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

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TITLE PAGE

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

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SHORT TITLE:

ECCO-ESPGHAN Guideline on Management of Paediatric Crohn's Disease

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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 1 January 1991 to 19 March 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 $\geq 80\%$ 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-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.

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

KEYWORDS:

Practice guideline; Crohn's Disease/therapy; Child; Algorithms

1. INTRODUCTION

Approximately 10% of patients with Crohn's disease [CD] are diagnosed before their seventeenth 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 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 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 that 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] that were deemed to be clinically relevant [Supplementary file 1]. 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.

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.

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.

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. While 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 $\mu\text{g/g}$ [$p = 0.001$] 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 two 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 $\mu\text{g/g}$] 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 to higher calprotectin concentrations.⁵

Data from the RISK study⁶ 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 anti-flagellin [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 a 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, while 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, however repeat endoscopies to evaluate resolution of inflammation is 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, while 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 [e.g., 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 preanalytical 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 $> 250 \mu\text{g/g}$ measured in stool obtained prior to 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 $250 \mu\text{g/g}$ 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 $250 \mu\text{g/g}$ until treatment intensification, was longer in children in whom initial induction treatment had been successful within 12 weeks.

In the multicenter 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 $300 \mu\text{g/g}$, but a lower cut-off [$< 100 \mu\text{g/g}$] was needed to identify children with 'deep healing' [i.e., 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 to 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 than 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 [MRE] and intestinal ultrasound [IUS]

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 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, while 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 distention.

Cooperative children may be able to drink sufficient volumes of oral contrast, while 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 while 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 found both for the CDAI in adults⁴⁸ 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 to 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, reintroduction 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 to 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-TREAT⁵⁷ 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 formula, or between diets of similar protein composition with different fat composition, or between bolus oral feeding and continuous enteral feeding.^{51,59} Considering the reduced palatability, the risk of early withdrawal, and the high costs associated with elemental diets, the primary choice being 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.⁶⁰⁻⁶² Corticosteroid use varies greatly between centres and countries and possibly depends on local expertise, bias, and health economic arguments.^{63,64} Corticosteroid use has been associated with increased risk of infection and elevated risk of intra-abdominal or pelvic abscesses,^{65,66} but when asked, the side effect of most importance to users are weight gain, insomnia, and Cushingoid facies.⁶⁷

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.⁶⁸ 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.⁶⁹

Patients who require major surgery while taking supraphysiologic doses [> 50% of prednisolone starting dose; Table 2] for three weeks or more should be assumed to have adrenal insufficiency [A] and will need additional peri-operative hydrocortisone coverage. Patients with unclear adrenal suppression [i.e. 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.^{70,71}

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 [e.g., 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.^{72,73} 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.⁷⁴

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.^{75,76} Although promising, these studies are limited by the non-randomised trial design and relatively short follow up. The TISKIDS trial⁷⁷ 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.⁷⁸ 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, albeit the regimen used in the TISKIDS trial [discontinuation of infliximab after five infusions] is outdated and no longer advised. 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 $\mu\text{g/g}$] 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 [week 0-2-6], followed by maintenance therapy of 5 mg/kg every 8 weeks. However, there is ample evidence⁷⁹ 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 and 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]^{72,73} was approximately 2 years. They were eligible when they had active CD [i.e., 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.⁷² In an open-label extension study, 80% of those who initially responded had at most mild disease at last follow up.⁸⁰ 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; NS].⁷³

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.⁸¹ 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 [2 RCTs, 10 case series] found only one study of sufficient methodological quality.⁸² In this paediatric RCT, the effect of thalidomide versus placebo was evaluated in patients with active CD refractory to immunosuppressive medications.⁸³ 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.⁸⁴ 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 prior to 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 [RR: 0.87; 95% CI: 0.71–1.06], with remission rates of 48% and 37%, respectively.⁸⁵ 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.^{86,87} Currently, the most efficacious treatment for fistulising perianal

disease is anti-TNF therapy.^{88,89} 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.⁹⁰ In complex fistulas, anti-TNF failure is common with a risk for the need of a diverting ostomy.⁹¹⁻⁹³

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.⁹⁴ 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.⁹⁵⁻⁹⁷ In a large adult cohort with active perianal Crohn's disease the success rate of vedolizumab was low.⁹⁸

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.⁹⁹

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.¹⁰⁰ 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 with mean durations of remission of 21–24 months.¹⁰¹ In terms of safety, adverse events most often included nausea and vomiting, elevated liver function tests, headache, infections, and haematological toxicity.¹⁰¹ 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%.¹⁰²

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.¹⁰³ 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].¹⁰⁴⁻¹¹⁴ 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 a 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/m² [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/m² 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.¹¹⁵ 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.¹⁰⁴ 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.^{101,111}

Nausea and vomiting are major problems both at start of methotrexate therapy and during maintenance use; administration of ondansetron 1 hour prior to dosing and for 1 [occasionally more] days afterwards from the outset may reduce nausea and improve tolerance.¹¹⁶ 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 RCT 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 9.¹¹⁷ 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 that 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%; $p = 0.007$].⁶² The remaining published studies were observational and reported 12-months corticosteroid-free remission rates of 23 to 60%.^{74,118-122}

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.¹²³ 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 prior to drug initiation, but up-front thiopurine dose reduction in those with heterozygosity led to an 89% risk reduction of haematologic adverse drug reactions.¹²⁴⁻¹²⁶ 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.^{127,128} Pre-treatment genotyping does not replace haematologic 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.¹²⁹⁻¹³¹

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].¹³² 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.¹³³ 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.¹³⁴ In a prospective survey of paediatric IBD patients in 25 countries over 42 months, 20 of 21 cases with a hematopoietic malignancy were exposed to thiopurines, and 15 were exposed in the last 3 months prior to diagnosis.¹³⁵ These findings support the observations made in 5,766 participants in another prospective registry of long-term outcomes of paediatric IBD patients. Thirteen of 15 patients who developed a malignancy and all 5 patients who developed haemophagocytic lymphohistiocytosis [HLH] had been exposed to thiopurines; 10

patients with malignancy had also been exposed to a biologic agent.¹³⁶ Risk factors for the development of HSTCL include male gender, age < 35 years, and at least 2 years of thiopurine exposure.¹³⁷ 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.¹³⁸ In a consensus guideline on the management of opportunistic infections in patients with IBD, ECCO recommended knowing the EBV serological status before beginning immunomodulatory treatment,¹³⁹ but routine testing has not been widely accepted in paediatric practice.¹⁴⁰

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.¹⁴¹

Given the non-melanoma skin cancer risk, especially after several years of therapy, patients should be monitored routinely in clinic, including dermatologic evaluation, and use sun protection measures.¹⁴²

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. MEN and 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, i.e., > 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.¹⁴³ In addition, in two studies comparing MEN for 1 year to free diet, the MEN-treated patients had lower endoscopic disease activity, lower mucosal inflammatory cytokine levels, and a significant reduction in relapse.^{144,145} The same feeding regimen was also associated with a reduced risk for postoperative recurrence after bowel resection for CD.¹⁴⁶ 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.¹⁴⁷ 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.^{23,148-152} 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 [e.g., 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, while 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.¹⁵³⁻¹⁵⁵

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%; $p = 0.0006$].¹⁵³ 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 to the placebo group [30.6% vs 60.0%; $p < 0.001$].¹⁵⁴

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 to standard care [i.e. no colonoscopy].¹⁵⁶ 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%; $p = 0.028$].¹⁵⁵

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.^{157,158} 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 IUS¹⁵⁹ complemented with faecal calprotectin.^{158,160}

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 before. Infliximab and adalimumab are probably equally effective in reducing postoperative recurrence.¹⁶¹

In patients with diarrhoea following ileal resection, a therapeutic trial of bile acid sequestrants [i.e., 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 anti-drug 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%; $p = 0.02$].¹⁶² 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.¹⁶³

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; $p = 0.08$].¹⁶⁴ The clinical efficacy of infliximab monotherapy and 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 development¹⁶⁵ and a greater likelihood of remaining on infliximab over time^{166,167} 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.¹⁶⁸ 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.¹⁶⁹ 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 × 10⁸ RBCs may be sufficient to reduce the risk of anti-infliximab antibody development.^{170,171} 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 [e.g., 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.¹⁷² 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].¹⁷³ 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%].^{73,174}

Recently, in the PANTS cohort study of 1,610 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].¹⁷⁵ 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].¹⁷⁶

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 sensitized 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 pro-active 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 [i.e., primary non-responders] and approximately 50% of initial responders lose response at a later time [i.e. 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.¹⁷⁷⁻¹⁸²

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.¹⁸³ Several retrospective studies demonstrated that routine measurements of trough concentrations and ADA [i.e. proactive TDM] in adult patients with CD treated with infliximab^{184,185} and adalimumab¹⁸⁶ 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 to those managed with reactive TDM [82% and 48%, respectively; $p = 0.002$]. Moreover, calprotectin levels declined to the target range of $< 150 \mu\text{g/g}$ in a higher percentage of patients in the proactive TDM cohort versus the reactive TDM group [42% versus

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 [i.e., 4 weeks after the first dose]. Patients treated with infliximab should have their first proactive TDM just before the fourth infusion [i.e., 14 weeks after the first dose]. Patients at risk for accelerated infliximab clearance during induction [i.e. 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 use TDM to guide treatment changes over empirically escalating 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 [i.e., 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 adults¹⁹⁶ and children¹⁹⁷ 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 biologicals [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.

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 [i.e. 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].⁹⁴

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 that are well in range should be switched to an out-of-class biological. 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 UNIFI-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 UNIFI-1 that 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 UNIFI-IM maintenance trial, which included both anti-TNF naïve patients and those with prior 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 prior 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 UNIFI 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 prior 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 m²] 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 a RCT and clinical experience among paediatric patients with psoriasis.²⁰⁶ The immunogenicity of ustekinumab is low, 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 humanized monoclonal antibody targeting the $\alpha 4\beta 7$ 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 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,²¹²⁻²¹⁷ six reported no difference²¹⁸⁻²²⁴, and one reported higher rates of clinical response in CD.²²⁵ Mucosal healing is observed in 6%–63% of CD patients who used vedolizumab,^{213,214,224,226-232} which is lower than in UC [33%–77%].^{213-215,224,228,230,233} Higher rates of

clinical response are observed when vedolizumab is given as a first-line biologic treatment [i.e., no prior anti-TNF therapy].^{210,234,235}

Anti-drug antibody development is uncommon.^{236,237} Severe adverse events leading to discontinuation of treatment with vedolizumab are rare [5%–10%].^{210,211,237} Vedolizumab use is not associated with increased risk of opportunistic infections²³⁸⁻²⁴² or malignancy.^{238,240-244}

Practical guidance

In patients ≥ 40 kg, vedolizumab should be administered intravenously at 300 mg with three induction doses over 6 weeks [week 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 individualized dose of 6 mg/kg up to a maximum of 300 mg, or a BSA-based dose [considering a standard adult of 1.73 m²]. 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 suggests that an exposure-efficacy relationship may exist for vedolizumab, but robust target vedolizumab trough levels are currently lacking.²⁴⁵ Dose intensification by shortening the vedolizumab infusion interval to every 4 weeks may restore responsiveness in patients with LOR.²⁴⁶

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 to placebo, but no statistical

significance was noted between the groups.²⁴⁷ Similarly, Cochrane reviews on probiotics for induction or maintenance of remission in adult CD patients^{248,249} and a more recent systematic review²⁵⁰ 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.²⁵¹

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 to placebo.²⁵² The effect of antimycobacterial therapy is not clear in CD patients due to the very low quality of evidence.²⁵³

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.²⁵¹ 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

ECCO-ESPGHAN statement 22

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.²⁵⁴ 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.²⁵⁵ Only 20 children were reported in these case series.

12. CONCLUSION

The aim of this ECCO-ESPGHAN guideline update is to guide the 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.

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Kommentoinut [PvR1]: @Dauren: could you please provide the names

AUTHOR CONTRIBUTIONS

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

TABLES

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	Growth delay	Medium	Consider accelerated step-up to anti-TNF therapy
B1+G1	Extensive disease* or deep colonic ulcers	High	High	Exclusive enteral nutrition; consider up-front anti-TNF therapy
B1 (L3+L4)	Perianal disease	High	High	Up-front anti-TNF therapy
B1+p	Strictureing disease**	None	High	Up-front anti-TNF therapy in combination with antibiotic therapy, surgery, or both
B2	Prestenotic dilatation, obstructive signs or symptoms, or both	High	High	Up-front anti-TNF therapy
B3	Penetrating disease***	High	High	Bowel resection in combination with postoperative anti-TNF therapy
				Surgery in combination with postoperative anti-TNF therapy

* defined as pan-enteric inflammation (i.e., involvement of proximal small bowel, terminal ileum, and colon);

** defined as the occurrence of constant luminal narrowing demonstrated by radiologic or endoscopic examination;

*** 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)

Table 2 | Prednisone or prednisolone tapering scheme (once daily administration)

Week	Body weight		
	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 empiric 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.

Table 3 | Interpretation of thiopurine metabolite profiles

6-TGN (pmol/8×10 ⁸ RBC)*	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 hyper-metabolizer	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

* The cut-off values given in this table are based on the method according to Lennard;²⁵⁶ higher cut-off values (therapeutic range of 6-TGN from 300 to 600 pmol/8×10⁸ RBC) are necessary when analyses are based on the method of Dervieux and Bouliou.²⁵⁷

Table 4 | Rutgeerts scoring system for endoscopic recurrence of Crohn's Disease¹⁵⁷

Endoscopic remission	i₀ No lesions in neo-terminal ileum
	i₁ ≤ 5 aphthous ulcers
Endoscopic recurrence	i₂ > 5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions confined to ileocolonic anastomosis
	i₃ Diffuse aphthous ileitis with diffusely inflamed mucosa
	i₄ Diffuse inflammation with large ulcers, nodules and/or stenosis

FIGURES

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

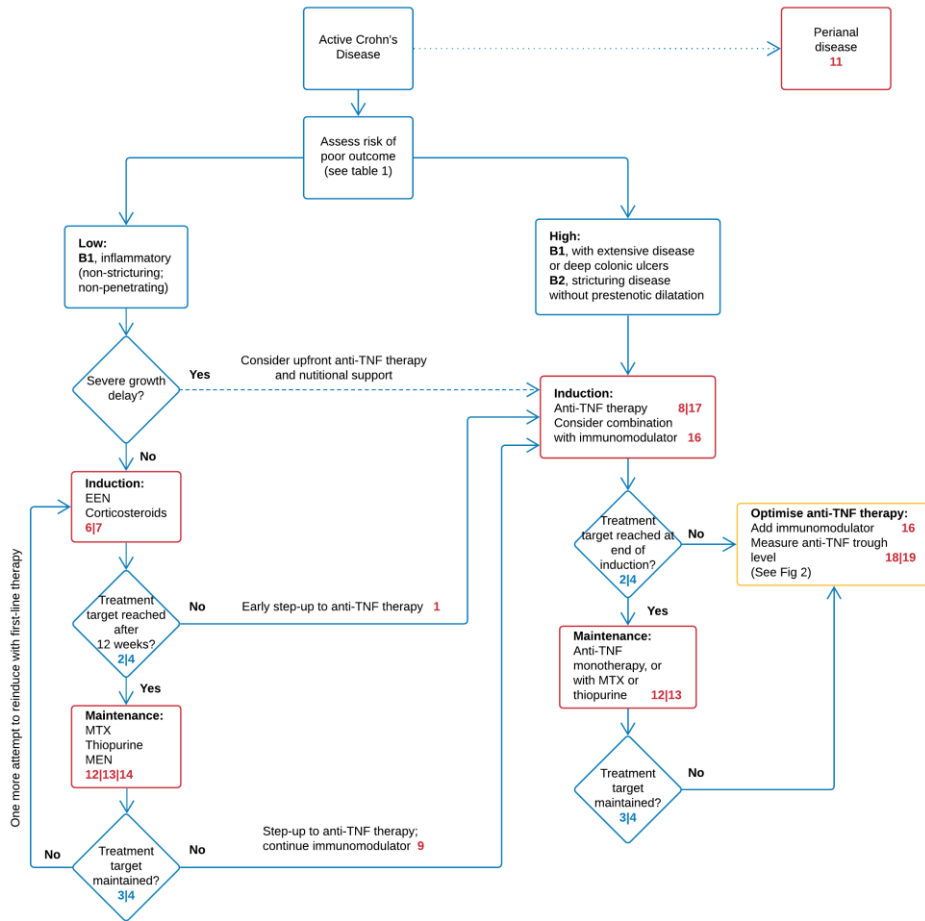


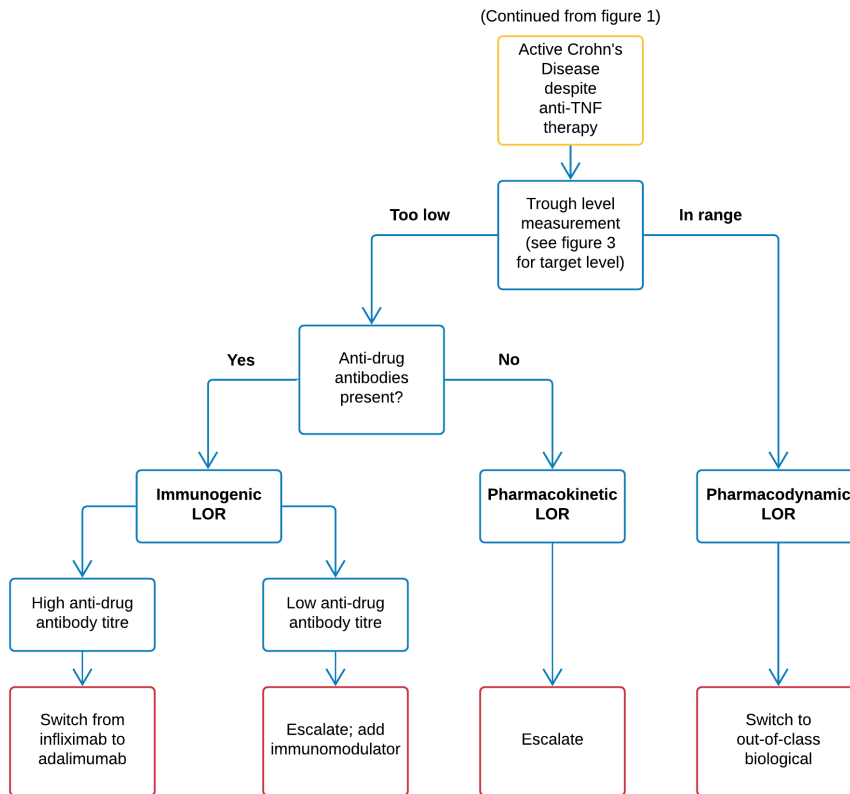
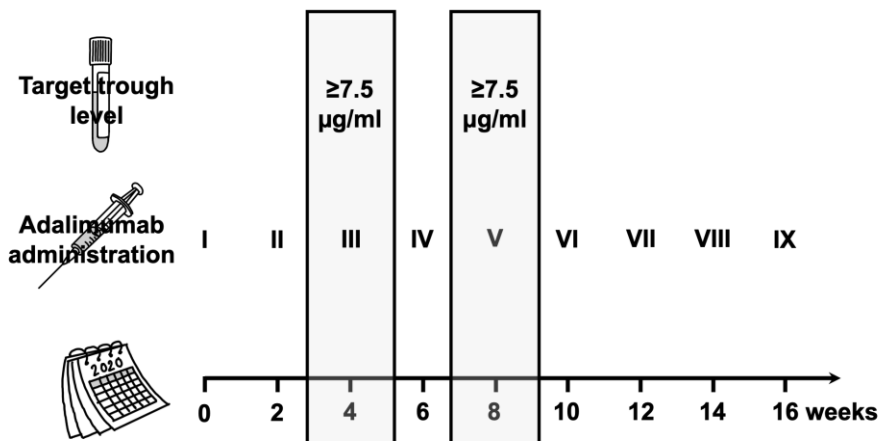
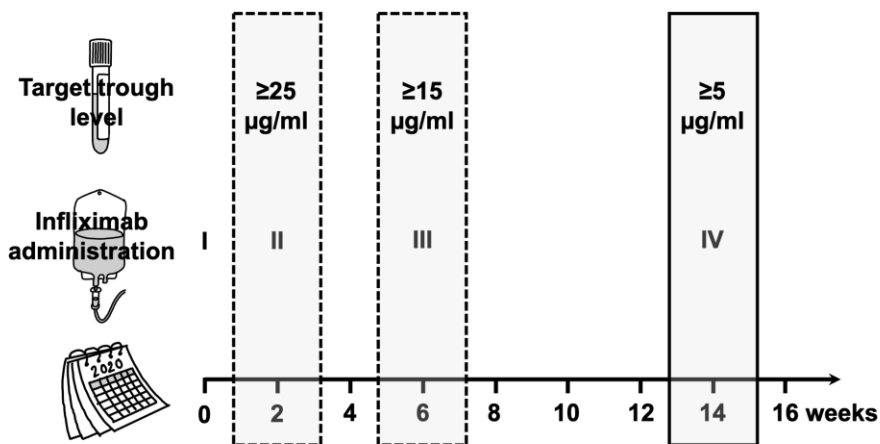
Figure 2 | Anti-TNF therapeutic drug monitoring

Figure 3 | Target trough levels for anti-TNF agents to achieve mucosal healing in luminal CD.

At the end of induction [i.e., before the fourth infliximab infusion, or before the third adalimumab injection] the target trough level is $\geq 5 \mu\text{g/ml}$ for infliximab and $\geq 7.5 \mu\text{g/ml}$ for adalimumab. In patients at risk for accelerated infliximab clearance during induction, an infliximab concentration ≥ 25 and $\geq 15 \mu\text{g/ml}$ at infusion 2 and 3, respectively, are associated with better outcomes.¹⁸⁹



REFERENCES

1. Ghione S, Sarter H, Fumery M, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. *The American journal of gastroenterology* 2018; **113**(2): 265-72.
2. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *Journal of Crohn's and Colitis* 2014; **8**(10): 1179-207.
3. Levine A, Turner D, Gik TP, et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflammatory bowel diseases* 2014; **20**(2): 278-85.
4. Levine A, Chanchlani N, Hussey S, et al. Complicated Disease and Response to Initial Therapy Predicts Early Surgery in Paediatric Crohn's Disease: Results From the Porto Group GROWTH Study. *Journal of Crohn's & colitis* 2020; **14**(1): 71-8.
5. Haisma SM, Verkade HJ, Scheenstra R, van der Doef HPJ, Bodewes F, van Rheezen PF. Time-to-reach Target Calprotectin Level in Newly Diagnosed Patients With Inflammatory Bowel Disease. *Journal of pediatric gastroenterology and nutrition* 2019; **69**(4): 466-73.
6. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet* 2017; **389**: 1710-18.
7. Gupta N, Cohen SA, Bostrom AG, et al. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology* 2006; **130**(4): 1069-77.
8. Rinawi F, Assa A, Hartman C, et al. Incidence of Bowel Surgery and Associated Risk Factors in Pediatric-Onset Crohn's Disease. *Inflammatory bowel diseases* 2016; **22**(12): 2917-23.
9. Dubinsky MC, Kugathasan S, Mei L, et al. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2008; **6**(10): 1105-11.
10. Amre DK, Lu SE, Costea F, Seidman EG. Utility of serological markers in predicting the early occurrence of complications and surgery in pediatric Crohn's disease patients. *The American journal of gastroenterology* 2006; **101**(3): 645-52.
11. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *The American journal of gastroenterology* 2015; **110**(9): 1324-38.
12. Ferrante M, Colombel J-F, Sandborn WJ, et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. *Gastroenterology* 2013; **145**: 978-86.
13. Oliva S, Thomson M, de Ridder L, et al. Endoscopy in Pediatric Inflammatory Bowel Disease: A Position Paper on Behalf of the Porto IBD Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Journal of pediatric gastroenterology and nutrition* 2018; **67**(3): 414-30.
14. Fernandes MA, Verstraete SG, Garnett EA, Heyman MB. Addition of Histology to the Paris Classification of Pediatric Crohn Disease Alters Classification of Disease Location. *Journal of pediatric gastroenterology and nutrition* 2016; **62**(2): 242-5.
15. Sipponen T, Savilahti E, Karkkainen P, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflammatory bowel diseases* 2008; **14**(10): 1392-8.
16. D'Haens G, Vermeire S, Lambrecht G, et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. *Gastroenterology* 2018; **154**(5): 1343-51.
17. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2018; **390**(10114): 2779-89.

18. Battat R, Kopylov U, Bessissow T, et al. Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn's Disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2017; **15**(9): 1427-34.
19. Hamalainen A, Sipponen T, Kolho KL. Infliximab in pediatric inflammatory bowel disease rapidly decreases fecal calprotectin levels. *World journal of gastroenterology* 2011; **17**(47): 5166-71.
20. Kolho KL, Sipponen T. The long-term outcome of anti-tumor necrosis factor-alpha therapy related to fecal calprotectin values during induction therapy in pediatric inflammatory bowel disease. *Scandinavian journal of gastroenterology* 2014; **49**(4): 434-41.
21. Zubin G, Peter L. Predicting Endoscopic Crohn's Disease Activity Before and After Induction Therapy in Children: A Comprehensive Assessment of PCDAI, CRP, and Fecal Calprotectin. *Inflammatory bowel diseases* 2015; **21**: 1386-91.
22. Ziv-Baran T, Hussey S, Sladek M, et al. Response to treatment is more important than disease severity at diagnosis for prediction of early relapse in new-onset paediatric Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2018; **48**(11-12): 1242-50.
23. Logan M, Clark CM, Ijaz UZ, et al. The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction. *Alimentary pharmacology & therapeutics* 2019; **50**(6): 664-74.
24. Oord T, Hornung N. Fecal calprotectin in healthy children. *Scand J Clin Lab Invest* 2014; **74**(3): 254-8.
25. Rugtveit J, Fagerhol MK. Age-dependent variations in fecal calprotectin concentrations in children. *Journal of pediatric gastroenterology and nutrition* 2002; **34**(3): 323-4; author reply 4-5.
26. Padoan A, D'Inca R, Scapellato ML, et al. Improving IBD diagnosis and monitoring by understanding preanalytical, analytical and biological fecal calprotectin variability. *Clin Chem Lab Med* 2018; **56**(11): 1926-35.
27. Haisma SM, van Rheenen PF, Wagenmakers L, Muller Kobold A. Calprotectin instability may lead to undertreatment in children with IBD. *Arch Dis Child* 2019: Epub ahead of print.
28. Kopylov U, Yung DE, Engel T, et al. Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. *European journal of gastroenterology & hepatology* 2016; **28**(10): 1137-44.
29. Foster AJ, Smyth M, Lakhani A, Jung B, Brant RF, Jacobson K. Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients. *World J Gastroenterol* 2019; **25**(10): 1266-77.
30. Weinstein-Nakar I, Focht G, Church P, et al. Associations Among Mucosal and Transmural Healing and Fecal Level of Calprotectin in Children With Crohn's Disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2018; **16**(7): 1089-97.
31. Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. *Inflammatory bowel diseases* 2017; **23**(6): 894-902.
32. Minderhoud IM, Steyerberg EW, van Bodegraven AA, et al. Predicting Endoscopic Disease Activity in Crohn's Disease: A New and Validated Noninvasive Disease Activity Index (The Utrecht Activity Index). *Inflammatory bowel diseases* 2015; **21**(10): 2453-9.
33. Cozijnsen MA, Ben Shoham A, Kang B, et al. Development and Validation of the Mucosal Inflammation Noninvasive Index For Pediatric Crohn's Disease. *Clin Gastroenterol Hepatol* 2019.
34. van Rheenen PF. Role of fecal calprotectin testing to predict relapse in teenagers with inflammatory bowel disease who report full disease control. *Inflamm Bowel Dis* 2012; **18**(11): 2018-25.
35. Haisma SM, Galaurchi A, Almahwzi S, Adekanmi Balogun JA, Muller Kobold AC, van Rheenen PF. Head-to-head comparison of three stool calprotectin tests for home use. *PLoS one* 2019; **14**(4): e0214751.

36. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(6): 1042-50 e2.
37. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *Journal of pediatric gastroenterology and nutrition* 2014; **58**(6): 795-806.
38. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *Journal of Crohn's & colitis* 2019; **13**(2): 144-64.
39. Yoon HM, Suh CH, Kim JR, et al. Diagnostic Performance of Magnetic Resonance Enterography for Detection of Active Inflammation in Children and Adolescents With Inflammatory Bowel Disease: A Systematic Review and Diagnostic Meta-analysis. *JAMA Pediatr* 2017; **171**(12): 1208-16.
40. Church PC, Turner D, Feldman BM, et al. Systematic review with meta-analysis: magnetic resonance enterography signs for the detection of inflammation and intestinal damage in Crohn's disease. *Alimentary pharmacology & therapeutics* 2015; **41**(2): 153-66.
41. Calabrese E, Maaser C, Zorzi F, et al. Bowel Ultrasonography in the Management of Crohn's Disease. A Review with Recommendations of an International Panel of Experts. *Inflammatory bowel diseases* 2016; **22**: 1168-83.
42. Moreno N, Ripolles T, Paredes JM, et al. Usefulness of abdominal ultrasonography in the analysis of endoscopic activity in patients with Crohn's disease: changes following treatment with immunomodulators and/or anti-TNF antibodies. *Journal of Crohn's & colitis* 2014; **8**: 1079-87.
43. Aloï M, Di Nardo G, Romano G, et al. Magnetic resonance enterography, small-intestine contrast US, and capsule endoscopy to evaluate the small bowel in pediatric Crohn's disease: a prospective, blinded, comparison study. *Gastrointestinal endoscopy* 2015; **81**(2): 420-7.
44. Giles E, Barclay AR, Chippington S, Wilson DC. Systematic review: MRI enterography for assessment of small bowel involvement in paediatric Crohn's disease. *Alimentary pharmacology & therapeutics* 2013; **37**(12): 1121-31.
45. Absah I, Bruining DH, Matsumoto JM, et al. MR enterography in pediatric inflammatory bowel disease: retrospective assessment of patient tolerance, image quality, and initial performance estimates. *AJR Am J Roentgenol* 2012; **199**(3): W367-75.
46. Sadigh S, Chopra M, Sury MR, Shah N, Olsen OE, Watson TA. Paediatric magnetic resonance enteroclysis under general anaesthesia - initial experience. *Pediatr Radiol* 2017; **47**(7): 877-83.
47. Riccabona M, Lobo ML, Augdal TA, et al. European Society of Paediatric Radiology Abdominal Imaging Task Force recommendations in paediatric uro-radiology, part X: how to perform paediatric gastrointestinal ultrasonography, use gadolinium as a contrast agent in children, follow up paediatric testicular microlithiasis, and an update on paediatric contrast-enhanced ultrasound. *Pediatr Radiol* 2018; **48**(10): 1528-36.
48. Peyrin-Biroulet L, Reinisch W, Colombel J-F, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63**: 88-95.
49. Turner D, Levine A, Walters TD, et al. Which PCDAI Version Best Reflects Intestinal Inflammation in Pediatric Crohn Disease? *Journal of pediatric gastroenterology and nutrition* 2017; **64**(2): 254-60.
50. Turner D, Griffiths AM, Walters TD, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. *Inflammatory bowel diseases* 2012; **18**(1): 55-62.
51. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2018; **2018**(4): CD000542.
52. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li Ferry S. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2017; **46**(7): 645-56.

53. da Silva JSV, Seres DS, Sabino K, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract* 2020; **35**(2): 178-95.
54. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2006; **4**(6): 744-53.
55. Pigneur B, Lepage P, Mondot S, et al. Mucosal Healing and Bacterial Composition in Response to Enteral Nutrition Vs Steroid-based Induction Therapy-A Randomised Prospective Clinical Trial in Children With Crohn's Disease. *Journal of Crohn's & colitis* 2019; **13**(7): 846-55.
56. Svolos V, Gerasimidis K, Buchanan E, et al. Dietary treatment of Crohn's disease: perceptions of families with children treated by exclusive enteral nutrition, a questionnaire survey. *BMC gastroenterology* 2017; **17**(1): 14.
57. Svolos V, Hansen R, Nichols B, et al. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. *Gastroenterology* 2019; **156**(5): 1354-67.e6.
58. Levine A, Wine E, Assa A, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. *Gastroenterology* 2019; **157**(2): 440-50.e8.
59. Rubio A, Pigneur B, Garnier-Lengline H, et al. The efficacy of exclusive nutritional therapy in paediatric Crohn's disease, comparing fractionated oral vs. continuous enteral feeding. *Alimentary pharmacology & therapeutics* 2011; **33**(12): 1332-9.
60. Levine A, Turner D, Pfeffer Gik T, et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflamm Bowel Dis* 2014; **20**(2): 278-85.
61. Escher JC, European Collaborative Research Group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. *European journal of gastroenterology & hepatology* 2004; **16**(1): 47-54.
62. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**(4): 895-902.
63. Krishnakumar C, Ballengee CR, Liu C, et al. Variation in Care in the Management of Children With Crohn's Disease: Data From a Multicenter Inception Cohort Study. *Inflammatory bowel diseases* 2019; **25**(7): 1208-17.
64. Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn's Disease: Results From the GROWTH CD Study. *Journal of Crohn's & colitis* 2018; **12**(3): 306-12.
65. Agrawal A, Durrani S, Leiper K, Ellis A, Morris AI, Rhodes JM. Effect of systemic corticosteroid therapy on risk for intra-abdominal or pelvic abscess in non-operated Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2005; **3**(12): 1215-20.
66. Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients with Inflammatory Bowel Diseases: a Systematic Review and Meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019.
67. Costello R, Patel R, Humphreys J, McBeth J, Dixon WG. Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. *BMJ open* 2017; **7**(4): e014603.
68. Levine A, Kori M, Dinari G, et al. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: a randomized placebo-controlled trial. *Inflammatory bowel diseases* 2009; **15**(7): 1055-61.

69. Kuenzig ME, Rezaie A, Kaplan GG, et al. Budesonide for the Induction and Maintenance of Remission in Crohn's Disease: Systematic Review and Meta-Analysis for the Cochrane Collaboration. *J Can Assoc Gastroenterol* 2018; **1**(4): 159-73.
70. Hicks CW, Wick EC, Salvatori R, Ha CY. Perioperative corticosteroid management for patients with inflammatory bowel disease. *Inflammatory bowel diseases* 2015; **21**(1): 221-8.
71. Sidoroff M, Kolho KL. Screening for adrenal suppression in children with inflammatory bowel disease discontinuing glucocorticoid therapy. *BMC gastroenterology* 2014; **14**: 51.
72. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; **132**(3): 863-73.
73. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012; **143**(2): 365-74.e2.
74. Walters TD, Kim MO, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. *Gastroenterology* 2014; **146**(2): 383-91.
75. Kang B, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal Healing in Paediatric Patients with Moderate-to-Severe Luminal Crohn's Disease Under Combined Immunosuppression: Escalation versus Early Treatment. *Journal of Crohn's & colitis* 2016; **10**(11): 1279-86.
76. Lee YM, Kang B, Lee Y, Kim MJ, Choe YH. Infliximab "Top-Down" Strategy is Superior to "Step-Up" in Maintaining Long-Term Remission in the Treatment of Pediatric Crohn Disease. *Journal of pediatric gastroenterology and nutrition* 2015; **60**(6): 737-43.
77. Cozijnsen MA, Van Pieterse M, Samsom JN, Escher JC, De Ridder L. Top-down Infliximab Study in Kids with Crohn's disease (TISKids): an international multicentre randomised controlled trial. *BMJ open gastroenterology* 2016; **3**(1): e000123.
78. Jongsma MA, M., Cozijnsen, M; et al. Top-down infliximab superior to step-up in children with Moderate-to-Severe Crohn's disease: A multicentre randomised controlled trial. *Journal of Crohn's and Colitis* 2020; **14**(Supplement 1): S039.
79. Winter DA, Joosse ME, de Wildt SN, Taminiou J, de Ridder L, Escher JC. Pharmacokinetics, Pharmacodynamics and Immunogenicity of Infliximab in Paediatric Inflammatory Bowel Disease; a Systematic Review and Revised Dosing Considerations. *Journal of pediatric gastroenterology and nutrition* 2020.
80. Hyams J, Walters TD, Crandall W, et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. *Current Medical Research and Opinion* 2011; **27**(3): 651-62.
81. deBruyn JC, Jacobson K, El-Matary W, et al. Long-term Outcomes of Infliximab Use for Pediatric Crohn Disease: A Canadian Multicenter Clinical Practice Experience. *Journal of pediatric gastroenterology and nutrition* 2018; **66**(2): 268-73.
82. Yang C, Singh P, Singh H, Le ML, El-Matary W. Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2015; **41**(11): 1079-93.
83. Lazzarini M, Martelossi S, Magazzu G, et al. Effect of thalidomide on clinical remission in children and adolescents with refractory Crohn disease: a randomized clinical trial. *JAMA : the journal of the American Medical Association* 2013; **310**(20): 2164-73.
84. Lazzarini M, Villanacci V, Pellegrin MC, et al. Endoscopic and Histologic Healing in Children With Inflammatory Bowel Diseases Treated With Thalidomide. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2017; **15**(9): 1382-9.
85. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2013; (4): CD000545.
86. Amil-Dias J, Kolacek S, Turner D, et al. Surgical Management of Crohn Disease in Children: Guidelines from the Paediatric IBD Porto Group of ESPGHAN. *Journal of pediatric gastroenterology and nutrition* 2017; **64**(5): 818-35.

87. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP Consensus on Surgery for Crohn's Disease. *Journal of Crohn's & colitis* 2018; **12**(1): 1-16.
88. Crandall W, Hyams J, Kugathasan S, et al. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. *Journal of pediatric gastroenterology and nutrition* 2009; **49**(2): 183-90.
89. Ruemmele FM, Rosh J, Faubion WA, et al. Efficacy of Adalimumab for Treatment of Perianal Fistula in Children with Moderately to Severely Active Crohn's Disease: Results from IMAGINE 1 and IMAGINE 2. *Journal of Crohn's & colitis* 2018; **12**(10): 1249-54.
90. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *The American journal of gastroenterology* 2011; **106**(4): 661-73.
91. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. *Colorectal Disease* 2016; **18**(7): 667-75.
92. Rosen MJ, Moulton DE, Koyama T, et al. Endoscopic ultrasound to guide the combined medical and surgical management of pediatric perianal Crohn's disease. *Inflammatory bowel diseases* 2010; **16**(3): 461-8.
93. Schwartz DA, Wang A, Ozbay B, et al. Comparison of Health Care Utilization and Costs Between Patients with Perianal Fistulizing Crohn's Disease Treated with Biologics with or Without Previous Seton Placement. *Inflammatory bowel diseases* 2017; **23**(10): 1860-6.
94. El-Matary W, Walters TD, Huynh HQ, et al. Higher Postinduction Infliximab Serum Trough Levels Are Associated With Healing of Fistulizing Perianal Crohn's Disease in Children. *Inflammatory bowel diseases* 2019; **25**(1): 150-5.
95. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2018; **16**(12): 1879-92.
96. Sands BE, Gasink C, Jacobstein D, et al. Fistula healing in pivotal studies of ustekinumab in Crohn's disease. *Gastroenterology* 2017; **152**(5): S185.
97. Biemans V, Van Der Meulen-De Jong A, Van Der Woude C, et al. Ustekinumab for Crohn's disease: a nationwide real-life observational cohort study (ICC case series). *Journal of crohn's and colitis Conference: 13th congress of european crohn's and colitis organisation, ECCO 2018 Austria* 2018; **12**(Supplement 1): S55?S6.
98. Chapuis-Biron C, Bourrier A, Nachury M, et al. Vedolizumab for perianal Crohn's disease: a multicentre cohort study in 151 patients. *Alimentary pharmacology & therapeutics* 2020; **51**(7): 719-27.
99. Patel V, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014; (8): Cd006884.
100. Colman RJ, Lawton RC, Dubinsky MC, Rubin DT. Methotrexate for the treatment of pediatric Crohn's disease: A Systematic Review and Meta-analysis. *Inflammatory bowel diseases* 2018; **24**(10): 2135-41.
101. Scherkenbach LA, Stumpf JL. Methotrexate for the Management of Crohn's Disease in Children. *Ann Pharmacother* 2016; **50**(1): 60-9.
102. Valentino PL, Church PC, Shah PS, et al. Hepatotoxicity caused by methotrexate therapy in children with inflammatory bowel disease: a systematic review and meta-analysis. *Inflammatory bowel diseases* 2014; **20**(1): 47-59.
103. Ardizzone S, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; **35**(9): 619-27.
104. Turner D, Doveh E, Cohen A, et al. Efficacy of oral methotrexate in paediatric Crohn's disease: a multicentre propensity score study. *Gut* 2015; **64**(12): 1898-904.
105. Hojsak I, Misak Z, Jadresin O, Mocić Pavić A, Kolacek S. Methotrexate is an efficient therapeutic alternative in children with thiopurine-resistant Crohn's disease. *Scandinavian journal of gastroenterology* 2015; **50**(10): 1208-13.

106. Haisma SM, Lijftogt T, Kindermann A, et al. Methotrexate for maintaining remission in paediatric Crohn's patients with prior failure or intolerance to thiopurines: A multicenter cohort study. *Journal of Crohn's and Colitis* 2015; **9**(4): 305-11.
107. Sunseri W, Hyams JS, Lerer T, et al. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. *Inflammatory bowel diseases* 2014; **20**(8): 1341-5.
108. Willot S, Noble A, Deslandres C. Methotrexate in the treatment of inflammatory bowel disease: An 8-year retrospective study in a Canadian pediatric IBD center. *Inflammatory bowel diseases* 2011; **17**(12): 2521-6.
109. Boyle B, Mackner L, Ross C, Moses J, Kumar S, Crandall W. A single-center experience with methotrexate after thiopurine therapy in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition* 2010; **51**(6): 714-7.
110. Weiss B, Lerner A, Shapiro R, et al. Methotrexate treatment in pediatric Crohn disease patients intolerant or resistant to purine analogues. *Journal of pediatric gastroenterology and nutrition* 2009; **48**(5): 526-30.
111. Turner D, Grossman AB, Rosh J, et al. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. *The American journal of gastroenterology* 2007; **102**(12): 2804-12; quiz 3, 13.
112. Ravikumara M, Hinsberger A, Spray CH. Role of methotrexate in the management of Crohn disease. *Journal of pediatric gastroenterology and nutrition* 2007; **44**(4): 427-30.
113. Uhlen S, Belbouab R, Narebski K, et al. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. *Inflammatory bowel diseases* 2006; **12**(11): 1053-7.
114. Mack DR, Young R, Kaufman SS, Ramey L, Vanderhoof JA. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. *The Journal of pediatrics* 1998; **132**(5): 830-5.
115. Liu L, Liu S, Wang C, et al. Folate Supplementation for Methotrexate Therapy in Patients With Rheumatoid Arthritis: A Systematic Review. *J Clin Rheumatol* 2019; **25**(5): 197-202.
116. Kempinska A, Benchimol EI, Mack A, Barkey J, Boland M, Mack DR. Short-course ondansetron for the prevention of methotrexate-induced nausea in children with Crohn disease. *Journal of pediatric gastroenterology and nutrition* 2011; **53**(4): 389-93.
117. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015; (10): Cd000067.
118. Boyle BM, Kappelman MD, Colletti RB, Baldassano RN, Milov DE, Crandall WV. Routine use of thiopurines in maintaining remission in pediatric Crohn's disease. *World journal of gastroenterology* 2014; **20**(27): 9185-90.
119. Riello L, Talbotec C, Garnier-Lengline H, et al. Tolerance and efficacy of azathioprine in pediatric Crohn's disease. *Inflammatory bowel diseases* 2011; **17**(10): 2138-43.
120. Punati J, Markowitz J, Lerer T, et al. Effect of early immunomodulator use in moderate to severe pediatric Crohn disease. *Inflammatory bowel diseases* 2008; **14**(7): 949-54.
121. Jaspers GJ, Verkade HJ, Escher JC, de Ridder L, Taminiau JA, Rings EH. Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease. *Inflammatory bowel diseases* 2006; **12**(9): 831-6.
122. Banerjee S, Bishop WP. Evolution of thiopurine use in pediatric inflammatory bowel disease in an academic center. *Journal of pediatric gastroenterology and nutrition* 2006; **43**(3): 324-30.
123. Teich N, Mohl W, Bokemeyer B, et al. Azathioprine-induced Acute Pancreatitis in Patients with Inflammatory Bowel Diseases--A Prospective Study on Incidence and Severity. *Journal of Crohn's & colitis* 2016; **10**(1): 61-8.
124. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. *Gastroenterology* 2015; **149**(4): 907-17.
125. Newman WG, Payne K, Tricker K, et al. A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study. *Pharmacogenomics* 2011; **12**(6): 815-26.

126. Sayani FA, Prosser C, Bailey RJ, Jacobs P, Fedorak RN. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie* 2005; **19**(3): 147-51.
127. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nature genetics* 2014; **46**(9): 1017-20.
128. Walker GJ, Harrison JW, Heap GA, et al. Association of Genetic Variants in NUDT15 With Thiopurine-Induced Myelosuppression in Patients With Inflammatory Bowel Disease. *JAMA : the journal of the American Medical Association* 2019; **321**(8): 773-85.
129. Hoentjen F, Seinen ML, Hanauer SB, et al. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. *Inflammatory bowel diseases* 2013; **19**(2): 363-9.
130. Friedman AB, Brown SJ, Bampton P, et al. Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study). *Alimentary pharmacology & therapeutics* 2018; **47**(8): 1092-102.
131. Gerich ME, Quiros JA, Marcin JP, Tennyson L, Henthorn M, Prindiville TP. A prospective evaluation of the impact of allopurinol in pediatric and adult IBD patients with preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. *Journal of Crohn's & colitis* 2010; **4**(5): 546-52.
132. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374**(9701): 1617-25.
133. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(5): 847-58.
134. Lemaitre M, Kirchgessner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA : the journal of the American Medical Association* 2017; **318**(17): 1679-86.
135. Joosse ME, Aardoom MA, Kemos P, et al. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. *Alimentary pharmacology & therapeutics* 2018; **48**(5): 523-37.
136. Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab Is Not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease. *Gastroenterology* 2017; **152**(8): 1901-14.
137. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2011; **9**(1): 36-41.
138. de Francisco R, Castano-Garcia A, Martinez-Gonzalez S, et al. Impact of Epstein-Barr virus serological status on clinical outcomes in adult patients with inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2018; **48**(7): 723-30.
139. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *Journal of Crohn's & colitis* 2014; **8**(6): 443-68.
140. Martinelli M, Giugliano FP, Strisciuglio C, et al. Vaccinations and Immunization Status in Pediatric Inflammatory Bowel Disease: A Multicenter Study From the Pediatric IBD Porto Group of the ESPGHAN. *Inflammatory bowel diseases* 2019.
141. Mack DR, Benchimol EI, Critch J, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease. *Gastroenterology* 2019; **157**(2): 320-48.

142. Annese V, Beaugerie L, Egan L, et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *Journal of Crohn's & colitis* 2015; **9**(11): 945-65.
143. Hanai H, Iida T, Takeuchi K, et al. Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease. *Digestive and Liver Disease* 2012; **44**(8): 649-54.
144. Yamamoto T, Nakahigashi M, Saniabadi AR, et al. Impacts of long-term enteral nutrition on clinical and endoscopic disease activities and mucosal cytokines during remission in patients with Crohn's disease: A prospective study. *Inflammatory bowel diseases* 2007; **13**(12): 1493-501.
145. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial. *Alimentary Pharmacology and Therapeutics* 2006; **24**(9): 1333-40.
146. Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of long-term enteral nutrition on clinical and endoscopic recurrence after resection for Crohn's disease: A prospective, non-randomized, parallel, controlled study. *Alimentary pharmacology & therapeutics* 2007; **25**(1): 67-72.
147. Nguyen DL, Palmer LB, Nguyen ET, McClave SA, Martindale RG, Bechtold ML. Specialized enteral nutrition therapy in Crohn's disease patients on maintenance infliximab therapy: A meta-analysis. *Therapeutic Advances in Gastroenterology* 2015; **8**(4): 168-75.
148. Duncan H, Buchanan E, Cardigan T, et al. A retrospective study showing maintenance treatment options for paediatric CD in the first year following diagnosis after induction of remission with EEN: supplemental enteral nutrition is better than nothing! *BMC gastroenterology* 2014; **14**: 50.
149. Kim HJ, Kim Y, Cho JM, Oh SH, Kim KM. Therapeutic efficacy of oral enteral nutrition in pediatric Crohn's disease: A single center non-comparative retrospective study. *Yonsei medical journal* 2016; **57**(5): 1185-91.
150. Gavin J, Ashton JJ, Heather N, Marino LV, Beattie RM. Nutritional support in paediatric Crohn's disease: outcome at 12 months. *Acta paediatrica (Oslo, Norway : 1992)* 2018; **107**(1): 156-62.
151. Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996; **38**(4): 543-8.
152. Schulman JM, Pritzker L, Shaoul R. Maintenance of Remission with Partial Enteral Nutrition Therapy in Pediatric Crohn's Disease: A Retrospective Study. *Canadian Journal of Gastroenterology and Hepatology* 2017; **2017**: 5873158.
153. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology* 2009; **136**(2): 441-50.
154. Regueiro M, Feagan BG, Zou B, et al. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. *Gastroenterology* 2016; **150**(7): 1568-78.
155. De Cruz P, Kamm MA, Hamilton AL, et al. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. *Alimentary pharmacology & therapeutics* 2015; **42**(7): 867-79.
156. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; **385**(9976): 1406-17.
157. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**(4): 956-63.
158. Hukkinen M, Pakarinen MP, Merras-Salmio L, Koivusalo A, Rintala R, Kolho KL. Fecal calprotectin in the prediction of postoperative recurrence of Crohn's disease in children and adolescents. *Journal of pediatric surgery* 2016; **51**(9): 1467-72.
159. Yung DE, Har-Noy O, Tham YS, et al. Capsule Endoscopy, Magnetic Resonance Enterography, and Small Bowel Ultrasound for Evaluation of Postoperative Recurrence in Crohn's Disease: Systematic Review and Meta-Analysis. *Inflammatory bowel diseases* 2017; **24**(1): 93-100.
160. Tham YS, Yung DE, Fay S, et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. *Therap Adv Gastroenterol* 2018; **11**: 1756284818785571.

161. Bakouny Z, Yared F, El Rassy E, et al. Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease: A Systematic Review and Network Meta-Analysis of Prospective Trials. *Journal of clinical gastroenterology* 2019; **53**(6): 409-17.
162. Ruffolo C, Scarpa M, Bassi N. Infliximab, azathioprine, or combination therapy for Crohn's disease. *The New England journal of medicine* 2010; **363**(11): 1086-7; author reply 7-8.
163. Colombel JF, Adedokun OJ, Gasink C, et al. Combination Therapy With Infliximab and Azathioprine Improves Infliximab Pharmacokinetic Features and Efficacy: A Post Hoc Analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019; **17**(8): 1525-32.
164. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; **146**(3): 681-8.
165. Church PC, Guan J, Walters TD, et al. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. *Inflammatory bowel diseases* 2014; **20**(7): 1177-86.
166. Grossi V, Lerer T, Griffiths A, et al. Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn's Disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(10): 1748-56.
167. van Rheenen H, van Rheenen P. Long-Term Efficacy of Anti-Tumor Necrosis Factor Agents in Pediatric Luminal Crohn's Disease: A Systematic Review of Real-World Evidence Studies. *Pediatric gastroenterology, hepatology & nutrition* 2020; **23**(2): 121-31.
168. Kierkus J, Iwanczak B, Wegner A, et al. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. *Journal of pediatric gastroenterology and nutrition* 2015; **60**(5): 580-5.
169. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008; **134**(7): 1861-8.
170. Yarur AJ, Kubiliun MJ, Czul F, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(6): 1118-24.
171. Roblin X, Boschetti G, Williet N, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Alimentary pharmacology & therapeutics* 2017; **46**(2): 142-9.
172. Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. *Journal of Crohn's & colitis* 2016; **10**(11): 1259-66.
173. Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti-Tumor Necrosis Factor Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(13): 2233-40.
174. Hyams JS, Dubinsky M, Rosh J, et al. The effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in paediatric patients with Crohn's disease: a post hoc analysis. *Alimentary pharmacology & therapeutics* 2019; **49**(2): 155-64.
175. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; **4**(5): 341-53.
176. Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. *Gastroenterology* 2020; **158**(1): 189-99.

177. Franca R, Curci D, Lucafo M, Decorti G, Stocco G. Therapeutic drug monitoring to improve outcome of anti-TNF drugs in pediatric inflammatory bowel disease. *Expert Opin Drug Metab Toxicol* 2019; **15**(7): 527-39.
178. Nakase H, Motoya S, Matsumoto T, et al. Significance of measurement of serum trough level and anti-drug antibody of adalimumab as personalised pharmacokinetics in patients with Crohn's disease: a subanalysis of the DIAMOND trial. *Alimentary pharmacology & therapeutics* 2017; **46**(9): 873-82.
179. Bodini G, Giannini EG, Savarino V, et al. Infliximab trough levels and persistent vs transient antibodies measured early after induction predict long-term clinical remission in patients with inflammatory bowel disease. *Dig Liver Dis* 2018; **50**(5): 452-6.
180. Bodini G, Giannini EG, Savarino V, et al. Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcome of patients with Crohn's disease. *Scandinavian journal of gastroenterology* 2016; **51**(9): 1081-6.
181. Drobne D, Kurent T, Golob S, et al. Success and safety of high infliximab trough levels in inflammatory bowel disease. *Scandinavian journal of gastroenterology* 2018; **53**(8): 940-6.
182. Merras-Salmio L, Kolho KL. Clinical Use of Infliximab Trough Levels and Antibodies to Infliximab in Pediatric Patients With Inflammatory Bowel Disease. *Journal of pediatric gastroenterology and nutrition* 2017; **64**(2): 272-8.
183. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic Drug Monitoring Guides the Management of Crohn's Patients with Secondary Loss of Response to Adalimumab. *Inflammatory bowel diseases* 2018; **24**(7): 1531-8.
184. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2017; **15**(10): 1580-8.
185. Papamichael K, Juncadella A, Wong D, et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. *Journal of Crohn's & colitis* 2019; **13**(8): 976-81.
186. Papamichael K, Cheifetz AS. Proactive adalimumab monitoring in inflammatory bowel disease: current data and future perspectives. *Journal of Crohn's & colitis* 2019.
187. Assa A, Matar M, Turner D, et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. *Gastroenterology* 2019; **157**(4): 985-96.
188. Frymoyer A, Piester TL, Park KT. Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease. *Journal of pediatric gastroenterology and nutrition* 2016; **62**(5): 723-7.
189. Clarkston K, Tsai YT, Jackson K, Rosen MJ, Denson LA, Minar P. Development of Infliximab Target Concentrations During Induction in Pediatric Crohn Disease Patients. *Journal of pediatric gastroenterology and nutrition* 2019; **69**(1): 68-74.
190. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. *Inflammatory bowel diseases* 2018; **24**(10): 2266-71.
191. Zittan E, Kabakchiev B, Milgrom R, et al. Higher Adalimumab Drug Levels are Associated with Mucosal Healing in Patients with Crohn's Disease. *Journal of Crohn's & colitis* 2016; **10**(5): 510-5.
192. Hoekman DR, Brandse JF, de Meij TG, et al. The association of infliximab trough levels with disease activity in pediatric inflammatory bowel disease. *Scandinavian journal of gastroenterology* 2015; **50**(9): 1110-7.
193. Papamichael K, Vajravelu RK, Osterman MT, Cheifetz AS. Long-Term Outcome of Infliximab Optimization for Overcoming Immunogenicity in Patients with Inflammatory Bowel Disease. *Digestive diseases and sciences* 2018; **63**(3): 761-7.

194. Selinger CP, Lenti MV, Clark T, et al. Infliximab therapeutic drug monitoring changes clinical decisions in a virtual biologics clinic for inflammatory bowel disease. *Inflammatory bowel diseases* 2017; **23**(12): 2083-8.
195. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *American Journal of Gastroenterology* 2014; **109**(8): 1250-6.
196. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2017; **23**(7): 1202-9.
197. Deora V, Kozak J, El-Kalla M, Huynh HQ, El-Matary W. Therapeutic drug monitoring was helpful in guiding the decision-making process for children receiving infliximab for inflammatory bowel disease. *Acta paediatrica (Oslo, Norway : 1992)* 2017; **106**(11): 1863-7.
198. Martelli L, Olivera P, Roblin X, Attar A, Peyrin-Biroulet L. Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review. *Journal of gastroenterology* 2017; **52**(1): 19-25.
199. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019; **17**(9): 1655-68.
200. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England journal of medicine* 2016; **375**(20): 1946-60.
201. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *New England journal of medicine* 2012; **367**(16): 1519-28.
202. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008; **135**(4): 1130-41.
203. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016; **11**: Cd007572.
204. JR D. Real World Experience With Ustekinumab in Children and Young Adults at a Tertiary Care Pediatric Inflammatory Bowel Disease Center. *J Pediatr Gastroenterol Nutr* 2019 2019; **69**(1): 61-7.
205. Chavannes M, Martinez-Vinson C, Hart L, et al. Management of Paediatric Patients With Medically Refractory Crohn's Disease Using Ustekinumab: A Multi-Centred Cohort Study. *Journal of Crohn's & colitis* 2019; **13**(5): 578-84.
206. Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol* 2015; **73**(4): 594-603.
207. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2016; **22**(10): 2425-31.
208. Ledder O, Assa A, Levine A, et al. Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN. *Journal of Crohn's & colitis* 2017; **11**(10): 1230-7.
209. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; **147**(3): 618-27.
210. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naive to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. *Inflammatory bowel diseases* 2017; **23**(1): 97-106.
211. Vermeire S, Loftus EV, Jr., Colombel JF, et al. Long-term Efficacy of Vedolizumab for Crohn's Disease. *Journal of Crohn's & colitis* 2017; **11**(4): 412-24.

212. Yajnik V, Khan N, Dubinsky M, et al. Efficacy and Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease Patients Stratified by Age. *Advances in therapy* 2017; **34**(2): 542-59.
213. Christensen B, Colman RJ, Micic D, et al. Vedolizumab as Induction and Maintenance for Inflammatory Bowel Disease: 12-month Effectiveness and Safety. *Inflammatory bowel diseases* 2018; **24**(4): 849-60.
214. Kotze PG, Ma C, Almutairdi A, et al. Real-world clinical, endoscopic and radiographic efficacy of vedolizumab for the treatment of inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2018; **48**(6): 626-37.
215. Ledder O, Assa A, Levine A, et al. Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN. *Journal of Crohn's & colitis* 2017; **11**(10): 1230-7.
216. Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study. *Dig Liver Dis* 2018; **50**(12): 1299-304.
217. Singh N, Rabizadeh S, Jossen J, et al. Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2016; **22**(9): 2121-6.
218. Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice--a nationwide consecutive German cohort study. *Alimentary pharmacology & therapeutics* 2016; **43**(10): 1090-102.
219. Kopylov U, Avni-Biron I, Ron Y, et al. Effectiveness and safety of vedolizumab for maintenance treatment in inflammatory bowel disease-The Israeli real world experience. *Dig Liver Dis* 2019; **51**(1): 68-74.
220. Plevris N, Chuah CS, Allen RM, et al. Real-world Effectiveness and Safety of Vedolizumab for the Treatment of Inflammatory Bowel Disease: The Scottish Vedolizumab Cohort. *Journal of Crohn's & colitis* 2019; **13**(9): 1111-20.
221. Samaan MA, Pavlidis P, Johnston E, et al. Vedolizumab: early experience and medium-term outcomes from two UK tertiary IBD centres. *Frontline gastroenterology* 2017; **8**(3): 196-202.
222. Shelton E, Allegretti J, Stevens B, Lucci M, Ananthakrishnan A, Yajnik V. Efficacy of vedolizumab as induction therapy in refractory IBD patients: A multicentre cohort. *Journal of Gastroenterology and Hepatology (Australia)* 2015; **30**(SUPPL. 3): 138-9.
223. Chaparro M, Garre A, Ricart E, et al. Short and long-term effectiveness and safety of vedolizumab in inflammatory bowel disease: results from the ENEIDA registry. *Alimentary pharmacology & therapeutics* 2018; **48**(8): 839-51.
224. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *Journal of gastroenterology* 2018; **53**(9): 1048-64.
225. Kopylov U, Verstockt B, Biedermann L, et al. Effectiveness and Safety of Vedolizumab in Anti-TNF-Naive Patients With Inflammatory Bowel Disease-A Multicenter Retrospective European Study. *Inflammatory bowel diseases* 2018; **24**(11): 2442-51.
226. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Alimentary pharmacology & therapeutics* 2017; **45**(10): 1291-302.
227. Christensen B, Gibson PR, Micic D, et al. Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019; **17**(3): 486-93.
228. Engel T, Ungar B, Yung DE, Ben-Horin S, Eliakim R, Kopylov U. Vedolizumab in IBD-Lessons From Real-world Experience; A Systematic Review and Pooled Analysis. *Journal of Crohn's & colitis* 2018; **12**(2): 245-57.

229. Noman M, Ferrante M, Bisschops R, et al. Vedolizumab Induces Long-term Mucosal Healing in Patients With Crohn's Disease and Ulcerative Colitis. *Journal of Crohn's & colitis* 2017; **11**(9): 1085-9.
230. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice. *Journal of Crohn's & colitis* 2016; **10**(4): 402-9.
231. Yarur AJ, Bruss A, Naik S, et al. Vedolizumab Concentrations Are Associated with Long-Term Endoscopic Remission in Patients with Inflammatory Bowel Diseases. *Digestive diseases and sciences* 2019; **64**(6): 1651-9.
232. Ylisaukko-Oja T, Aaltonen J, Nuutinen H, et al. High treatment persistence rate and significant endoscopic healing among real-life patients treated with vedolizumab - a Finnish Nationwide Inflammatory Bowel Disease Cohort Study (FINVEDO)(). *Scandinavian journal of gastroenterology* 2018; **53**(2): 158-67.
233. Dreesen E, Verstockt B, Bian S, et al. Evidence to Support Monitoring of Vedolizumab Trough Concentrations in Patients With Inflammatory Bowel Diseases. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2018; **16**(12): 1937-46.
234. Feagan BG, Lasch K, Lissos T, et al. Rapid Response to Vedolizumab Therapy in Biologic-Naive Patients With Inflammatory Bowel Diseases. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019; **17**(1): 130-8.
235. Rosario M, French JL, Dirks NL, et al. Exposure-efficacy Relationships for Vedolizumab Induction Therapy in Patients with Ulcerative Colitis or Crohn's Disease. *Journal of Crohn's & colitis* 2017; **11**(8): 921-9.
236. Al-Bawardy B, Ramos GP, Willrich MAV, et al. Vedolizumab Drug Level Correlation With Clinical Remission, Biomarker Normalization, and Mucosal Healing in Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2019; **25**(3): 580-6.
237. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *The New England journal of medicine* 2013; **369**(8): 711-21.
238. Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). *Dig Liver Dis* 2017; **49**(4): 338-58.
239. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017; **66**(5): 839-51.
240. Luthra P, Peyrin-Biroulet L, Ford AC. Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2015; **41**(12): 1227-36.
241. Meserve J, Aniwani S, Koliiani-Pace JL, et al. Retrospective Analysis of Safety of Vedolizumab in Patients With Inflammatory Bowel Diseases. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019; **17**(8): 1533-40.
242. Scribano ML. Vedolizumab for inflammatory bowel disease: From randomized controlled trials to real-life evidence. *World journal of gastroenterology* 2018; **24**(23): 2457-67.
243. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn's & colitis* 2017; **11**(1): 3-25.
244. Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY. Risk for Overall Infection with Anti-TNF and Anti-integrin Agents Used in IBD: A Systematic Review and Meta-analysis. *Inflammatory bowel diseases* 2017; **23**(4): 570-7.
245. Pouillon L, Vermeire S, Bossuyt P. Vedolizumab trough level monitoring in inflammatory bowel disease: a state-of-the-art overview. *BMC Med* 2019; **17**(1): 89.
246. Shmidt E, Kochhar G, Hartke J, et al. Predictors and Management of Loss of Response to Vedolizumab in Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2018; **24**(11): 2461-7.

247. Bousvaros A, Guandalini S, Baldassano RN, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflammatory bowel diseases* 2005; **11**(9): 833-9.
248. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2006; (4): CD004826.
249. Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008; (3): CD006634.
250. Ganji-Arjenaki M, Rafieian-Kopaei M. Probiotics are a good choice in remission of inflammatory bowel diseases: A meta analysis and systematic review. *Journal of cellular physiology* 2018; **233**(3): 2091-103.
251. Levine A, Kori M, Kierkus J, et al. Azithromycin and metronidazole versus metronidazole-based therapy for the induction of remission in mild to moderate paediatric Crohn's disease : a randomised controlled trial. *Gut* 2019; **68**(2): 239-47.
252. Townsend CM, Parker CE, MacDonald JK, et al. Antibiotics for induction and maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2019; **2**: Cd012730.
253. Patton PH, Parker CE, MacDonald JK, Chande N. Anti-tuberculous therapy for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016; **7**: Cd000299.
254. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2018; (11).
255. Fang H, Fu L, Wang J. Protocol for Fecal Microbiota Transplantation in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2018; **2018**: 8941340.
256. Lennard L. Assay of 6-thioinosinic acid and 6-thioguanine nucleotides, active metabolites of 6-mercaptopurine, in human red blood cells. *J Chromatogr* 1987; **423**: 169-78.
257. Dervieux T, Bouliou R. Simultaneous determination of 6-thioguanine and methyl 6-mercaptopurine nucleotides of azathioprine in red blood cells by HPLC. *Clin Chem* 1998; **44**(3): 551-5.