 0.003).

3.3.6. Comparison IFX vs. ADA

A retrospective cohort study[209] compared 100 IFX treated with 100 ADA treated adult CD patients but no difference was noted in the clinical response rates; at 1 and 2 years, 62% and 41% of those receiving ADA vs. 65% and 49% of those receiving IFX had responded, respectively. In pediatric CD, the 54 week steroid-free remission rate of IFX in the REACH trial was 55.8% in the q8 week arm,[210] versus 45.1% with ADA in the IMAgINE trial, among those who were anti-TNF naïve and were in the standard dose arm.[168] However, in the latter trial all children were randomized whereas in the former only the 88% responding to induction therapy, making the results not easily comparable. Rates of concomitant immune-modulator use also differed, particularly after week 26, when discontinuation was permitted in the IMAgINE trial.

3.3.7. Anti-TNF safety and side effects

Antibodies to anti-TNF drugs may lead to acute infusion reactions (AIR), delayed hypersensitivity reactions, decreased serum drug levels, as well as loss of response.[211–213] Episodic treatment may increase the risk of antibody formation.[213] In three small pediatric studies, ATI was detected in about a third of CD patients.[212,166,213] A meta-analysis of 18 studies (3326 adult patients on IFX)[214] showed that the prevalence of ATIs was 45.8% with episodic infusions and 12.4% in maintenance therapy. In the IMAgINE study, only 2.3% of patients in the high-dose group and 4.4% (all had prior IFX experience) in the low-dose group developed anti-ADA antibodies (AAA) at any time during the study. One third of AAA-positive patients were on immunomodulators.

The most common symptoms of AIR are shortness of breath, flushing, nausea, headache, hypoxemia, and tachycardia. Pooling of 18 pediatric studies showed AIR in 168 of 1100 IFX-treated patients (15%), and in 228 of 7137 infusions (3%).[157–159,161–163,166,180,181,212,213,215–221] Most reactions were mild and responded rapidly to treatment: temporarily stopping the infusion or reducing the infusion rate. Premedication (antihistamines, antipyretics, or corticosteroids) did not seem to prevent the development of AIR.[218,222–224] In general, the rate of infusion reactions in children is similar to that in adults.[197,225] Severe infusion reactions manifested as hypoxia, hypotension, or breathing difficulty, are a contraindication to further IFX treatment.

Delayed hypersensitivity reactions may occur at least one day post-infusion and are characterized by arthralgia and joint swelling that may be associated with fever and/or rash. These reactions occur in up to 8% of IFX-treated children,[157,158,181,215,219,220] as reported in adults.[197,225] Positive antinuclear antibodies (ANA), without any clinical symptoms, were detected in 20%–29% of pediatric CD patients.[157,158,162,216] The clinical relevance of having a positive ANA following treatment with anti-TNFα drugs is still unclear.

Pooling of pediatric IBD studies shows serious infections in 49 of 1483 IFX-treated patients (3.3%) such as sepsis, meningitis, pneumonia, abscesses, herpes zoster or varicella infections, EBV-associated hemophagocytic lymphohistiocytosis, cutaneous tinea infections and opportunistic fungal infections.[226] In the pediatric ADA-treated CD patients from the BSPGHN cohort there was a 6% severe adverse event rate reported including two sepsis-related deaths in patients receiving also immunomodulators and home parenteral nutrition.[170]

The risk of opportunistic infections (e.g., invasive fungal infections, reactivation of latent tuberculosis) is increased especially in patients on a combination of immunomodulators and those with malnutrition.[227] In adult patients, there were no differences in numbers of side effects or opportunistic infections whether treated with IFX or ADA.[209] Testing for tuberculosis prior to anti-TNF therapy is mandatory and reduces related infections and mortality. There are case reports of adult IBD patients who had a hepatitis B relapse following IFX treatment, but no reports in children.[228] Screening for hepatitis B before the start of anti-TNF is advisable in cases of known risk. In patients who have no history of chickenpox and are seronegative, immunization against varicella zoster virus should be considered if the treatment can be delayed (as a 4–6 week interval time is required between the immunization and starting an immune suppressive treatment).

The long term safety with anti-TNF regimen is heralded by potential risk for malignancy. Hepato-splenic T cell lymphoma (HSTCL), has been reported in over 30 IBD patients treated with anti-TNFα therapy but all patients also received thiopurines[229–231] raising the possibility that the development of HSTCL is associated with thiopurine use and the combination with IFX is only a catalysator.[206] In children on biologicals, as of April 2008, 48 cases of malignancy including lymphoma and skin cancers, melanoma were identified by the FDA (31 following IFX use, two following ADA use, and 15 following etanercept use).[232] This rate of malignancy was higher than background rates in the general U.S. pediatric population, but it is currently impossible to associate the risk to the anti-TNF and not to other concomitant medications.

Anti-TNF therapy has been associated with adverse outcomes in adult IBD patients with congestive heart failure[232,233] but this is still debatable. Cases of posterior reversible encephalopathy syndrome in pediatric CD treated with IFX have been described.[234] Dermatological symptoms such as eczema, or psoriasiform lesions reported in 20% of adult IBD patients,[225] are an emerging observation also in pediatric IBD. IFX-induced psoriasis was observed in 8% (6/73) of pediatric IBD patients,[235] whereas another study reported a wide variety of skin eruptions in 8% (12/152) of pediatric CD patients.[236] Most psoriasis cases may be managed locally without the need to stopping the drug.

3.3.8. Loss of response

Primary non-response can be defined as lack of response to the induction phase of therapy over the first 6 weeks of therapy. Loss of response (LOR) indicates that a patient who had previously responded to a biologic has developed deterioration in the disease, or relapse, despite scheduled therapy with the biologic, typically with shortening intervals

since the last infusion. Measurement of trough levels can be helpful in determining the cause of LOR and guide further treatment if LOR persists.

Disease related factors leading to LOR include an increase in inflammation, recruitment of inflammatory pathways that may not be targeted by the current treatment, disease phenotypes or extent that may be refractory to certain medications, and importantly, fibrostricturing or penetrating complications of the disease. Medication related factors include problems in adherence, suboptimal treatment, or decrease in viable drug or metabolite levels. IBD unrelated factors commonly encountered are opportunistic or other infections or irritable bowel like symptoms unrelated to inflammation. Therefore, it is always critical to reassess a patient who fails therapy and to verify that the symptoms suggestive of LOR are indeed due to persistent inflammation.

The available dose escalation strategies for treating LOR are doubling the dose or shortening the intervals between infusions/injections, which may be helpful in children with low trough levels even in the presence of antibodies, albeit not in high titers. Retrospective studies from both Israel[237] and Belgium[203] found no advantage for IFX dose doubling versus interval shortening and for cost and patient-convenience reasons, dose escalation may be preferred initially. Overall, 47% had a 1-year sustained response to dose escalation or interval shortening.[237] Similarly, Kopylov et al.[238] retrospectively compared IFX 5 mg/kg q 6 weeks versus 10 mg/kg q 8 weeks in LOR adult CD patients of whom 69% and 67% regained response, respectively. Regueirro et al.[239] studied 108 CD patients who received at least 8 infusions, 54 (50%) required dose escalation over 30 months with 76% regaining a clinical response. Sandborn and colleagues evaluated LOR occurring while patients were treated with ADA 40 mg every other week. Response was regained by shortening of the interval to weekly injections.[240] In another retrospective study of 39 adults who lost response,[241] intensification of IFX therapy was successful in 27 patients (69%). Ten ATI-positive patients in that study had an intensification of IFX therapy and six (60%) demonstrated a clinical response. After intensification of IFX therapy the ATI concentration decreased in five patients.

Recent evidence suggest that adding thiopurines or MTX to patients treated with IFX monotherapy and who lost response secondary to ATI, may reverse the immunogenicity state (i.e. disappearance of ATI and regaining trough levels and clinical response).[242] In practice, both dose intensification and adding an immunomodulator may be needed when relevant ATI is detectable. When dose intensification and combination therapy is not successful or when ATI is present in high titer, a switch to an alternative biologic may be considered. Karmiris et al.[243] reviewed 168 patients who started ADA because of LOR due to high ATIs. A clinical response occurred in 93% and was sustained in 62% over a median follow up of 20 months. The GAIN placebo-controlled trial[172] evaluated adult patients who had lost response or were intolerant to IFX. In the ADA group, 21% (vs. 7% on placebo) entered remission. These strategies are unlikely to be successful in active patients who have adequate trough levels when switching to a different class of molecules is indicated.

3.4. Thalidomide

Statement 16

Even if there are some reports showing efficacy of Thalidomide in refractory pediatric CD there are insufficient data to recommend thalidomide therapy (EL4) 88% agreement

Practice points:

1. Due to the numerous potential side effects and to its teratogenicity, thalidomide as maintenance therapy is restricted to a very selected cohort of pediatric CD patients
2. Thalidomide maintenance therapy can be an alternative for anti-TNF agent responders who do not tolerate or lost response to biologic anti-TNF agents
3. Careful neurological and psychological examination and assessment of vibration sensitivity at regular intervals (6-monthly) is indicated
4. Thalidomide starting doses of 50 mg daily orally are usually administered in adult patients and then subsequently increased according to response and tolerance; this seems appropriate also for adolescents with CD, however, reduced doses should be considered for young children. Dosing of 2 mg/kg was suggested
5. Contraception is mandatory when appropriate

A recent double-blind, placebo-controlled, clinical trial randomized 56 children with active CD despite immunosuppressive treatment to thalidomide 1.5 to 2.5 mg/kg/day, or placebo for 8 weeks.[244] In an open-label extension, non-responders to placebo also received thalidomide. All responders continued to receive thalidomide for an additional minimum 52 weeks. Clinical remission was achieved by 13/28 (46.4%) in the thalidomide group vs. 3/26 (11.5%) receiving placebo (P = 0.01). Including cross over patients, 31/49 treated children (63.3%) achieved clinical remission. Cumulative incidence of severe adverse events was 2.1 per 1000 patient-weeks, with peripheral neuropathy the most frequent severe adverse event. Since this study was published after the cut-off of our systematic literature research it was not included in the statements with voting.

These findings of the trial of Lazzerini et al.[244] are in line with previous open label pediatric studies. Felipez et al.[245] reported 10/12 children treated with thalidomide entering complete remission and Lazzerini et al.[246] observed thalidomide-induced remission in 21 of 28 (75%) patients (17 with Crohn's disease, 4 with ulcerative colitis).

The teratogenicity of thalidomide has been extensively documented and thus it is absolutely contraindicated during pregnancy.[247] Neuropathy has been observed after high cumulative doses and it may be irreversible. In the studies of Lazzerini[244,246] and Felipez[245] peripheral neuropathy was frequent in 25% and 42%, respectively. It is vital to inform children and parents of this risk and to regularly monitor symptoms of tingling, paresthesia, and numbness. Other side effects requiring thalidomide suspension were vertigo/somnolence (1/28) and agitation/hallucinations (1/28). Minor adverse events, such as sedation and agitation or anxiety are well-described dose-dependent side effects occurring in approximately 10% of IBD patients.[246]

3.5. Aminosalicylates

Statement 17

5-ASA is only recommended to be used in selected patients with a very mild disease (EL2) 88% agreement

Practice points

1. 5-ASA might be used for induction of remission in children with mild colonic inflammation
2. Sulfasalazine seems superior compared to other 5-ASA for inducing clinical remission in adult patients with colonic disease, but not in those with disease limited to small bowel
3. Dosing of oral 5-ASA for pediatric CD is similar to pediatric UC with 50–80 mg/kg/day up to 4 g daily
4. There is no evidence that 5-ASA induces mucosal healing and should thus be viewed as an adjuvant therapy. If 5-ASA is used as a solitary therapy mucosal healing should be verified

3.5.1. Efficacy of 5ASA

Although clearly documented to be efficacious in the treatment of UC, the role of aminosalicylates in CD remains controversial. There are no evidence-based data indicating an advantage of using 5-ASA as induction therapy for CD.[81] In the only pediatric placebo-controlled cross over trial[248] 5-ASA showed no benefit for inducing remission in 14 children with active CD involving the small bowel. The efficacy of 5-ASA to maintain remission was not clearly demonstrated in adult CD trials with inconsistent results seen in the published meta-analyses. In the only maintenance clinical trial in pediatrics, 122 CD children in remission were randomized to receive mesalazine 50 mg/kg per day or placebo.[249] Patients were recruited over two time periods after: (i) medical and/or nutritional treatments; and (ii) nutritional treatments only. The authors found a two-fold lower risk of relapse in the first and a two-fold increased risk in the second recruitment period. Overall, the one-year relapse risk was 57% and 63% in the mesalazine and placebo groups, respectively. There are no data to support 5-ASA as maintenance therapy in children with CD.[60,81] Close monitoring of CRP, ESR and fecal calprotectin should ensure complete remission and a low threshold should be set for treatment escalation.

The pediatric dosing is extrapolated from adults based on three studies showing that pharmacokinetics in children is comparable to adults.[60,250–252]

3.6. Supplemental enteral nutrition and nutritional supplements

Statement 18

Partial Enteral nutrition may be an option together with other medications to maintain remission in selected patients [EL4] 84% agreement

Statement 19

There are insufficient data to recommend partial enteral nutrition as a standalone maintenance therapy (EL4) 96% agreement

Statement 20

Omega 3 fatty acids preparations are not recommended for maintenance of remission [EL4 (pediatrics) EL2 (adults)] 96% agreement

Practice points:

1. Partial enteral nutrition is not efficacious to induce remission. However, it may be considered as a maintenance treatment in selected patients with very mild disease or low risk of relapse
2. Supplementary nutritional therapy can be administered by overnight NG feeds in conjunction with normal daytime eating, short bursts of NG feeds every few months, or as oral supplements in addition to oral intake throughout the day. None had been proven to be superior to others. There are no studies comparing PEN with standard medical therapy
3. Polymeric feeds should be preferred for PEN, while elemental diet is indicated in case of allergy to cow's milk proteins

3.6.1. Efficacy of nutritional supplementation

Wilschanski et al.[253] retrospectively described 28 children treated with an elemental formula delivered overnight by a NG tube while consuming a normal daytime diet compared with 19 children in whom partial EN (PEN) was discontinued after achieving remission. At 12 months, 43% (12/28) of patients receiving nocturnal elemental feedings had relapsed compared with 79% (15/19) of the comparison group ($P < 0.02$). In the study of Belli et al.[254] 8 children received periods of NG elemental formula (70% of energy requirements) for 1 of 4 months during a 1-year period with improved growth, decreased PCDAI, and decrease in prednisone use.

Day et al.[56] studied 27 CD children on EEN with polymeric formula. Four continued supplementary polymeric formula and all have maintained remission during an average follow-up of 15.2 months. Takagi et al.[255] evaluated 51 adult patients with CD in remission who were randomized to receive half their calories in the form of an elemental formula or to an unrestricted diet for up to 2 years. The treatment group had a much lower relapse rate (34%) than the unrestricted diet group (64%), (OR 0.3, 95% CI: 0.09–0.94). This study was halted before the expected end as a result of the interim analyses by the monitoring board, who found a significant benefit for the use of EN formula to maintain remission.

In the recent review of Yamamoto et al.[256] on the efficacy of PEN for the maintenance of remission in adult CD, ten studies were included: one RCT, three prospective non-randomized trials and six retrospective studies. Clinical remission rate was significantly higher in patients receiving PEN in all seven studies comparing PEN to non supplementation. In two studies, PEN showed suppressive effects on endoscopic disease activity. In all four studies investigating impacts of the quantity of enteral formula on clinical remission, higher amounts of enteral formula were associated with higher remission rates.

3.6.2. Efficacy of omega 3 fatty acids

Turner et al.,[257] performed a meta analysis of six RCTs that evaluated omega-3 fatty acids in the maintenance of remission in CD, all in adults. There was a marginal benefit of n-3 therapy over placebo (RR 0.77; 95%CI 0.61–0.98; $P = 0.03$). However, the studies were both clinically and statistically heterogeneous

and there was a significant publication bias. The two largest and most rigorous clinical trials showed negative results. When considering the estimated rather than the observed 1-year relapse rate of these two studies, the benefit was no longer statistically significant: the placebo-controlled trials EPIC-1 and EPIC-2[258] included 363 and 375 patients with quiescent CD, respectively. The rate of relapse at 1 year in EPIC-1 was 31.6% in patients who received omega-3 free fatty acids and 35.7% in those who received placebo (hazard ratio, 0.82; 95%CI, 0.51–1.19; $P = 0.30$). Corresponding values for EPIC-2 were 47.8% and 48.8% (hazard ratio = 0.90; 95%CI, 0.67–1.21; $P = 0.48$).

3.7. Probiotics

Statement 21

Probiotics are not recommended for maintenance of remission [EL3 (pediatrics) EL2 (adults)] 96% agreement

Evidence suggests that probiotics may be effective in reducing inflammation in experimental colitis models, and may be of benefit in some clinical situations, such as pouchitis and UC. Rolfe et al.[259] in their Cochrane review summarized 7 small studies in CD patients that varied according to probiotics tested, methodological quality and medication regimen. There was no statistically significant benefit of probiotics for reducing the risk of relapse compared to standard maintenance therapy.

3.8. Maintenance therapy after surgery

Statement 22

Maintenance treatment is recommended in children and adolescents after surgically induced remission (EL 2 (pediatrics)) 92% agreement

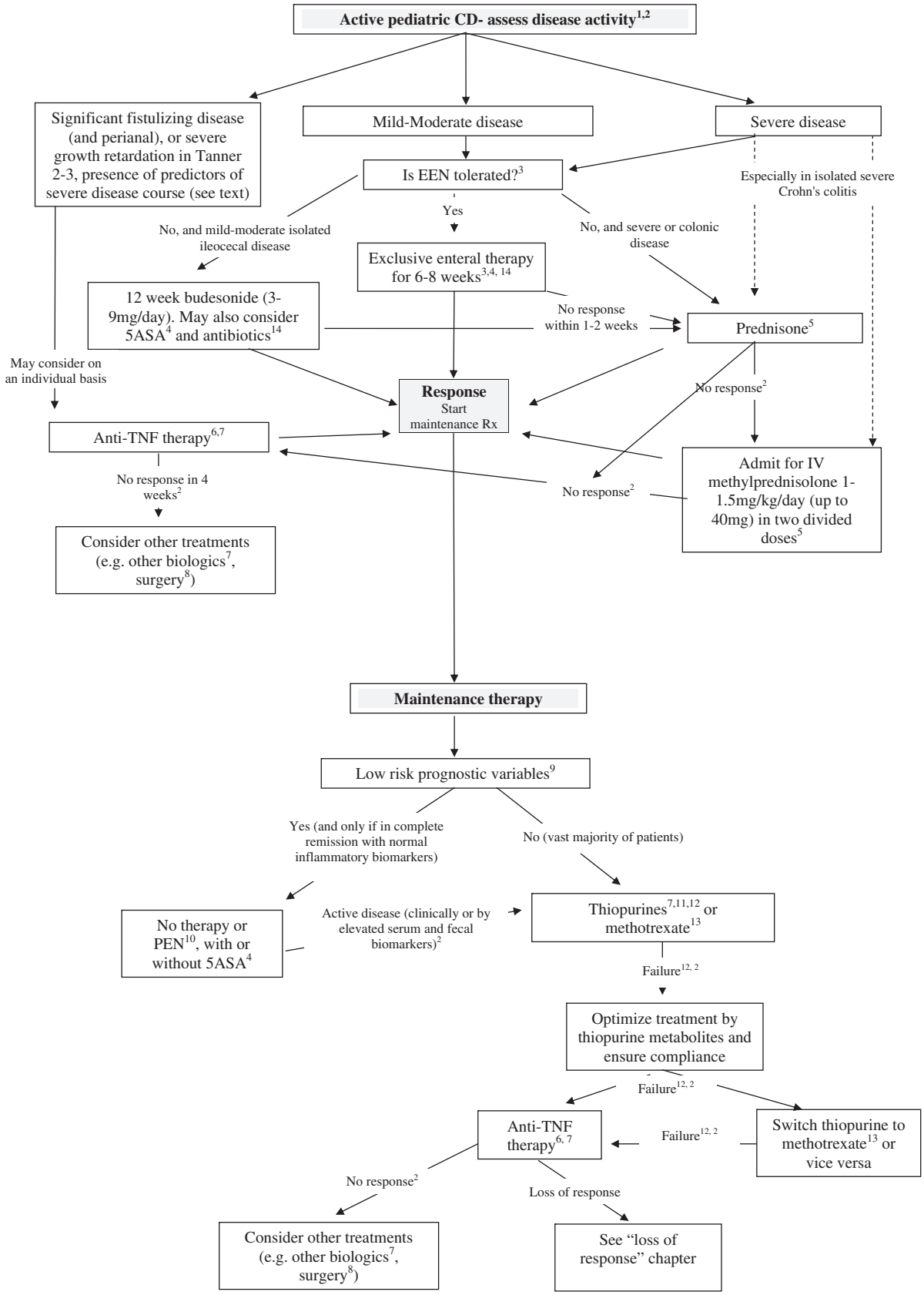
Statement 23

Thiopurines may be used as first choice drug for postoperative maintenance therapy (EL3 (pediatrics), EL2 (adults)), while supplementary enteral nutrition (EL3 (pediatrics) EL2

Figure 1

1. The weighted pediatric Crohn's disease activity index (wPCDAI) can be used to assess disease severity supplemented by serum and fecal inflammatory markers, growth, endoscopic and radiographic evaluation and other lab results.
2. Consider: symptoms due to stenosis, irritable bowel syndrome, lactose intolerance, infection (e.g. *C. difficile* and CMV), wrong diagnosis, side effects of medication, bacterial overgrowth, and bile-salt diarrhea.
3. EEN should be especially preferred in children with poor growth, low weight and those with catabolic state (e.g. hypoalbuminemia). If EEN is not tolerated orally, a nasogastric tube may be used, however, the emotional and financial implication of this strategy must be carefully weighed against the pros and cons of a short course of steroid therapy, which is a valid alternative.
4. The use of 5-ASA in Crohn's disease is controversial and generally not recommended. In some selected mild cases, 5-ASA may be considered to supplement induction therapy (50–80 mg/kg/day up to 4 g daily in 2 divided doses) especially in colonic disease. Sulfasalazine may be more effective than the newer regimens but is also associated with higher adverse effect rate. Gradual dose increase of sulfasalazine over 7–14 days may decrease adverse event rate.
5. Prednisone/prednisolone (1 mg/kg once daily up to 40 mg) must be tapered over ~10 weeks. Repeated steroid courses or steroid dependency should not be tolerated.
6. The risk for malignancy and perhaps also infections is higher when anti-TNF is combined with thiopurines (i.e. combo therapy). Since good evidence is lacking to support combo therapy in *thiopurine-failure* children, thiopurines should be discontinued within 6 months of combination therapy. However, combo therapy is superior to mono therapy in *thiopurine-naïve* patients and may be considered in high risk patients, especially in girls for whom the risk of lymphoma is smaller. Stepping down to either drug may be considered after a period of sustained deep remission.
7. Immunization status should be checked prior to starting immunomodulator or anti-TNF therapy, similarly when history of chickenpox is unclear, screen immunity and consider immunization of seronegative patients against varicella zoster prior to starting immunomodulator or anti-TNF therapy. In cases of primary anti-TNF failure, the switch to another anti TNF regimen is associated with a low success rate.
8. Surgery is particularly attractive in children with refractory short segment ileal disease without colonic involvement and those with stenotic disease unresponsive to anti-inflammatory therapy.
9. High risk patients include the presence of perianal disease, severe growth retardation, the presence of deep ulcers in endoscopy or extensive disease (including upper GI and proximal small bowel), the need for corticosteroids at diagnosis.
10. Although PEN has been shown to be inferior to EEN in *inducing* remission, some weak evidence suggest that it may be partially effective in *maintaining* remission in pediatric Crohn's disease.
11. Oral azathioprine 2–2.5 mg/kg once daily or 6-mercaptopurine 1–1.5 mg/kg once daily. Typical onset of action is 8–14 weeks. CBC and liver enzymes should be closely monitored. Measurement of TPMT (genotyping or enzymatic activity) at baseline and the drug metabolites (i.e. 6-TG and 6-MMP) levels after 2–4 months may aid in optimizing thiopurine dosing.
12. Failure of immunomodulators should be considered in frequent relapses, inability to wean off corticosteroids and may be considered in an asymptomatic child with signs of significant mucosal inflammation as evident by marked abnormal blood tests, fecal markers, endoscopic or radiographic evaluation.
13. Methotrexate dose is 15 mg/m2 (max 25 mg) once weekly. Subcutaneous administration is likely as effective as intramuscular. There is insufficient data to support oral treatment at any time. Daily folic acid should be prescribed to minimize adverse events. Liver enzymes and complete blood count should be frequently monitored. After sustained remission has been achieved (typical onset of action 2–3 months), MTX dose may be reduced by 40%.
14. Antibiotics may have some role in induction of remission in Crohn's disease such as metronidazole, ciprofloxacin, azithromycin and rifaximin.

Therapeutic paradigm for pediatric Crohn's disease (excluding perianal disease)



(adults)) or anti-TNF-agents (EL 3 (pediatrics)), are also possible options in selected patients 84% agreement

Practice points

1. In contrast to adult CD patients, it is unusual not to prescribe maintenance therapy after surgically induced remission in pediatric CD. For the individual patient the decision should be based on pre-surgical therapy, and the risk for disease recurrence. Cost/benefit ratio may also be considered
2. Thiopurine is the treatment of choice in patients with extended disease and at risk for relapse (specified below), regardless of whether thiopurines were administered prior to the surgery or not
3. Supplementary nutritional therapy is a treatment option for children in whom immunosuppressive therapy is either not warranted or contraindicated, particularly children with malnutrition
4. Ileocolonoscopy may be considered 6–9 months after surgery to guide treatment adaption
5. Metronidazole (20 mg/kg day) given for 3 months post-surgery may be effective to reduce the risk for relapse, but is not recommended for longer due to significant side effects and questionable long-term benefit
6. Data on anti-TNF treatment to maintain a surgically-induced remission are limited, and the decision to use anti-TNF agents to maintain remission should be reserved to patients with signs of severe disease evolution based on predictors of poor outcome
7. Neither budesonide nor probiotics are recommended for postsurgical prevention of relapse

Clinical and endoscopic recurrence after surgical resection is seen in 20–25% and 65–90%, respectively, within one year.[260] Factors that appear to increase the recurrence risk include: younger age of onset, smoking, longer disease duration, prior resection, small intestine or ileocolonic disease, perforating disease, NOD2/CARD15 mutations, and the presence of granulomas in the resected specimens.[261,262] A Cochrane review of interventions for prevention of post-operative recurrence in adults reported that thiopurines were associated with a reduced risk of clinical recurrence (RR 0.59; 95%CI 0.38–0.92, NNT = 7), and severe endoscopic recurrence (RR 0.64; 95%CI 0.44–0.92, NNT = 4), when compared to placebo.[263] However, the absolute effect size is modest, averaging 8–13% at 1 year for clinical recurrence and 15% for endoscopic recurrence.[264]

The role of 5-ASA for maintenance of surgically-induced remission in adult CD was analyzed in a recent Cochrane review of 9 RCT's with inconsistent results.[265] Although there was a slight advantage to use 5-ASA as relapse prevention (based on the meta-analysis of 7 studies) (OR 0.68;95%CI 0.52 to 0.90) the number needed to treat to avoid 1 relapse was high with 16 to 19 patients. Given the lack of pediatric data and in keeping with the adult ECCO guidelines,[81] we do not recommend the routine use of 5-ASA as maintenance therapy.

Treatment with IFX vs. placebo for one year was investigated in one RCT of adults following ileocolonic resection for CD: the rate of recurrence in the IFX group was 9.1% compared with 84.6% with patients receiving placebo, P = 0.0006,[266] indicating a clear advantage of IFX use.

In the recent POCER study[267]174 adult CD patients were separated after ileo-cecal resection into two distinct groups according to their risk for relapse: the low risk group (17%) without post-operative therapy and a high risk group (83%) treated with thiopurines (or ADA in case of intolerance). Two treatment strategies were compared, treatment optimization only in case of clinical symptoms vs. systematic endoscopic evaluation at 6 months with treatment escalation in case of mucosal lesions. At the endpoint (18 months), endoscopic evaluation showed a clear advantage of systematic evaluation at 6 months with treatment adaption for low and high risk patients. There was no significant difference in the high risk group between patients receiving ADA post-surgery compared to step-up at 6 months (relapse rate 43% vs 59%, p = 0.20, Rutgeerts score i3 and i4: 11% vs 9% p = NS) further comforting this treatment strategy for adult patients.

Budesonide and probiotics have not shown any beneficial effect over placebo in the post-operative setting.[268] Partial enteral nutrition with continuous nighttime feeding over 12 months has been shown in a non-randomized adult study to be effective in maintaining remission post-surgery.[269]

Nitroimidazole antibiotics (e.g. ornidazole or metronidazole at a dose of 20 mg/kg/day) given for 3 months post-surgery have been shown in adult patients to reduce the risk of relapse after ileocecal resection, but the effect was not sustained beyond 12 months.[269] More side effects occurred in the antibiotic group compared to placebo. Long-term treatment with nitroimadazole antibiotics should be avoided because of the cumulative risk of irreversible neuropathies.

4.1. Treatment strategies according to disease activity

4.2. Treatment strategies according to growth behavior

4.3. Exit strategies

Practice points

1. If proven effective, immunosupressants and anti-TNF agents should generally be continued for a prolonged period of time, at least for several years.
2. Drug discontinuation may be considered in some patients who are in complete sustained steroid-free remission for several years after an individual benefit-risk discussion with the family, but not before growth and puberty is completed. The risk of recurrence is lower in those without evidence of mucosal inflammation. Therefore, before stepping down, complete mucosal healing should be verified by endoscopic evaluation, fecal calprotectin and/or MRE/capsule endoscopy. Ensuring normal hemoglobin, WBC, CRP and ESR is mandatory but not enough for assessing the risk.
3. Stepping down from combination therapy of anti-TNF with thiopurines or MTX to anti-TNF monotherapy is recommended following 6 months of therapy, after ensuring complete remission with mucosal healing.

4. Stepping down from anti-TNF, if chosen, should be to thiopurines or MTX. Stopping all treatments is usually not advisable in children except for a small minority of patients with very mild and limited disease who entered deep remission for a long period of time after careful discussion with the family on the risk of relapse and other complications.

Treatment de-escalation may be considered in patients with longstanding remission in order to reduce cost and side effects. The latter is especially important in children and adolescents since they have many potential future treatment years. Data are limited to base recommendations on drug cessation but as a general rule reflected consistently from different adult studies, the presence of biological inflammation is associated with a higher risk of 1–2 year relapse after drug cessation.[271]

In a retrospective study of 120 CD patients who were in steroid-free remission on 6MP for at least 6 months, 36 stopped treatment.[272] The cumulative probabilities of relapse for those continuing treatment at 1, 2, 3, and 5 years were 29%, 45%, 55%, and 61%, respectively, as compared with 36%, 71%, 85%, and 85%, for those stopping treatment, respectively. The median length of remission was considerably shorter in those stopping 6MP (16 months; range 0.4–55) compared to those who continued 6MP (32 months; range 6–109, $P < 0.0004$).

In a retrospective study by Bouhnik et al.,[273] including 157 CD adult patients in remission after 4 years on AZA/6MP, the risk of relapse appeared to be similar, whether the therapy was maintained or stopped. However, due to the small number of patients followed for the longer time period, the data should be interpreted with caution. The GETAID then published a placebo-controlled trial of stopping AZA after treatment beyond 42 months of sustained remission.[106] The 18-month relapse rate was significantly higher in those who stopped the drug (21 ± 6% as compared with 8 ± 4% in those who continued). Risk factors for relapse included age younger than 30 years, elevated CRP and anemia. In a non-randomized study, Mantzaris et al.[274] compared the efficacy and safety of AZA in patients treated continuously for 2 to 4 (group A) or 4–8 years (group B). No difference in efficacy of safety was found suggesting that long-term treatment with AZA may be effective and safe.

Treton et al.[275] followed 66 patients off AZA for an additional 5 years. Three and 5 years after stopping AZA 53% and 63% of patients had relapsed, respectively. Among the 32 relapsing patients, 23 were retreated by AZA alone and all except one achieved remission. The average relapse rate at 1 and 5 years after stopping 6MP/AZA was 38% (range 21%–41%), and 74% (range 61%–85%), respectively.[271,274–276]

There are limited long term data after stopping MTX treatment. A retrospective review on 70 adult IBD patients (48 CD, 22 UC) showed that the likelihood of remission at 12, 24 and 36 months were 90%, 73% and 51%, respectively, if MTX treatment was continued.[277] This contrasts with remission rates of 42%, 21% and 16% after stopping MTX treatment for 6, 12 and 18 months.

While some studies have focused on anti-TNF withdrawal in patients receiving immunosupressants/anti-TNF combination therapies, no evidence-based recommendations on treatment duration can be formulated for anti-TNF agents used as monotherapy.[81] In contrast to rheumatologic disorders, a progressive reduction of anti-TNF dosages has not been tested in CD.[278]

In a landmark RCT of 80 CD adult patients, Van Assche et al.[202] showed that maintaining azathioprine after 6 months of combination therapy with IFX did not provide clinical benefit after a 2-year follow-up (mucosal healing rate at 2 year 64% with combo therapy vs. 61% with monotherapy, and similar rate of the need to change dose or stop IFX). A retrospective study confirmed that, with or without AZA withdrawal, about half of CD patients required IFX cessation or optimization after two years.[279] This is in line with the notion that antibodies to IFX develop during the first few months of IFX treatment and those in sustained remission with IFX will likely stay that way. No study explored MTX discontinuation after MTX/anti-TNF combination therapy.

In the pivotal prospective STORI study, 44% adult CD patients who were treated for at least 1 year with IFX and an immunomodulator experienced a relapse within one year after discontinuation of IFX while continuing the immunosuppressive drug.[280] Risk factors for relapse included male sex, the absence of surgical resection, leukocyte counts $>6.0 \cdot 10^9$/L, and levels of hemoglobin <145 g/L, C-reactive protein >5 mg/L, and fecal calprotectin >300 μg/g. Mucosal healing at time of discontinuation was significantly associated with a good prognosis but was not retained among the major risk factors of relapse.[280] Patients with no more than 2 of these risk factors had a 15% risk of relapse within 1 year. IFX re-treatment was effective and safe in the majority of relapsing patients. In a retrospective study of 48 CD patients who discontinued IFX, while being maintained on thiopurines (n = 23) or MTX (n = 9), 50% relapsed within 477 days after IFX discontinuation. In contrast, 35% of patients remained well, and without clinical relapse, up to the end of the nearly 7-year follow-up.[281]

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2014.04.005.

Conflict of interest statement

ECCO has diligently maintained a disclosure policy of potential conflicts of interests (CoI). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website (https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html) providing a comprehensive overview of potential conflicts of interest of authors.

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The following ECCO National Representatives participated in the review process of this consensus:

Austria: Gottfried Novacek; Belgium: Peter Bossuyt; Czech Republic: Tomas Douda; Denmark: Torben Knudsen; France: Franck Carbonnel; Germany: Andreas Sturm; Greece: Ioannis Koutroubakis; Hungary: Peter Lakatos; Italy: Paolo Gionchetti; Netherlands: Marieke Pierik; Norway: Ingrid Prytz-Berset; Poland: Jaroslaw Kierkus, Edyta Zagorowicz; Portugal: Fernando Magro; Romania: Mihai Mircea Diculescu; Russia: Alexander Potapov; Spain:

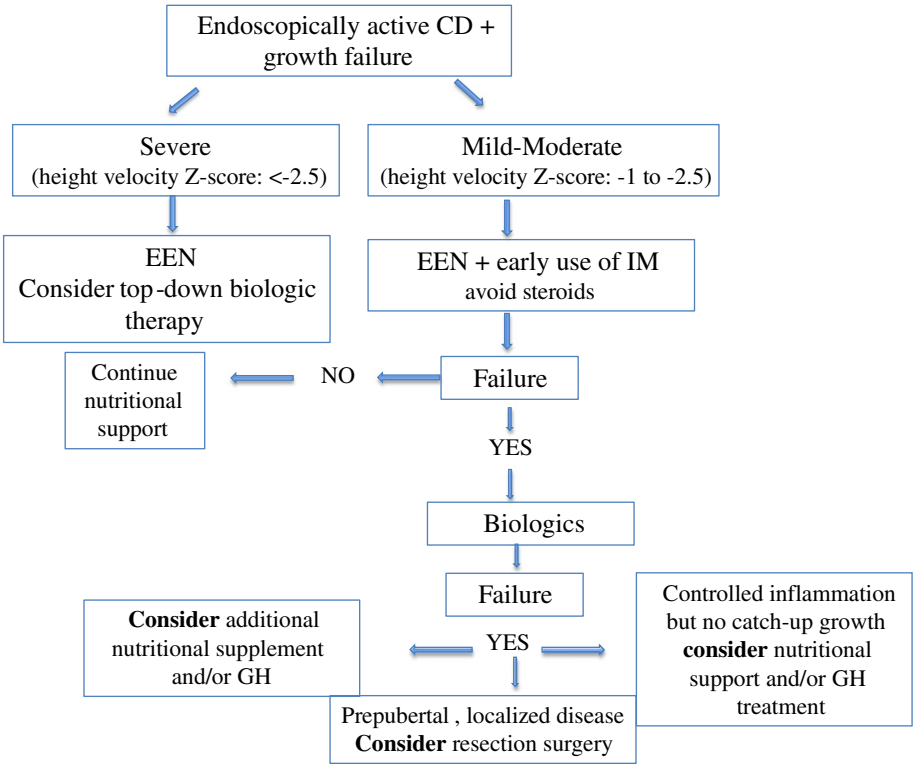

Figure 2

1. Marked growth retardation is considered a factor predictive of poor outcome[270]
2. Insufficient attention to linear growth and bone health may result in impaired adult height and increased risk for fractures.
3. Growth failure in CD is best described in terms of growth velocity over a period of 6–12 months in standard deviation scores (Z score), if unavailable, by variations height-for-age z-scores.
4. Corticosteroids should be avoided as much as possible as they induce protein breakdown and have a negative effect on growth.
5. Resection surgery can be an option for localized disease, particularly in a child with marked growth retardation and previous failure to immunomodulatory/anti-TNF therapy. Resection surgery should be performed prior to puberty to increase the patient's chances for catch-up growth.
6. During remission, in low risk patients, additional intermittent courses of EEN or PEN can be beneficial for growth.
7. Because little is known about the possible beneficial effects of growth hormone (GH) on linear growth, it may be considered only in very selected cases.
8. Evaluation of bone age is extremely helpful in the estimation of the remaining potential for catch-up growth.

Fernando Gomollón; Sweden: Hans Strid; United Kingdom: Peter Irving

In addition, the following expert also participated in the revision of the statements: Raanan Shamir

The following persons from the Gastro-Committee of ESPGHAN also participated in the review process of this consensus:

Belgium: Yvan Vandenplas; France: Frederic Gottrand; Greece: Alexandra Papadopoulou; Israel: Michael Wilschanski; Slovenia: Rok, Orel; Switzerland: Michela Schaeppi; United Kingdom: Jackie Falconer, Robert Heuschkel, Savas Karkelis, Nikil Thapar

The following persons from the ESPGHAN council also participated in the review process of this consensus:

Germany: Ulrich Baumann, Bert Koletzko; Italy: Lorenzo D'Antiga,Riccardo Troncone; Netherlands: Mark Benninga, Louisa Mearin; United Kingdom: Alan Phillips.

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