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ECCO Guideline/Consensus Paper

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The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update

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Abstract

Objective: We aimed to provide an evidence-supported update of the ECCO-ESPGHAN guideline on the medical management of paediatric Crohn's disease [CD].

Methods: We formed 10 working groups and formulated 17 PICO-structured clinical questions [Patients, Intervention, Comparator, and Outcome]. A systematic literature search from January 1, 1991 to March 19, 2019 was conducted by a medical librarian using MEDLINE, EMBASE, and Cochrane Central databases. A shortlist of 30 provisional statements were further refined during a consensus meeting in Barcelona in October 2019 and subjected to a vote. In total 22 statements reached ≥ 80% agreement and were retained.

Results: We established that it was key to identify patients at high risk of a complicated disease course at the earliest opportunity, to reduce bowel damage. Patients with perianal disease, stricturing or penetrating behaviour, or severe growth retardation should be considered for up-front anti-tumour necrosis factor [TNF] agents in combination with an immunomodulator. Therapeutic drug monitoring to guide treatment changes is recommended over empirically escalating anti-TNF dose or switching therapies. Patients with low-risk luminal CD should be induced with exclusive enteral nutrition [EEN], or with corticosteroids when EEN is not an option, and require immunomodulator-based maintenance therapy. Favourable outcomes rely on close monitoring of treatment response, with timely adjustments in therapy when treatment targets are not met. Serial faecal calprotectin measurements or small bowel imaging [ultrasound or magnetic resonance enterography] are more reliable markers of treatment response than clinical scores alone.

Conclusions: We present state-of-the-art guidance on the medical treatment and long-term management of children and adolescents with CD.

Key Words: Practice guideline; Crohn's disease/therapy; child; algorithms

1. Introduction

Approximately 10% of patients with Crohn's disease [CD] are diagnosed before their 17th birthday.[1] The past decade has seen significant advances in the care of children with CD. With an expanding therapeutic armamentarium, there has been a shift of therapeutic goals from symptom control alone towards mucosal and transmural healing with consequent reduction of bowel damage.

The objective of this evidence-based guideline update by the European Crohn's and Colitis Organisation [ECCO] and the Paediatric IBD Porto group of the European Society of Paediatric Gastroenterology, Hepatology And Nutrition [ESPGHAN] was to review existing data on the efficacy of available medical therapies and provide therapeutic algorithms for paediatric practice, including advice on how to monitor response to treatment. This guideline replaces the first ECCO-ESPGHAN guideline published in April 2014.[2]

2. Methodology

We followed the ECCO standard operating procedures for guideline development. After an open call for interest, ECCO and ESPGHAN selected a panel of 25 paediatric inflammatory bowel disease [IBD] experts who were supported by a medical librarian and a webmaster for the online guideline platform. A core group of six paediatric IBD opinion leaders identified 10 domains within the medical treatment of CD which should be addressed by this guideline. Ten working groups were then formed. All panellists were assigned to one or two working groups, coordinated by working group leaders, all under the supervision of the two guideline coordinators [PFvR, FMR]. The working groups formulated a series of specific questions using the PICO format [Population, Intervention, Comparator, Outcomes] which were deemed to be clinically relevant [Supplementary File 1, available as Supplementary data at ECCO-*JCC* online]. A systematic search of the literature relevant to the clinical questions from 1 January 1991 to 19 March 2019 was then conducted by a medical librarian using MEDLINE, EMBASE, and Cochrane Central databases. Focused top-up searches were performed until 1 March 2020 to provide evidence as up to date as possible. Two working group members independently assessed the relevance of each abstract against predefined inclusion criteria. Eligible publications were randomised controlled trials [RCTs], cohort studies, and case-control studies that followed patients with luminal or perianal fistulising CD. Publications presented only in abstract form were excluded. In the case of positive concordance between physician screeners, the full-text manuscript of each eligible publication was obtained. Disagreements were resolved by discussion. The criteria of the Oxford Centre for Evidence-Based Medicine were used to assess the level of evidence [https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf]. The evidence was downgraded if the publication did not address the PICO question directly in terms of patients, interventions, and outcomes. An exception to this rule was the situation where observational paediatric studies supported the findings of adult randomised trials. In this case, the evidence was not downgraded.

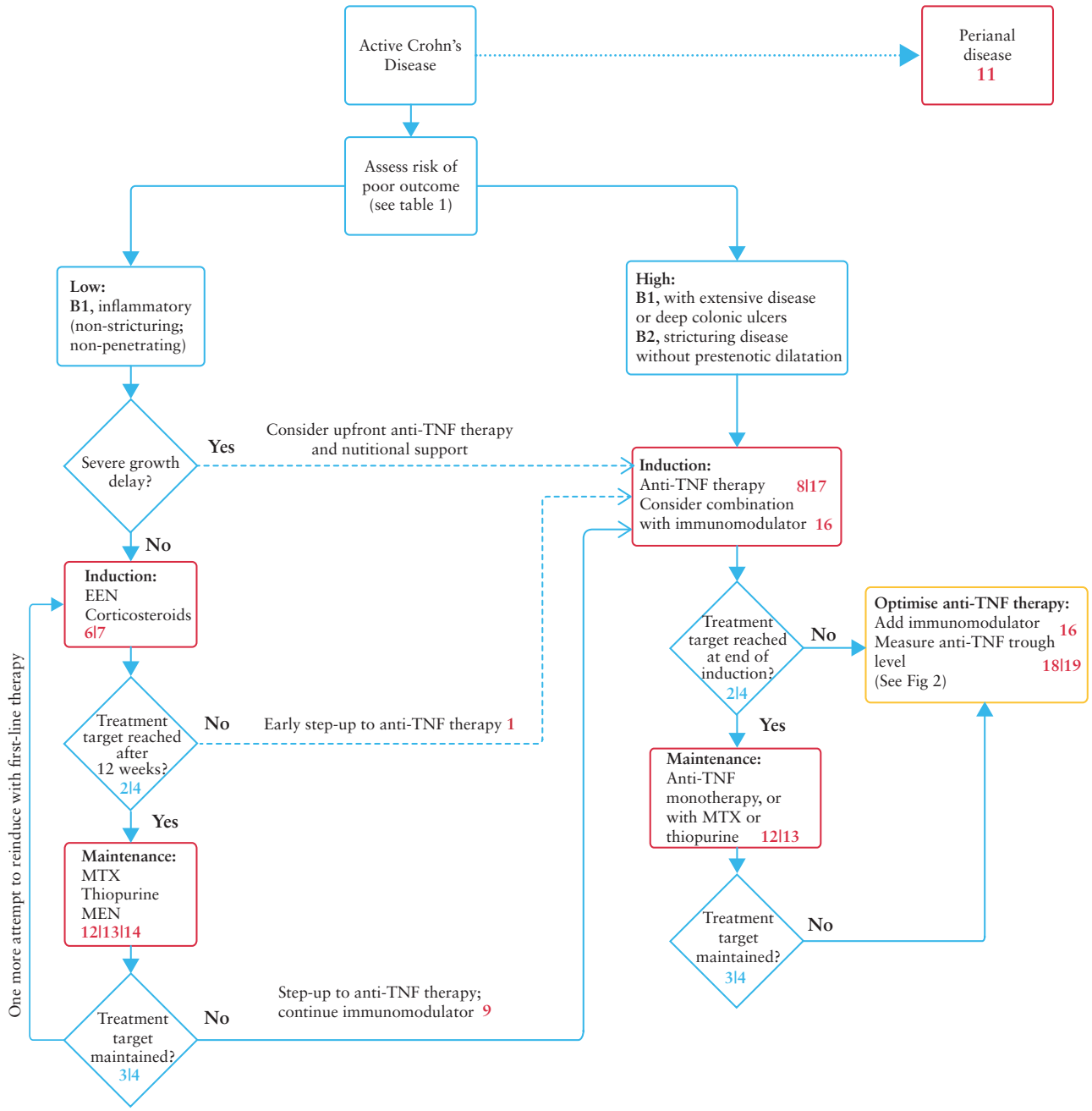

Figure 1. Summary flowchart of medical management of paediatric luminal Crohn's disease. The numbers displayed in the boxes refer to the statements in this guideline.

Each working group reviewed the selected full-text manuscripts, created evidence tables, and generated provisional guideline statements. The provisional statements and the supporting evidence tables were then submitted to an online platform. Using a Delphi consensus process, two online voting rounds were conducted to shortlist the provisional statements that were deemed to be of clinical importance for the medical treatment of CD. The first round involved all guideline panellists, and for the second voting round all national representatives of ECCO and an international sounding board [applicants who showed an interest in being part of the panel, but were not selected for this position] were also invited to vote. Thirty provisional statements emerged from this iterative process and were discussed among panellists during a consensus meeting in Barcelona in October 2019. Some statements were further refined during this meeting and then subjected to a vote. The statement was considered as final when at least 80% agreement was reached during voting. Eight provisional statements were ultimately rejected with the remaining 22 statements contained in this guideline. Each statement is framed and followed by a discussion of the evidence. Practical guidance sections complement the evidence by providing additional information not covered by the statements. Summary flowcharts of medical management and drug monitoring are shown in Figures 1 and 2.

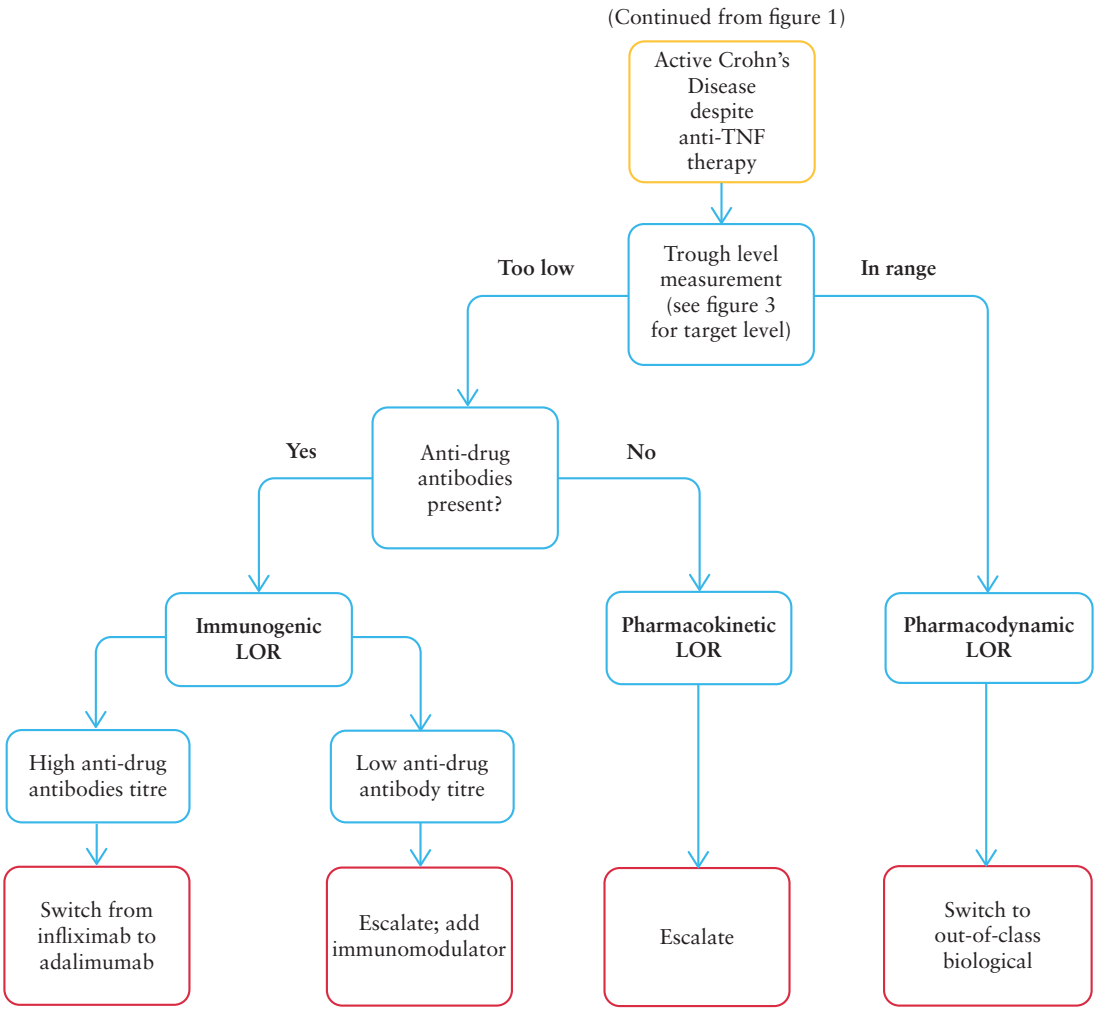

Figure 2. Anti-tumour necrosis factor [TNF] therapeutic drug monitoring.

Table 1. Predictors of poor outcome in paediatric Crohn's disease and suggested induction therapy.

Paris classification [at diagnosis]		Additional risk factors	Risk stratification	Suggested induction therapy
B1	Inflammatory [non-stricturing, non-penetrating]	None	Low	Exclusive enteral nutrition; corticosteroids
B1		No clinical and biochemical remission 12 weeks after start induction therapy	Medium	Consider accelerated step-up to anti-TNF therapy
B1 + G1		Growth delay	Medium	Exclusive enteral nutrition; consider up-front anti-TNF therapy
B1 [L3 + L4]		Extensive disease[a] or deep colonic ulcers	High	Up-front anti-TNF therapy
B1 + p		Perianal disease	High	Up-front anti-TNF therapy in combination with antibiotic therapy, surgery, or both
B2	Stricturing disease[b]	None	High	Up-front anti-TNF therapy
		Prestenotic dilatation, obstructive signs or symptoms, or both	High	Bowel resection in combination with postoperative anti-TNF therapy
B3	Penetrating disease[c]		High	Surgery in combination with postoperative anti-TNF therapy

TNF, tumour necrosis factor.

[a]Defined as pan-enteric inflammation [ie, involvement of proximal small bowel, terminal ileum, and colon].

[b]Defined as the occurrence of constant luminal narrowing demonstrated by radiological or endoscopic examination.

[c]Defined as the occurrence of bowel perforation, intra-abdominal fistulae, inflammatory masses, and/or abscesses at any time in the course of the disease [not the result of surgical complications].

3. Key Points in the Medical Treatment of Paediatric CD

There is increasing evidence that the treatment plan for a paediatric patient with CD should be individualised. The plan should consider factors such as age, disease location, disease behaviour, presence of growth delay, potential side effects of medications, and quality of life. A key point in designing an optimal treatment plan is the identification of patients at high risk of a complicated disease course, with the overall aim to obtain rapid control of inflammation to reduce long-term bowel damage. The previous paediatric CD guidelines introduced the notion of predictors of poor outcome [POPOs] that were mainly expert-driven.[2] Since then, some of the initially proposed POPOs have been validated, such as disease behaviour [B2, stricturing disease; B3, penetrating disease; p, perianal involvement] or non-response to adequate induction therapy [see section 4].

4. Risk Stratification of Patients

ECCO-ESPGHAN statement 1

Patients with newly diagnosed Crohn's disease [CD] who do not achieve clinical and biochemical remission after induction therapy are at risk of a more complicated disease course. Level of evidence [LoE]: 3 | Agreement: 92%.

Evidence

Few studies have adequately addressed the issue of predicting disease outcomes in patients with paediatric-onset CD at diagnosis. Table 1 presents predictors for poor outcome, defined as either the early need for surgery or risk for rapid progression of bowel damage. Whereas these predictors should be considered when choosing the appropriate induction therapy, it should be noted that these features are not consistently recognised across all studies.

Several observational studies following newly diagnosed paediatric patients with CD have consistently shown that failure to reach clinical and biochemical remission after induction therapy is a predictor for poor outcome. The GROWTH CD study, a multicentre study with 222 treatment-naïve paediatric CD patients followed for 52 weeks, demonstrated that patients with Paediatric Crohn's Disease Activity Index [PCDAI] >5 [$p = 0.012$], C-reactive protein [CRP] >20 mg/L [$p = 0.019$], and faecal calprotectin > 400 µg/g [$p = 0.001$] at Week 12 after starting induction therapy were at higher risk of relapse at the end of the observation period.[3] A subset of patients from the same cohort were followed for 104 weeks to evaluate predictors for early surgery. Again, active disease at Week 12 appeared to be a risk factor, as well as stricturing [B2] disease at diagnosis.[4] Approximately 26% of children presenting with stricturing disease at diagnosis required early surgery in the first 2 years after diagnosis compared with 8% of patients without stricturing disease [p <0.001]. Additionally, a Dutch cohort of new-onset CD showed that achieving low levels of faecal calprotectin [i.e. <250 µg/g] within the first 12 weeks after induction with corticosteroids or exclusive enteral nutrition [EEN] was associated with a favourable disease course in the first year, compared with higher calprotectin concentrations.[5]

Data from the RISK study[6] suggested that early anti-tumour necrosis factor [TNF] treatment may prevent progression to penetrating [B3] disease, but does not have added value in preventing stricturing complications. Nonetheless, the number of patients developing the B3 phenotype was small, indicating a high number-needed-to-treat value. A pro-fibrotic signature detected with RNA sequencing of ileal biopsies taken during diagnostic colonoscopy predicted future stricturing complications, with a sensitivity of 69% and a specificity of 71%. Another potentially useful predictor for stricturing and penetrating disease is presence of antibodies against one or more microbial antigens, including *Escherichia coli* outer membrane porin C [OmpC], *Saccharomyces cerevisiae* [ASCA], and antiflagellin [CBir1]. However, the results of these studies were heterogeneous.[7–10]

5. Treatment Targets and Monitoring Response

Achieving endoscopic or mucosal healing [MH] in response to induction therapy is associated with favourable long-term outcomes.[11] Endoscopic response is commonly defined by a decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] or Crohn's Disease Endoscopic Index of severity [CDEIS] of at least 50% from baseline.[12,13] MH is usually defined as the absence of macroscopic inflammation or an SES-CD <3 points. Normal histology has been gaining increasing attention as a possible treatment target,[14] but there is no evidence that histological remission is superior to MH in achieving long-term clinically important outcomes. Moreover, there are 14 different numerical histological indices in CD, and there is no consensus on how to standardise the assessment. Thus, although histological remission is considered a 'deeper' remission than merely mucosal healing, it is currently still controversial as a treatment target in CD.

5.1. Faecal calprotectin

ECCO-ESPGHAN statement 2

In patients with luminal CD following induction therapy, a decrease of faecal calprotectin in the context of clinical improvement can be used as a marker of treatment response. LoE: 3 | Agreement: 100%.

Evidence

There is no evidence-based consensus of when best to re-evaluate disease activity after initiation of induction therapy; repeat endoscopies to evaluate resolution of inflammation are impractical. There is an increasing demand to replace invasive procedures with surrogate non-invasive markers. High-quality evidence for serial measurement of faecal calprotectin as a non-invasive diagnostic strategy to determine resolution of inflammation comes from adult studies.[15–18] In these studies, stool testing and ileocolonoscopy were performed simultaneously to evaluate success of induction therapy. Low levels of faecal calprotectin [below 150 to 250 µg/g] corresponded well with endoscopic remission, and a failure to reach these levels often reflected ongoing intestinal inflammation. Several observational paediatric studies support these findings.[5,19–23] In all studies, calprotectin values were longitudinally tracked in children following induction therapy. In one study, treatment success was predefined as a calprotectin result <250 µg/g in combination with absence of symptoms.[5] Patients who achieved this target within 12 weeks had a higher probability of sustained remission during the first year. The other five paediatric studies did not define a target range, but interpreted a falling trend in calprotectin combined with a reduction of symptoms as a proxy marker for treatment success.[19–23]

Practical guidance

There is no linear correlation between calprotectin levels and the severity or extent of mucosal inflammation. Although a decrease of calprotectin during induction therapy [eg, from 2000 to 1000 µg/g] may be statistically significant, the latter result is still indicative of active disease. A decrease of calprotectin within the high range should therefore not be considered a true treatment response. On the other hand, a decrease of faecal calprotectin to <250 µg/g [which is the upper limit of the target range] could be considered a reliable indicator of treatment success. The closer the calprotectin value gets to 50 µg/g, the higher the likelihood for complete endoscopic healing.

From birth, normal calprotectin levels exhibit a downward trend with increasing age to reach 'adult' levels around the age of 5 years.[24,25] Other issues around the use of faecal calprotectin for disease monitoring include the lack of agreement between different test kits and limited protein stability at room temperature.[26,27] Currently, the best advisable standard for pre-analytical calprotectin handling is refrigeration of the filled stool container until delivery to the laboratory.[27] The diagnostic gain of measuring calprotectin in patients with inflammation localised to the colon is well recognised, but the marker was thought to be less sensitive in isolated small-bowel disease. A meta-analysis addressing adult patients with active small-bowel CD seen on capsule endoscopy demonstrated that the diagnostic accuracy of faecal calprotectin is also meaningful for detection of inflammation in the small bowel.[28]

ECCO-ESPGHAN statement 3

In patients with luminal CD in clinical remission, a significant rise of faecal calprotectin should trigger further investigations and consideration of treatment escalation. LoE: 3 | Agreement: 92%.

Evidence

The utility of periodic calprotectin measurements in children with inactive CD was recently evaluated in two prospective, single-centre cohort studies. In the first study of children receiving infliximab maintenance therapy, a calprotectin level >250 µg/g measured in stool obtained before each infusion was a reliable predictor of clinical relapse in the next 3 months.[29] In the other study, children with new-onset luminal CD were followed over time with periodic measurements of calprotectin.[5] Patients in clinical remission with an upward trend of calprotectin crossing the 250 µg/g margin were considered to have recurrence of disease activity and had a treatment intensification. Time to recurrence, defined as the time from the first calprotectin measurement below 250 µg/g until treatment intensification, was longer in children in whom initial induction treatment had been successful within 12 weeks.

In the multicentre ImageKids study, 151 children with new-onset or established CD underwent magnetic resonance enterography [MRE], ileocolonoscopy, and faecal calprotectin measurement. The best suitable calprotectin threshold to predict mucosal healing was 300 µg/g, but a lower cut-off [<100 µg/g] was needed to identify children with 'deep healing' [ie, a combination of mucosal and transmural healing].[30]

Practical guidance

Repeat faecal calprotectin measurements in patients in clinical remission [tight control] makes it possible to identify a disease flare early. Several studies have shown that an increase in faecal calprotectin precedes the recurrence of symptoms by 2 to 3 months.[31] Nonetheless, pre-emptive treatment escalation based solely on faecal calprotectin results is currently not recommended. Both adult and paediatric studies have shown that the combination of faecal calprotectin with CRP is superior to faecal calprotectin alone. The landmark CALM trial on the treat-to-target strategy in adult CD showed that faecal calprotectin levels <250 µg/g, in combination with Crohn's disease activity score [CDAI] < 150 and CRP <5 mg/L, can be used as a treatment target, with step-by-step dose escalation of adalimumab until these levels are reached.[17] Using this strategy enhanced mucosal endoscopic healing compared with reliance on symptoms alone to guide treatment. In another adult study, the combination of faecal calprotectin with CRP was superior in detecting endoscopic disease activity compared with using faecal calprotectin alone.[32] This has also been shown in the paediatric ImageKids and comparator cohorts while developing the MINI [Mucosal Inflammation Noninvasive Index].[33] This composite score was statistically more accurate in detecting endoscopic healing than faecal calprotectin alone, albeit with a modest clinical benefit.

Unlike endoscopic assessment, periodic measuring of faecal calprotectin and CRP is feasible also in children. Calprotectin monitoring has clinical benefit particularly in teenage patients, who tend to under-report complaints, and in those who have irritable bowel syndrome in addition to IBD.[34] To minimise misinterpretation of calprotectin changes over time, it is prudent to use calprotectin assays from the same manufacturer.[35]

5.2. Small-bowel imaging: magnetic resonance enterography and intestinal ultrasound

ECCO-ESPGHAN statement 4

In patients with luminal CD, assessment of transmural involvement by bowel ultrasound or magnetic resonance imaging can be used as a marker of treatment response. LoE: 3 | Agreement: 100%.

Evidence

Cross-sectional imaging techniques, including magnetic resonance enterography [MRE] and intestinal ultrasound [IUS], can be used to periodically evaluate the effect of therapy on the bowel wall.[36] MRE is currently the modality of choice to evaluate small-bowel involvement.[37,38] In a recently published diagnostic meta-analysis, the sensitivity and specificity of MRE to identify active CD in children was 83% (95% confidence interval [CI]: 75%–89%) and 93% [95% CI: 90%–95%], respectively.[39]

Active inflammation is best described by features that include wall enhancement, mucosal ulcers, and wall T2 hyperintensity, whereas damage is best recognised by the presence of a fibrotic stricture, abscess, or fistula.[40]

Both MRE and IUS are non-invasive imaging techniques without ionising radiation; IUS has the additional advantages of low costs and easier access. The downside is that the interpretation of IUS strongly depends on the operator's skills and experience.[41] Among the features that can be evaluated during IUS, parietal thickness <3 mm better predicts transmural healing than colour Doppler grade and the percent increase of parietal enhancement.[42] In a prospective paediatric study comparing the diagnostic performance of

MRE, IUS, and capsule endoscopy to assess small-bowel activity, no significant differences in the accuracy of the three imaging modalities were reported.[43]

Practical guidance

Adequate bowel preparation is required for MRE to promote good intestinal loop distension. Cooperative children may be able to drink sufficient volumes of oral contrast, but others require temporary placement of a nasojejunal tube for administration. Many centres now use a small-volume lactulose protocol that has significantly improved compliance.[44] MRE can be completed without sedation in the majority of children ≥ 9 years,[45] whereas for young children sedation or general anaesthesia is likely to be required.[46] There have been recent reports of gadolinium deposits in the human body, particularly in the brain, especially after repeated intravenous administration.[47] The use of gadolinium-based MRI contrast agents should therefore be carefully individualised, especially when future repetition of small-bowel imaging is anticipated.

5.3. Clinical disease activity scores

ECCO-ESPGHAN statement 5

In patients with luminal CD, clinical scores alone [PCDAI, wPCDAI, shPCDAI, abbrPCDAI] do not adequately reflect mucosal healing. LoE: 3 | Agreement: 100%.

Evidence

Clinical disease activity scores are not accurate in assessing mucosal inflammation, as has been found both for the CDAI in adults[48] and for the various versions of the PCDAI in children.[21,49] Approximately half of patients in clinical remission will still have residual mucosal ulceration. Therefore, although the weighted PCDAI has better diagnostic accuracy for clinical remission compared with the other PCDAI versions,[49,50] if MH is the treatment target, clinical assessment alone is insufficient for assessing therapeutic effect.

Practical guidance

A composite score of faecal calprotectin, CRP, and clinical score is currently considered to be the best suitable non-invasive test to evaluate MH in paediatric CD.

6. Induction Therapy in Luminal CD

6.1. Exclusive enteral nutrition

ECCO-ESPGHAN statement 6

In children with active luminal CD, dietary therapy with exclusive enteral nutrition [EEN] is recommended as first line for induction of remission. LoE: 2 | Agreement: 92%.

Evidence

EEN involves the use of a complete liquid formula as the sole source of food for 6 to 8 weeks. Several meta-analyses have compared the efficacy of EEN with corticosteroid induction therapy in paediatric patients with luminal CD, and concluded that there was no statistical difference in clinical remission in the intention-to-treat analysis.[51,52] When only those patients who completed the treatment originally allocated were compared [per-protocol analysis], a slightly [but statistically significant] larger proportion of patients on EEN reached clinical remission.[52] However, patients on EEN were more likely to withdraw from the allocated treatment than those on corticosteroid therapy. The most common reason for withdrawal included unpalatable formulations and poor acceptance of a nasogastric tube. Frequently reported side effects by patients on EEN included diarrhoea and vomiting. In paediatric CD patients with an extended period of nutrition deprivation, re-introduction of calories may lead to refeeding syndrome.[53]

An Italian RCT that was included in two meta-analyses failed to show a significant difference in clinical remission rates between EEN and corticosteroid therapy. However, a significant difference in mucosal healing in favour of EEN was observed.[54] These findings were recently replicated in a French RCT that included 19 children with CD and demonstrated a 89% mucosal healing rate with EEN compared with 17% upon induction therapy with corticosteroids.[55]

When asked, patients would have a preference for a solid food-based dietary induction rather than liquid diet.[56] Until recently, more palatable and sustainable dietary strategies with similar efficacy to EEN were not available. Recently, several more tolerable food-based diets were introduced, including CD-TREAT[57] and the Crohn's Disease Exclusion Diet [CDED].[58] In a head-to-head RCT, paediatric CD patients tolerated the CDED coupled with partial enteral nutrition [PEN] better than EEN, and a larger proportion had sustained clinical remission at Week 12.[58] Replication studies, including data on mucosal healing, are required before strong recommendations can be made.

Practical guidance

Paediatric CD patients with purely inflammatory disease behaviour [B1] and low-to-medium risk at diagnosis [see Table 1] are eligible for EEN; this choice can be independent of disease location. There is no difference in efficacy between the elemental and non-elemental formulas, nor between diets of similar protein composition with different fat composition, nor between bolus oral feeding and continuous enteral feeding.[51,59] Considering the reduced palatability, the risk of early withdrawal, and the high costs associated

Table 2. Prednisone or prednisolone tapering scheme [once-daily administration].

	Body weight		
Week	10–20 kg	20–30 kg	> 30 kg
1–3	20 mg	30 mg	40 mg
4	15 mg	25 mg	35 mg
5	15 mg	20 mg	30 mg
6	12.5 mg	15 mg	25 mg
7	10 mg	15 mg	20 mg
8	7.5 mg	10 mg	15 mg
9	5 mg	10 mg	10 mg
10	2.5 mg	5 mg	5 mg

As tapering schemes are largely based on empirical recommendations rather than on clinical trials, large variability exists among physicians. Shortening each stage from 7 to 5 days or any other tapering modification may be considered individually.

with elemental diets, the primary choice of a polymeric formula is justifiable. Use of a nasogastric feeding tube may be considered to overcome aversion to the formula or not achieving the required daily intake. Food-based diets may be alternatives for patients who cannot tolerate EEN.

6.2. Corticosteroids

ECCO-ESPGHAN statement 7

In children with active luminal CD, when EEN is not an option, corticosteroids may be considered for inducing remission. LoE: 3 | Agreement: 94%.

Evidence

If EEN is poorly tolerated or is ineffective after 2 to 4 weeks of good compliance, systemic corticosteroids may be considered for inducing remission. Although corticosteroids have been used for decades to induce clinical remission in CD, surprisingly little evidence exists for their use in children.[3,60,61] Corticosteroid use varies greatly between centres and countries and possibly depends on local expertise, bias, and health economic arguments.[62,63] Corticosteroid use has been associated with increased risk of infection and elevated risk of intra-abdominal or pelvic abscesses,[64,65] but when asked, the side effects of most importance to users are weight gain, insomnia, and Cushingoid facies.[66]

Practical guidance

The prednisolone starting dose is weight-dependent [see Table 2] and should be tapered once clinical remission is reached, but not later than 4 weeks after initiation. In the case of mild ileocaecal disease [L1], if EEN is insufficiently effective, treatment with ileal-release budesonide is preferable to prednisolone. For patients > 40 kg, the initial dose of budesonide is 9 mg once daily for 6 weeks and then tapered as follows: 6 mg once daily for 2 weeks, 3 mg once daily for 2 weeks. Doses up to 12 mg have been used for the first 4 weeks.[67] There is no evidence of benefit for budesonide in more distal colonic inflammation. The likelihood of adverse events with budesonide is lower than with conventional corticosteroids.[68]

Patients who require major surgery while taking supraphysiological doses [>50% of prednisolone starting dose; Table 2] for 3 weeks or more should be assumed to have adrenal insufficiency [AI] and will need additional peri-operative hydrocortisone coverage. Patients with unclear adrenal suppression [ie, those who are in the last few weeks of their tapering scheme or those who finished corticosteroid therapy in the past 3 months] should be considered for endocrinologist counselling and preoperative hypothalamic–pituitary–adrenal axis testing.[69,70]

6.3. Anti-TNF therapy

ECCO-ESPGHAN statement 8

In new-onset patients with high risk for a complicated disease course, anti-TNF therapy is recommended for inducing remission. LoE: 3 | Agreement: 92%.

Evidence

Of all licensed drug therapies, anti-TNF agents [eg, infliximab and adalimumab] are highly effective to induce both clinical and endoscopic remission and therefore have had a significant impact on the care of paediatric patients since their registration studies.[71,72] A propensity-score matched analysis of the RISK study suggested that early anti-TNF monotherapy [within <3 months after diagnosis] had higher corticosteroid- and surgery-free remission rates at 1 year than induction with EEN or corticosteroids followed by immunomodulator therapy.[73]

As discussed in section 4 in connection with risk stratification, early treatment with anti-TNF agents was associated with a significantly lower risk of developing penetrating [B3] complications but did not seem to reduce the risk for stricturing [B2] complications.[6] Comparison of top-down [first-line infliximab; discontinuation when endoscopic remission was reached after 1 year] with step-up treatment in a South Korean cohort [$n = 76$] found that deep remission and mucosal healing rates were higher in the top-down group.[74,75] Although promising, these studies are limited by the non-randomised trial design and relatively short follow-up. The TISKIDS trial[76] has now been reported in abstract form and is the first head-to-head comparison of top-down infliximab and first-line EEN or corticosteroids in children with moderate to severe CD.[77] At 52 weeks, the primary end-point of clinical remission [wPCDAI <12.5 points without need for treatment escalation] was achieved in 41% on top-down infliximab versus 12% on conservative treatment [$p = 0.002$]. These data provide support for infliximab as first-line treatment option. The panellists recommend anti-TNF therapy as primary induction and maintenance therapy in children with a high risk of poor outcomes [see Table 1]. Anti-TNF agents should be considered early in the treatment plan in patients with severe growth delay or in those who do not reach clinical [PCDAI <10] and biochemical remission [faecal calprotectin <250 µg/g] after induction with EEN or corticosteroids.

Practical guidance

Intravenous administration of infliximab is usually at 5 mg/kg with three induction doses over 6 weeks [Weeks 0-2-6], followed by maintenance therapy of 5 mg/kg every 8 weeks. However, there is ample evidence[78] that children < 30 kg, and those with extensive disease and low serum albumin levels, require higher induction doses up to 10 mg/kg, shorter dosing intervals, or both, to reach target trough levels [see section 9.2].

Adalimumab is administered subcutaneously. For patients > 40 kg, the first induction dose is 160 mg, followed by 80 mg at Week 2, and then followed by a maintenance dose of 40 mg every other week. For patients <40 kg, the drug label recommends 80 mg at Week 0, 40 mg at Week 2, and 20 mg from Week 4 onwards; but in view of the evidence on underdosing of young children, higher doses may be required in specific cases. Weekly injections should be considered in patients losing response or with low trough levels [see section 9.2].

ECCO-ESPGHAN statement 9

In patients with active CD who fail to achieve or maintain remission with an immunomodulator, anti-TNF agents are recommended for induction and maintenance of remission. LoE: 2 | Agreement: 96%.

Evidence

The median disease duration in paediatric patients who participated in the initial infliximab and adalimumab RCTs [REACH and IMAgINE, respectively][71,72] was approximately 2 years. They were eligible when they had active CD [ie, PCDAI >30] despite corticosteroids and immunomodulator use. Accordingly, the evidence of efficacy of anti-TNF agents in this category of patients is stronger than in any other patient category.

The REACH study included 112 children with CD who received a standard infliximab induction and then one of two maintenance schedules every 8 or 12 weeks. At 54 weeks, remission rates were 56% versus 23.5%, respectively.[71] In an open-label extension study, 80% of those who initially responded had at most mild disease at last follow-up.[79] The IMAgINE study provided weight-based induction with adalimumab and then randomised patients to high- versus low-dose weight-based maintenance. Similar remission rates were observed at 26 weeks [39% and 29%, respectively; not significant, NS].[72] More recent 'real-life', retrospective, or registry studies suggest higher remission and durability rates than those reported in the original RCTs. For example, high durability was shown for 180 patients receiving infliximab for CD, where 86% remained on this therapy for a median of 86 weeks. However, 57% required dose escalation.[80] This reflects the need for paediatric-specific dosing and drug monitoring, as detailed in section 9.

6.4. Thalidomide

Evidence

Although thalidomide use to induce remission in CD has some support, a systematic review of 12 thalidomide studies [two RCTs, 10 case series] found only one study of sufficient methodological quality.[81] In this paediatric RCT, the effect of thalidomide versus placebo was evaluated in patients with active CD refractory to immunosuppressive medications.[82] Thalidomide was effective for the induction of remission in paediatric CD, and in a follow-up study the majority of patients who reached clinical remission had endoscopic and histological healing at 12 months.[83] Further evidence is needed to confirm the generalisability of these findings.

Practical guidance

Due to the numerous potential side effects, such as sedation [32%] and peripheral neuropathy [20%], and its teratogenicity, thalidomide as induction therapy is restricted to a very selected cohort of paediatric CD patients, such as those who are intolerant to parenterally administered therapies despite psychological support or those refractory to several biologics. 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. Reduced doses should be considered for young children. Pregnancy testing must be performed in young women with CD before starting and while on thalidomide. Contraception is mandatory in young women with CD starting thalidomide if there is any likelihood of sexual activity.

6.5. Thiopurines

ECCO-ESPGHAN statement 10

In children with active CD, thiopurine monotherapy should not be used to induce remission. LoE: 4 | Agreement: 100%.

Evidence

The effectiveness of thiopurines to induce remission in adult CD has been summarised in a Cochrane systematic review and meta-analysis of five placebo-controlled RCTs [small numbers, some methodological issues present] on 380 patients. Thiopurines were no more effective than placebo in inducing remission (risk ratio[RR]: 0.87; 95% CI: 0.71–1.06), with remission rates of 48% and 37%, respectively.[84] The evidence base is weak in paediatric CD, with merely extrapolated evidence if the thiopurine was started at the same time as corticosteroids to induce remission.

7. Induction Therapy in Fistulising Perianal CD

ECCO-ESPGHAN statement 11

In patients with fistulising perianal disease, anti-TNF therapy is recommended as the primary induction and maintenance therapy, in combination with antibiotic therapy, surgical treatment, or both. LoE: 3 | Agreement: 100%.

Evidence

Within the group of perianal abnormalities in CD, non-fistulising and fistulising lesions can be seen. The non-fistulising lesions, including fissures and skin tags, will improve on medical treatment alone. On the other hand, fistulising lesions [abscesses and fistulas] may require potent medical and surgical intervention. The various surgical techniques are described in two recently published consensus guidelines on surgery for CD.[85,86] Currently, the most efficacious treatment for fistulising perianal disease is anti-TNF therapy.[87,88] Before anti-TNF therapy is initiated, symptomatic fistulas require collections to be drained using loose non-cutting setons. This allows the inflammation around the tract to subside and prevents abscess recurrence.

Antibiotics [ciprofloxacin or metronidazole] can be used as an adjuvant, but not as a sole treatment. Patients treated with both ciprofloxacin and anti-TNF agents had better outcomes than anti-TNF agents alone.[89] In complex fistulas, anti-TNF failure is common, with a risk for the need of a diverting ostomy.[90–92]

Practical guidance

The usual daily doses for metronidazole are 30 mg/kg/day orally in two to three divided doses, and for ciprofloxacin 20 mg/kg/day orally in two divided doses. If healing is not optimal, anti-TNF dosing should be adjusted guided by trough level measurements [see section 9.2 on the optimisation of anti-TNF therapy] before changing to another therapy. Higher infliximab doses may be beneficial for perianal fistulising disease, with target trough levels >12.7 µg/mL associated with better response.[93] Ustekinumab may be attempted in children and adolescents with active perianal fistulising disease refractory to anti-TNF agents, but the quality of evidence for a significant effect for this indication in adults is low and data are sparse.[94–96] In a large adult cohort with active perianal Crohn's disease, the success rate of vedolizumab was low.[97]

8. Maintenance Therapy

8.1. Methotrexate

ECCO-ESPGHAN statement 12

Methotrexate can be used to maintain clinical remission as a first-choice immunomodulator, or after thiopurine failure or intolerance. LoE: 3 | Agreement: 96%.

Evidence

The effectiveness of methotrexate to maintain remission in adult CD has been summarised in a Cochrane review of five RCTs involving 333 patients. Weekly intramuscular or subcutaneous [SC] administration of 15 mg methotrexate was significantly more effective than placebo in maintaining clinical remission [RR: 1.67; 95% CI: 1.05–2.67], whereas low-dose oral methotrexate [12.5 mg] was not more effective than placebo.[98]

The evidence base is weaker in paediatric CD; there are no RCTs and almost all publications are on methotrexate use after thiopurine failure or intolerance. A systematic review of six observational studies of methotrexate use to maintain remission in 409 paediatric CD patients evaluated three retrospective cohort studies of 314 patients by meta-analysis, and revealed a pooled maintenance clinical remission rate of 37.1% [95% CI: 29.5%–45.5%] at 12 months.[99] A systematic review without meta-analysis of 10 observational studies [using less rigorous exclusion criteria for studies] showed a maintenance clinical remission rate of 25–53% at 12 months and mean durations of remission of 21–24 months.[100] In terms of safety, adverse events most often included nausea and vomiting, elevated liver function tests, headache, infections, and haematological toxicity.[100] A systematic review of hepatotoxicity in paediatric IBD patients on methotrexate revealed abnormal liver biochemistry in 10% and drug discontinuation due to hepatotoxicity in 5%.[101]

The only head-to-head comparison of methotrexate and azathioprine was in a small RCT of 54 adult CD patients with chronic active disease, randomised [after induction with prednisolone for at least 12 weeks] to receive methotrexate or azathioprine for a 6-month period. The quality of evidence was very low due to multiple methodological concerns, and there were no differences observed with respect to remission rate after 3 [methotrexate 44%, azathioprine 33%; $p = 0.28$] and 6 [methotrexate 56%, azathioprine 63%; $p = 0.39$] months, respectively.[102] Paediatric CD studies have all been observational, with 11 retrospective cohort studies or case series reporting on the sequential use of methotrexate after thiopurine failure [non-response, loss of response, intolerance, or non-adherence].[103–113] In contrast, there have been no studies reporting on the sequential use of thiopurine after methotrexate failure. The change in immunomodulator practice in North America has, however, been driven by concerns around relative safety rather than relative effectiveness.

Practical guidance

Intramuscular and SC routes have similar pharmacokinetics; however, self-injecting via an SC route may be easier and better tolerated by patients. Accordingly, methotrexate is usually administered in practice SC once weekly at a dose of 15 mg/m^2 [body surface area] to a maximum dose of 25 mg. If sustained clinical remission with mucosal healing is achieved, an attempt can be made to decrease the dose to 10 mg/m^2 once a week to a maximum of 15 mg. No therapeutic drug monitoring [TDM] is available for methotrexate. Oral administration of folate [5 mg 24–72 h after methotrexate once weekly or 1 mg once daily for 5 days per week] is advised to reduce hepatotoxicity and gastrointestinal side-effects.[114] There were no differences between oral and SC groups, in terms of sustained corticosteroid-free remission at 12 months, in a retrospective cohort study with propensity scoring for sub-group [mode of methotrexate administration] analyses of 226 paediatric CD patients, and no differences in need for treatment escalation or adverse effects.[103] Many centres will switch from SC to oral methotrexate once effectiveness has been demonstrated by 4 months. This obviates potentially painful injections and is more convenient, less expensive, and has no evidence of more adverse effects. The option exists to switch back to the SC route due to lost effectiveness or intolerance.[100,110]

Nausea and vomiting are major problems both at start of methotrexate therapy and during maintenance use; administration of ondansetron 1 hour before dosing, and for 1 [occasionally more] days afterwards from the outset, may reduce nausea and improve tolerance.[115] Methotrexate is teratogenic and is strictly contraindicated in pregnancy; an effective birth control method [if appropriate] must be used during therapy in CD and for 6 months after drug discontinuation.

8.2. Thiopurines

ECCO-ESPGHAN statement 13

In patients who have reached remission, thiopurines [azathioprine or 6-mercaptopurine] can be used to maintain remission. LoE: 3 | Agreement: 88%.

Evidence

The effectiveness of thiopurines [azathioprine or 6-mercaptopurine] to maintain remission in adult CD has been summarised in a Cochrane review of six RCTs with 489 patients. Azathioprine was significantly more effective than placebo in maintaining steroid-free remission in CD [RR: 1.19; 95% CI 1.05–1.34], giving a number needed to treat for additional beneficial outcome of nine.[116] At the same time, azathioprine users had a significantly greater risk of adverse events, such as pancreatitis, leukopenia, nausea, and infection [RR: 1.29; 95% CI: 1.02–1.64] and serious adverse events [RR: 2.45; 95% CI: 1.22–4.90].

The evidence in paediatric CD is weaker, with just one small RCT of early use of 6-mercaptopurine which had several methodological limitations. This study showed a shorter duration of steroid use in 6-mercaptopurine versus placebo, lower cumulative steroid dose at 6, 12, and 18 months, and lower relapse rate [9% vs 47%; $p = 0.007$].[61] The remaining published studies were observational and reported 12-month corticosteroid-free remission rates of 23% to 60%.[73,117–121]

Practical guidance

The maximum effectiveness of thiopurines may require 8–16 weeks. The recommended azathioprine dose is 2.0–2.5 mg/kg and 1.0–1.5 mg/kg once daily for its prodrug, 6-mercaptopurine. The full thiopurine dose may be prescribed from the outset without the need for gradual dose increase. Haematological toxicity occurs in 2–14% of cases, typically in the first months of treatment. Pancreatitis develops in up to 7% of patients, is usually idiosyncratic, occurs within the first weeks after treatment initiation, and typically requires cessation of the drug.[122] Increased transaminases up to twice the upper limit of normal may be transient or resolve after drug tapering or discontinuation. If newly raised transaminases are observed, treatment should be discontinued and thiopurine metabolites should be assessed, if available. Thiopurines should be withheld until transaminases are in the normal range again; if unresolved, further investigations for liver disease should be performed. In patients with nausea and vomiting

due to azathioprine therapy, interventions include split dosing, switch to 6-mercaptopurine, and use of low-dose thiopurine in combination with allopurinol [see 8.2.2.].

8.2.1. Pre-treatment genotyping

Variants in the gene encoding thiopurine S-methyltransferase [TPMT] alter its enzymatic activity. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity from thiopurines if conventional doses are given. Three RCTs that included more than 1100 IBD patients did not demonstrate clinical benefit of TPMT gene testing before drug initiation, but up-front thiopurine dose reduction in those with heterozygosity led to an 89% risk reduction of haematological adverse drug reactions.[123–125] In addition to considering testing for TPMT gene variants prior to initiation of thiopurines, testing for NUDT15 variants can also be considered, particularly in patients of Asian origin.[126,127] Pre-treatment genotyping does not replace haematological safety monitoring, but could be considered as an addition to optimise thiopurine treatment. CD patients initiating thiopurine therapy should have baseline complete blood counts and liver enzymes measurements. Close blood and liver monitoring should be performed monthly in the first 3 months and then at least once every 3 months thereafter. Thiopurine dose reduction is required in patients who are heterozygous for TPMT or with intermediate enzymatic activity.

8.2.2. Thiopurine metabolite testing

In patients on thiopurine maintenance therapy, determining metabolite levels (6-thioguanine nucleotides [6-TGN] and 6-methylmercaptopurine [6-MMP]) with TDM can guide management. Metabolite testing is helpful in patients with suboptimal response, for evaluation of cytopenia or elevated liver enzymes, for monitoring compliance, and for optimising drug dosing. Desired ranges are shown in Table 3. In children with suboptimal 6-TGN levels and high 6-MMP values, addition of allopurinol can be considered at 50 mg once daily with thiopurine dose reduced to 25–33% of original; this will harmonise metabolite levels and increase corticosteroid-free remission rates.[128–130]

8.2.3. Thiopurines and cancer risk

The absolute risk of malignancy in IBD patients treated with thiopurines is small but cannot be neglected. The main risk identified in different studies of IBD patients treated with thiopurines is for developing lymphomas (including the extremely rare but devastating hepatosplenic T cell lymphoma [HSTCL] which occurs predominantly in young males) and non-melanoma skin cancers. In the CESAME trial that included 19 486 adult IBD patients, the multivariate-adjusted hazard ratio [HR] of lymphoproliferative disorders between patients receiving thiopurines and those who had never received these drugs was 5.28 [95% CI: 2.01–13.9].[133] Another meta-analysis revealed a pooled standard incidence ratio for lymphoma of 4.92 [95% CI: 3.10–7.78] for thiopurine-exposed patients, especially in young men.[134] Importantly, the increased risk does not appear to persist after discontinuation of therapy. Finally, in a nationwide French cohort of 189 289 IBD patients, the risk of lymphoma was higher among those exposed to thiopurine monotherapy [adjusted HR: 2.60; 95% CI: 1.96–3.44], was equivalent to anti-TNF monotherapy [adjusted HR; 2.41, 95% CI: 1.60–3.64], and was higher for those on combination therapy with anti-TNF agents [adjusted HR 6.11; 95% CI: 3.46–10.8]. However, the absolute incidence rate was low.[135] In a prospective survey of paediatric IBD patients in 25 countries over 42 months, 20 of 21 cases with a haematopoietic malignancy were exposed to thiopurines, and 15 were exposed in the last 3 months preceding diagnosis.[136] These findings support the observations made in 5766 participants in another prospective registry of long-term outcomes of paediatric IBD patients. Thirteen of 15 patients who developed a malignancy, and all five patients who developed haemophagocytic lymphohistiocytosis [HLH], had been exposed to thiopurines; 10 patients with malignancy had also been exposed to a biologic agent.[137] Risk factors for the development of HSTCL include male gender, age <35 years, and at least 2 years of thiopurine exposure.[138] All patients started on thiopurines, alone or in combination with biologic agents, should be counselled on the risk of lymphoma, though the absolute risk increase is extremely low. There are concerns that a primary infection with Epstein-Barr virus [EBV] during thiopurine therapy increases the risk for HLH and lymphoma.[139] In a consensus guideline on the management of opportunistic infections in patients with IBD, ECCO

Table 3. Interpretation of thiopurine metabolite profiles.

6-TGN [pmol/8×10^8 RBC][a]	6-MMP [pmol/8×10^8 RBC]	Dose-dependent adverse event	Interpretation	Recommendation
Low [<230]	Normal [<5700]	-	Under-dosing or low compliance	Increase compliance or thiopurine dose as appropriate
Low [<230]	High [≥5700]	Hepatotoxicity and others	TPMT hypermetaboliser	Consider allopurinol co-treatment and thiopurine dose reduction to 25–33% of standard dose, or change medication
Therapeutic [230–450]	Normal or high	Refractoriness	Therapy failure	If clinically resistant, change medication
High [>450]	Normal	Myelosuppression	Low TPMT activity [heterozygote or homozygote]	Change drug category if homozygote, or reduce dose to half if heterozygote
High	High	Myelosuppression and hepatotoxicity	Overdosing	Reduce dose and if clinically resistant, change drug category

TGN, 6-thioguanine nucleotides; RBC, red blood cells; 6-MMP, 6-mercaptopurine; TPMT, thiopurine S-methyltransferase.

[a]The cut-off values given in this table are based on the method according to Lennard.[131] Higher cut-off values [therapeutic range of 6-TGN from 300 to 600 pmol/8×10^8 RBC] are necessary when analyses are bsed on the method of Dervieux and Boulieu.[132]

recommended knowing the EBV serological status before beginning immunomodulatory treatment,[140] but routine testing has not been widely accepted in paediatric practice.[141]

The benefits of long-term immunosuppressive regimens should be considered on an individual patient basis. To date, no such risk has been detected with low-dose once-weekly methotrexate as concomitant immunomodulator, a strategy that has been endorsed by other recent paediatric clinical practice guidelines.[142]

Given the non-melanoma skin cancer risk, especially after several years of therapy, patients should be monitored routinely in clinic, including dermatological evaluation, and use sun protection measures.[143]

8.3. Maintenance enteral nutrition

ECCO-ESPGHAN statement 14

In children with low-risk CD who achieved clinical remission, monotherapy with maintenance enteral nutrition [at least 50% of daily energy requirements] can prolong remission. LoE: 3 | Agreement: 87%.

Evidence

Maintenance enteral nutrition [MEN] refers to a proportion of diet provided by proprietary formula that is specifically used to reduce the risk of subsequent relapse after successful induction treatment, usually by EEN. Maintenance enteral nutrition [MEN] and partial enteral nutrition [PEN] are terms often used interchangeably in the literature, but in this guideline MEN will be used. The evidence for the clinical efficacy of MEN comes from RCTs [small numbers, methodological issues present] predominately performed in Japanese adults with CD. In a clinical trial in adult CD, for patients randomised to thiopurines or MEN [50% of total energy requirements ie, >900 kcal/day given as elemental formula], clinical relapse rates at 2 years were no different between the two groups and were significantly better than a third group with neither of these treatments.[144] In addition, in two studies comparing MEN for 1 year with free diet, the MEN-treated patients had lower endoscopic disease activity, lower mucosal inflammatory cytokine levels, and a significant reduction in relapse.[145,146] The same feeding regimen was also associated with a reduced risk for postoperative recurrence after bowel resection for CD.[147] A meta-analysis of three Japanese studies concluded that MEN in combination with infliximab was more effective in maintaining clinical remission after 1 year than infliximab monotherapy.[148] Several retrospective paediatric studies using 20–50% of daily requirements have been performed, but an analysis of the reports suggests that the findings are inconsistent.[23,149–153] Notwithstanding the low-quality evidence base, the panellists concluded that the desirable effects of adherence to MEN probably outweigh the undesirable effects, and therefore made a conditional recommendation.

Practical guidance

Adherence with MEN in the medium term is poor; hence lack of effect may be partially due to poor adherence rather than lack of efficacy per se. MEN may work well as a short-term bridge between treatments [eg, after EEN while waiting for immunosuppression to be fully effective, or as an adjunct to enhance the effect of other therapies, such as infliximab]. Despite elemental feeds being used in many studies, polymeric feeds as for EEN should be preferred for MEN; an elemental diet is usually only indicated in the case of allergy to cow's milk protein.

8.4. Maintenance therapy after surgical resection

ECCO-ESPGHAN statement 15

Following ileocaecal resection, patients should be monitored by endoscopy 6–12 months post-resection. In patients with high risk of recurrence, we recommend postoperative use of anti-TNF agents. LoE: 3 | Agreement: 100%.

Evidence

Surgical resection in children with CD is usually reserved for those who are refractory to anti-TNF therapy, have stricturing [B2] disease with pre-stenotic dilatation, or penetrating [B3] disease. For most patients, surgery is not curative. Postoperative disease recurrence is common, but the risk can be reduced by using prophylactic medical therapy. Support for the postoperative use of anti-TNF therapy to reduce the risk of recurrence at the anastomosis comes from three RCTs conducted in adult patients with ileocolonic resections and primary anastomoses.[154–156]

In a proof-of-concept study from Pittsburgh [USA], 24 patients were randomly assigned to receive infliximab, administered within 4 weeks of surgery and continued for 1 year, or placebo. Indications for surgery included small-bowel obstruction [$n = 2$] and penetrating complications related to intra-abdominal abscess formation [$n = 22$]. The rate of endoscopic recurrence at 1 year was dramatically lower in the infliximab-treated group [9% vs 85%; $p = 0.0006$].[154] These findings paved the way for an international, multicentre, placebo-controlled RCT among 297 patients. At 18 months post-resection, a significantly smaller proportion of patients in the infliximab-treated group had endoscopic recurrence compared with the placebo group [30.6% vs 60.0%; $p < 0.001$].[155]

The multicentre POCER study provided evidence that early colonoscopy 6 months postoperatively, followed by treatment escalation in case of endoscopic recurrence, was superior in preventing endoscopic recurrence at 18 months compared with standard care [ie, no colonoscopy].[157] In a secondary study among a subset of patients at high risk for disease recurrence, immediate and continuous postoperative treatment with adalimumab 40 mg every other week was superior to immediate and continuous daily thiopurine in preventing endoscopic recurrence at 6 months [21% vs 45%; $p = 0.028$].[156]

Practical guidance

Endoscopic recurrence is an early signal for clinical recurrence. Mucosal lesions are usually seen proximal to the ileocolonic anastomosis. The Rutgeerts score [Table 4] is used in both paediatric and adult CD to assess the severity of inflammation in the neo-terminal ileum.[158,159] Higher scores predict a higher risk of clinical recurrence and should trigger treatment escalation. The Rutgeerts score is simple to perform but has not been validated in children. If the anastomosis is not within reach of endoscopic examination, then disease recurrence may be evaluated with non-invasive modalities such as capsule endoscopy, MRE, and IUS[160] complemented with faecal calprotectin.[159,161]

Table 4. Rutgeerts scoring system for endoscopic recurrence [158] of Crohn's Disease.

Endoscopic remission	i_0 No lesions in neo-terminal ileum
	i_1 ≤5 aphthous ulcers
Endoscopic recurrence	i_2 >5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions confined to ileocolonic anastomosis
	i_3 Diffuse aphthous ileitis with diffusely inflamed mucosa
	i_4 Diffuse inflammation with large ulcers, nodules, and/or stenosis

Most paediatric CD patients in real-world settings will receive maintenance therapy administered within 4 weeks from surgery. Anti-TNF naïve patients may use a thiopurine to reduce postoperative recurrence of disease activity. Endoscopic recurrence on thiopurine monotherapy should trigger a step-up to anti-TNF therapy. In patients who had been following anti-TNF therapy until shortly before the operation, continuation of the same medical therapy is advised, provided that no anti-drug antibodies were detected beforehand. Infliximab and adalimumab are probably equally effective in reducing postoperative recurrence.[162]

In patients with diarrhoea following ileal resection, a therapeutic trial of bile acid sequestrants [ie, colestyramine or colesevelam] is appropriate, particularly when faecal calprotectin values are in the normal range and 7-hydroxycholestenone levels are elevated.

9. Optimisation of Anti-TNF Therapy

9.1. Combination therapy with an immunomodulator

ECCO-ESPGHAN statement 16

In patients starting with infliximab, we recommend combination therapy with an immunomodulator. LoE: 2 | Agreement: 96%.

Evidence

Immunomodulators, including thiopurines and methotrexate, administered concomitantly with anti-TNF agents, reduce the likelihood of antidrug antibody [ADA] development. In the SONIC trial, a double-blind RCT that compared infliximab plus thiopurine versus infliximab alone in adults receiving steroid induction therapy, clinical remission rates at Week 26 and endoscopic improvement were higher with combination therapy [57% vs 44%; $p = 0.02$].[163] Trough concentrations of infliximab in serum were higher and prevalence of ADA was lower with combination therapy. Administration of infliximab, however, was given precisely at 5 mg/kg every 8 weeks without optimising drug exposure via TDM. Indeed, a post-hoc analysis found clinical remission and endoscopic healing rates to be higher in higher quartiles of infliximab trough levels, irrespective of whether this greater exposure was achieved with or without concomitant thiopurine use.[164]

In the COMMIT trial, the combination of infliximab plus methotrexate was associated with a lower risk for ADA development [4% vs 20%; $p = 0.01$]. Combination therapy was also associated with a trend to higher median infliximab trough levels than infliximab monotherapy [6.35 µg/mL vs 3.75 µg/mL; $p = 0.08$].[165] The clinical efficacy of infliximab monotherapy and of combination therapy with methotrexate were comparable in this adult trial, where all patients also received full-dose steroids at induction.

Paediatric studies on combination versus monotherapy are limited to retrospective data and show a lower likelihood of secondary loss of response [LOR] due to ADA development[166] and a greater likelihood of remaining on infliximab over time[167,168] when infliximab was initiated in combination with an immunomodulator. One open-label, paediatric trial randomised patients to combination therapy for 54 weeks or to combination therapy for 26 weeks followed by 26 weeks of anti-TNF monotherapy.[169] At the end of the first year, there was no significant benefit of prolonged combination therapy. An adult follow-up study came to the same conclusion at the end of a 2-year observation period, with no difference between the groups in the likelihood of changing infliximab dosing or need to discontinue infliximab.[170] The benefits of continued immunomodulation should be balanced against the increased risk of adverse events including cancers and lymphoma [see section 8.2.3.].

Practical guidance

Either once-weekly oral or SC methotrexate or daily oral thiopurines reduce the likelihood of ADA development and the associated secondary LOR. Therefore patients with perianal disease, stricturing or penetrating behaviour, or severe growth retardation should be considered for up-front anti-TNF agents in combination with an immunomodulator. Lower thiopurine doses allowing achievement of 6-TGN levels around 125 pmol/8 × 10^8 red blood cells [RBCs] may be sufficient to reduce the risk of anti-infliximab antibody development.[171,172] Consideration should be given to stopping the concomitant immunomodulator after 6–12 months of combination therapy, provided that drug trough levels are well within the target range and treatment targets [eg, endoscopic and transmural healing] are achieved.

ECCO-ESPGHAN statement 17

In patients naïve to anti-TNF agents, adalimumab monotherapy is an alternative to adalimumab combination therapy. LoE: 3 | Agreement: 85%.

Evidence

In comparison with infliximab, there is less evidence to suggest concomitant immunomodulation when starting adalimumab. The open-label DIAMOND trial compared the efficacy of a combination of adalimumab plus azathioprine and adalimumab monotherapy.[173] Adult patients, all naive to immunomodulators and biologics at study baseline, had similar clinical remission rates at 26 weeks, irrespective of combination therapy or adalimumab monotherapy [68% vs 72%, respectively; $p = 0.63$]. Six months after study baseline, the rate of endoscopic improvement was significantly higher with combination therapy, but not at 12 months.

Post-hoc analyses of cohort data from RCTs in adults did not show a significant benefit with combination adalimumab and immunomodulator therapy [thiopurine or methotrexate] over adalimumab alone for induction (odds ratio [OR]: 0.88; 95% CI: 0.60–1.27) or maintenance of remission [OR: 0.88; 95% CI: 0.58–1.35].[174] In a post-hoc analysis of the paediatric IMAgINE-1 RCT, in which over 60% of patients received concomitant thiopurine or methotrexate therapy along with adalimumab, there was no

difference in remission rates between those who received a concomitant immunomodulator and those who did not [36% vs 30%].[72,175]

Recently, in the PANTS cohort study of 1610 patients [14% aged <18 years] with active luminal disease starting their first anti-TNF biologic, the proportion of adalimumab-treated patients not in remission at Week 54 was not different for those receiving a concomitant immunomodulator [64.2%; 95% CI: 57.6–70.4] compared with those receiving monotherapy [69.8%; 95% CI: 63.1–75.9].[176] Nonetheless, the PANTS study confirmed that ADA development is also significantly reduced in adalimumab-treated patients on combination therapy but with a smaller effect size [HR: 3.21; 95% CI: 2.61–3.95].[177]

Practical guidance

The available evidence overall suggests that adalimumab monotherapy is appropriate when started as a first anti-TNF agent. Although the data concerning adalimumab specifically as a second anti-TNF agent are very limited, it seems prudent to employ a concomitant immunomodulator when starting adalimumab in patients previously sensitised to infliximab or in high-risk patients when used as primary anti-TNF agent.

9.2. Therapeutic drug monitoring

ECCO-ESPGHAN statement 18

In patients on anti-TNF agents, early proactive therapeutic drug monitoring [TDM] followed by dose optimisation is recommended. LoE: 2 | Agreement: 87.5%.

Evidence

Anti-TNF agents are highly effective drugs for the treatment of paediatric CD, but 10–30% of patients do not respond to induction therapy [ie., primary non-responders] and approximately 50% of initial responders lose response at a later time [ie, secondary LOR]. Both primary non-response and secondary LOR in anti-TNF treated patients commonly result from either low trough concentration or high ADA titre or both.[178–183]

TDM involves measuring drug concentrations and interpreting these concentrations for adjusting further drug dosages to maintain drug concentrations within an optimal targeted therapeutic window. Measuring anti-TNF trough concentrations when LOR is observed is referred to as reactive TDM. This was shown to improve efficacy of adalimumab in adults.[184] Several retrospective studies demonstrated that routine measurements of trough concentrations and ADA [ie, proactive TDM] in adult patients with CD treated with infliximab[185,186] and adalimumab[186] led to better clinical outcomes. The recently published PAILOT trial, a paediatric RCT, convincingly showed that proactive TDM in children who initially responded to adalimumab induction resulted in higher clinical remission rates compared with those managed with reactive TDM [82% and 48%, respectively; $p = 0.002$]. Moreover, calprotectin levels declined to the target range of <150 µg/g in a higher percentage of patients in the proactive TDM cohort versus the reactive TDM group [42% vs 12.5%, $p = 0.003$].[187] Proactive TDM consequently resulted in higher treatment intensification rates, mainly early in the course of treatment. These findings emphasise the importance of early TDM in children with CD treated with anti-TNF agents, particularly in view of pharmacokinetic data implying that most paediatric patients are underdosed.[188]

Practical guidance

Proactive TDM is of benefit when performed early in the course of treatment [post-induction]. We recommend that paediatric patients with CD treated with adalimumab have their first proactive TDM just before the third injection [ie, 4 weeks after the first dose]. Patients treated with infliximab should have their first proactive TDM just before the fourth infusion [ie, 14 weeks after the first dose]. Patients at risk for accelerated infliximab clearance during induction [ie, children <30 kg, those with extensive disease, and those with low serum albumin] may have their first proactive TDM at the second or third infusion.[189] The aim is to achieve trough concentrations in the therapeutic range, as specified in the following section.

ECCO-ESPGHAN statement 19

In patients with active CD who are treated with anti-TNF agents, it is recommended to useTDM to guide treatment changes over empirically escalating the dose or switching therapies. LoE: 3 | Agreement: 96%.

Evidence

There is a positive association between higher trough concentrations and better response to anti-TNF therapy in both adults[190,191] and children.[189,192] In patients with ongoing symptoms and a persistently increased calprotectin concentration at the end of infliximab induction therapy [ie, around 14 weeks], the decision pathway will be based on the trough level measurement.[193–195] Results below the therapeutic threshold require dose escalation, interval shortening, or both. These interventions were shown to improve treatment efficacy in adults[196] and children[197] while being cost-effective at the same time.[198] In patients with ongoing symptoms despite adequate drug levels, a switch to a different class of biologics [Figure 2] or surgery is warranted.

In patients in whom active luminal disease subsided on anti-TNF agents but faecal calprotectin increased significantly during maintenance treatment, TDM can help guide the therapeutic strategy most likely to recapture response.

<<Figs 2 and 3 near here>>

Practical guidance

In patients who experience primary non-response to anti-TNF agents, drug trough level [and ADA titre, if available] should be measured at the end of induction [ie, before the fourth infliximab infusion, or before the third adalimumab injection] and in patients with secondary LOR at the time of losing response. Treatment changes should be based on TDM results and the consequent stratification to immunogenic [presence of ADA], pharmacokinetic [low trough concentrations without ADA], and pharmacodynamic loss of response [adequate trough concentrations], as shown in Figure 2. Target trough levels for anti-TNF agents are presented in Figure 3. A minimal maintenance threshold of 5 µg/ml for infliximab and 7.5 µg/ml for adalimumab should be targeted for endoscopic healing.[199] Specific phenotypes, in particular perianal fistulising disease, may require even higher drug exposure for fistula healing [≥12.7 µg/ml infliximab].[93]

Patients with low ADA titres may restore response following dose escalation, addition of an immunomodulator, or both, whereas patients with high ADA titre should be switched in-class [from infliximab to adalimumab or vice versa]. Patients with low trough levels without ADA should have a dose increase, and patients with trough levels

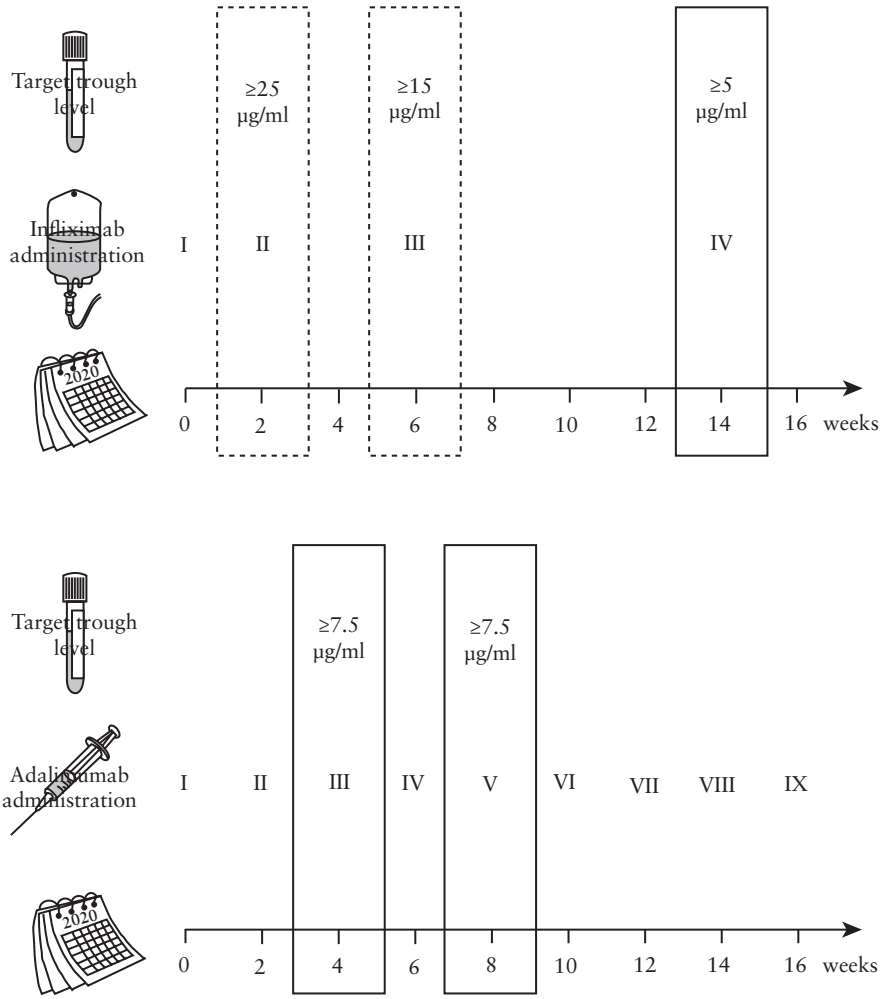

Figure 3. Target trough levels for anti-tumour necrosis factorTNF agents to achieve mucosal healing in luminal Crohn's disease [CD]. At the end of induction [ie, before the fourth infliximab infusion, or before the third adalimumab injection], the target trough level is ≥5 µg/ml for infliximab and ≥ 7.5 µg/ml for adalimumab. In patients at risk for accelerated infliximab clearance during induction, an infliximab concentration ≥25 and ≥15 µg/ml at infusion 2 and 3, respectively, are associated with better outcomes.[189]

that are well in range should be switched to an out-of-class biologic. Infliximab and adalimumab therapy should generally not be abandoned unless drug concentrations are greater than 10 µg/ml.[199]

10. Biologics After Anti-TNF Failure

ECCO-ESPGHAN statement 20

In patients who fail to achieve or maintain clinical remission on anti-TNF agents, despite anti-TNF dose optimisation and immunomodulator use, ustekinumab or vedolizumab can be considered. LoE: Adults: 1; Children: 4 | Agreement: 93%.

10.1. Ustekinumab

Evidence

Ustekinumab, a monoclonal antibody targeting interleukin 12 and 23, has demonstrated efficacy for induction and maintenance of clinical remission in randomised placebo-controlled trials conducted in adult patients with active CD, including those who had previously failed or were unable to tolerate anti-TNF therapy.[200–202] In the CERTIFI trial, response but not remission rate at Week 6 was higher with ustekinumab than placebo.[201] However, in the UNITI-1 trial among patients previously treated with anti-TNF agents, one intravenous infusion of ustekinumab at 6 mg/kg resulted in improved rates of both response [34%] and remission [21%] at Week 8 compared with placebo [22% and 7%, respectively].[200] In a substudy of UNITI-1 twhich examined endoscopic outcomes, mean change in SES-CD at week 8 with ustekinumab [-2.3 points] was better than with placebo [+0.2 points].[200]

In the UNITI-IM maintenance trial, which included both anti-TNF naïve patients and those with previous anti-TNF exposure, significantly more patients were in remission with ustekinumab 90 mg SC every 8 weeks after 1 year of treatment compared with placebo [53% vs 36%]. However, in the subgroup of patients with previous anti-TNF failure, there were no significant differences in clinical remission rates between ustekinumab and placebo at 1 year.[200] In a systematic review and meta-analysis of these trials involving in total 1947 adult patients, ustekinumab was significantly better than placebo for the outcome of inducing remission [RR: 0.91; 95% CI: 0.86–0.95].[203]

Data on ustekinumab efficacy in paediatric CD are still limited. Dayan *et al*. retrospectively reviewed outcomes with ustekinumab therapy administered similarly to the UNITI trials in 52 patients with median age 16.8 years [IQR: 14, 18], 42 of whom had CD. Steroid-free clinical remission was achieved in 40% at Week 52.[204] As observed in adult studies, higher remission rates were seen in biologic-naïve patients versus those with previous anti-TNF failure. Another multicentre retrospective study of 44 children, all previously exposed to anti-TNF agents, reported a 39% clinical remission rate at 12 months with SC ustekinumab induction and maintenance.[205]

Practical guidance

The first dose of ustekinumab is usually administered intravenously and is 6 mg/kg rounded to 130 mg [maximum 520 mg]. SC dosing starts at Week 8; adult patients receive a 90-mg injection. Children should receive a body surface area [BSA]-adjusted dose [considering a standard adult of 1.73 m^2] every 8 weeks. Clinical benefit can be observed from 8 weeks following intravenous induction. The safety profile of ustekinumab in adult and in the limited paediatric studies is very good. Additional paediatric safety data come from an RCT and clinical experience among paediatric patients with psoriasis.[206] The immunogenicity of ustekinumab is lo, and, although not assessed in a prospective RCT, concomitant administration of an immunomodulator does not appear to influence efficacy or durability of response. Target trough levels of ustekinumab are not yet well established.

10.2. Vedolizumab

Evidence

Vedolizumab is a gut-selective humanised monoclonal antibody targeting the α4β7 integrin that is effective in patients with IBD who are refractory or intolerant to systemic steroids, immunomodulators, or anti-TNF agents.[207–211] Vedolizumab is effective in both CD and ulcerative colitis [UC], but is likely more effective in UC.[212] Of the 13 studies identified, six studies reported higher rates of clinical response in patients with UC,[208, 212–216] six reported no difference,[217–223] and one reported higher rates of clinical response in CD.[224] Mucosal healing is observed in 6–63% of CD patients who used vedolizumab,[213,214,223,225–231] which is lower than in UC [33–77%].[208,213,214,223,227,229,232] Higher rates of clinical response are observed when vedolizumab is given as a first-line biologic treatment [ie, no previous anti-TNF therapy].[210,233,234]

Antidrug antibody development is uncommon.[235,236] Severe adverse events leading to discontinuation of treatment with vedolizumab are rare [5–10%].[210,211,236] Vedolizumab use is not associated with increased risk of opportunistic infections[237–241] or malignancy.[237,239–243]

Practical guidance

In patients ≥40 kg, vedolizumab should be administered intravenously at 300 mg with three induction doses over 6 weeks [Weeks 0-2-6], followed by maintenance therapy of 300 mg every 8 weeks. No specific guidelines exist for paediatric dosing. Younger paediatric patients may require an individualised dose of 6 mg/kg up to a maximum of 300 mg, or a BSA-based dose [considering a standard adult of 1.73 m^2]. Response to vedolizumab can take time [≥16 weeks]. Some centres prescribe oral corticosteroids as 'bridging therapy' while waiting for the effects of vedolizumab to manifest. Data from clinical trials and real-world evidence studies suggest that an exposure-efficacy relationship may exist for vedolizumab, but robust target vedolizumab trough levels are currently lacking.[244] Dose intensification by shortening the vedolizumab infusion interval to every 4 weeks may restore responsiveness in patients with LOR.[245]

11. Microbial Manipulation

11.1. Probiotics

ECCO-ESPGHAN statement 21

In patients with CD, probiotics should not be used to induce or maintain remission. LoE: 2 | Agreement: 100%.

Evidence

In the only paediatric RCT available, *Lactobacillus rhamnosus* strain *GG* given in addition to standard maintenance therapy had numerically higher relapse rates compared with placebo, but no statistical significance was noted between the groups.[246] Similarly, Cochrane reviews on probiotics for induction or maintenance of remission in adult CD patients,[247,248] and a more recent systematic review,[249] did not find any benefit of probiotics in CD.

11.2. Antibiotics

Evidence

In the only paediatric RCT, a combination of azithromycin and metronidazole for 8 weeks was more effective than metronidazole alone for induction of clinical remission at 8 weeks in mild-to-moderate CD [66% vs 39%; $p = 0.025$]. However, the primary outcome measure, defined as a decrease in PCDAI >12.5 points, was not statistically different between groups [66% vs 45%; $p = 0.07$]. Faecal calprotectin declined significantly in the combination group but not in the metronidazole group. However, levels in both groups remained high at 8 weeks.[250]

According to a recent Cochrane review in adults, the effect of antibiotics on both induction and maintenance of remission in CD is uncertain and adverse events were not increased with antibiotics compared with placebo.[251] The effect of antimycobacterial therapy is not clear in CD patients, due to the very low quality of evidence.[252]

Practical guidance

A combination of antibiotics may be considered for induction of remission in mild-to-moderate paediatric CD where nutritional therapy is not an option. Various antibiotics were used in adult studies, but in the previously mentioned paediatric RCT, azithromycin 7.5 mg/kg [5 days/week for 4 weeks, dropping to 3 days/week for the second 4 weeks] and metronidazole 20 mg/kg/day [for 8 weeks] were used.[250] In addition to bacterial infections complicating CD, antibiotics may also be considered when bacterial overgrowth is suspected and for perianal disease [see section 7].

11.3. Faecal microbiota transplantation

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In patients with CD, faecal microbiota transplantation should not be used to induce or maintain remission. LoE: 2 | Agreement: 100%.

Evidence

No RCTs evaluating faecal microbiota transplantation [FMT] in CD were identified in a Cochrane review.[253] In a recent systematic review including a case series of 94 children and adults with CD, FMT was associated with a short-term remission rate of 30% in total and 45% in children, but these findings should be interpreted with caution due to publication bias and heterogeneity.[254] Only 20 children were reported in these case series.

12. Conclusion

The aim of this ECCO-ESPGHAN guideline update is to guide clinicians' decisions with the best evidence available to achieve sustained remission and improve quality of life. Regular measurements of disease activity, timely drug interventions, monitoring the effect of treatment, and attention to the psychosocial aspects of CD are necessary to achieve these goals. It is up to every clinician to adapt these guidelines to local regulations and to the patient's individual characteristics and needs.

Both ECCO and ESPGHAN will disseminate these guidelines by educational activities [such as workshops, e-learning, and e-Guide] to ensure that they are integrated into clinical practice. The ECCO e-Guide will serve as a resource to examine how the statements can be implemented into daily clinical practice and patient care pathways.

Disclaimer

The ECCO consensus guidelines are targeted at health care professionals only and are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and may not be based exclusively on the content of the ECCO consensus guidelines. The European Crohn's and Colitis Organisation and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO consensus guidelines.

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Conflict of Interest

ECCO and ESPGHAN have 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 disclosures are not only stored at the ECCO Office and the editorial office of *JCC*, but are 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 the authors.

Author Contributions

All authors participated sufficiently, intellectually, and practically in the work and take public responsibility for the content of the article, including the concept, design, data interpretation, and writing of the manuscript. All authors approved the final manuscript.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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