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

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Conflicts of interest

DSS: lecturing fees from Takeda, scientific advisory board Tracells.
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RSB: Received funds for consulting or speaker - from Nestlé Health Science, Takeda, Megapharm and Janssen; serve on advisory board for Evinature.
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CaS: last 3 years received consultation fee, research grant, royalties, or honorarium from Alphasigma, Sanofi, Astrazeneca, Novalac,Takeda, Aboca, Nestlè.
LdR: Advisory board Celltrion, Data Monitoring Safety Board Alvotech, lecturing fees Janssen, Medtronic, Pfizer, grant Pfizer.
JB: honoraria/consultations/speakers fee or advisory board (all outside of the submitted work) from AbbVie, MSD, Nestlé, Nutricia, Sanofi, Pfizer and Vitabalans.
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Abstract

Objective:

To provide an updated, evidence-based ECCO–ESPGHAN guideline for the management, monitoring, and long-term care of paediatric Crohn's disease (CD).

Methods:

A multidisciplinary panel of 27 experts followed ECCO Standard Operating Procedures for guideline development. A systematic review of studies published between January 2018 and October 2024, with targeted updates through June 2025, was conducted across MEDLINE, EMBASE, and Cochrane Central. Evidence was graded using the Oxford Centre for Evidence-Based Medicine levels. Draft statements underwent two Delphi voting rounds involving the guideline panel, ECCO National Representatives, and an international sounding board; statements achieving ≥80% agreement were accepted.

Results:

The guideline provides updated recommendations across major domains of paediatric CD care, including risk stratification, treatment targets, induction and maintenance strategies, nutritional therapies, therapeutic drug monitoring, and the roles of imaging and endoscopy. High-risk patients should start anti-TNF therapy as first-line treatment, with proactive and reactive therapeutic drug monitoring to enhance efficacy. For low-risk luminal disease, exclusive enteral nutrition or the Crohn's Disease Exclusion Diet with partial enteral nutrition are preferred induction options. Long-term management emphasizes achieving endoscopic remission, normal growth, improved quality of life, and reduction of bowel damage. The guideline also reviews emerging advanced therapies,

including biologics and small molecules increasingly used in practice but mostly not yet approved for paediatric CD, to inform clinicians about their potential role.

Conclusions:

This updated ECCO–ESPGHAN guideline integrates new paediatric evidence with contemporary adult data and treat-to-target principles, providing practical recommendations to support personalized, multidisciplinary, and proactive management aimed at improving long-term outcomes.

Abbreviations

ACT	advanced combination therapy
ADA	anti-drug antibodies
ASCA	anti-Saccharomyces cerevisiae antibody
AUC	area under the curve
AUROC	area Under the Receiver Operating Characteristic
BMD	bone mineral density
BMI	body mass index
BR	bowel resection
BSA	body surface area
BWT	bowel wall thickness
CD	Crohn's disease
CDED	Crohn's disease Exclusion Diet
CRP	C-reactive protein
DEXA	dual-energy X-ray absorptiometry
EBD	endoscopic balloon dilatation
ECCO	European Crohn's and Colitis Organization
EEN	exclusive enteral nutrition
EH	endoscopic healing
EIM	extra-intestinal manifestations
ER	endoscopic remission
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESR	erythrocyte sedimentation rate
FC	fecal calprotectin
FCM	ferric carboxymaltose
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
IBUS-SAS	International Bowel Ultrasound Segmental Activity Score
IDA	Iron deficiency anemia
IUS	intestinal ultrasound
JAK	Janus Kinase
MA	meta-analyses
MEN	maintenance enteral nutrition
MMP	methyl mercaptopurine
MRE	magnetic resonance enterography
NUDT15	Nudix Hydrolase 15
pCD	perianal Crohn's disease
PCDAI	pediatric Crohn's disease activity index

PEN	partial enteral nutrition
PICMI	Pediatric Inflammatory Crohn’s Magnetic Resonance Enterography Index
PICO	population, Intervention, comparator, outcomes
PROs	patient-reported outcomes
QoL	quality of life
RCT	randomized controlled trials
SES-CD	simple endoscopic score for Crohn's disease
SR	systematic reviews
TC	trough concentrations
TDM	therapeutic drug monitoring
TGN	thioguanine nucleotides
TPMP	thiopurine S-methyltransferase
VEO	very early-onset
VTE	venous thromboembolism

1. Introduction

The global incidence and prevalence of inflammatory bowel disease (IBD) have risen steadily over recent decades worldwide, including among children and adolescents(1). The growing burden of paediatric-onset Crohn's disease (CD) is of particular concern, as these patients typically present with more extensive and aggressive phenotypes, often accompanied by growth failure and psychosocial consequences that can persist into adulthood(2, 3). In this context, the need for early diagnosis, optimized treatment strategies, and multidisciplinary care has become increasingly urgent.

Since the publication of the previous ECCO–ESPGHAN guidelines on the medical management of paediatric CD in 2020(4), there have been substantial advances in understanding disease pathogenesis, therapeutic drug monitoring (TDM), and the safety and efficacy of emerging therapies. Parallel developments in the adult CD guidelines have redefined therapeutic goals, emphasizing mucosal and transmural healing and the reduction of cumulative bowel damage(5, 6). The present guideline represents an updated, evidence-based consensus, jointly developed by ECCO and ESPGHAN, incorporating new data and clinical experience to refine recommendations across medical and surgical therapy, nutritional management, and long-term monitoring in paediatric patients with CD. Its objective is to provide clinicians with clear, pragmatic, and scientifically grounded guidance to optimize outcomes and quality of life (QoL) for young patients living with this chronic condition. In alignment with the evolving treat-to-target and disease-modification paradigms established in adult IBD care, this guideline underscores the importance of early risk stratification, objective assessment of treatment response, and proactive therapy adjustment to prevent irreversible bowel damage.

2. Methodology

Guideline development adhered to the ECCO Standard Operating Procedures(5). Following an open call for participation, ECCO and ESPGHAN convened a multidisciplinary panel of 27 specialists in IBD, encompassing paediatric and adult gastroenterologists, a dietitian, and a colorectal surgeon. The panel's work was supported by a medical librarian and a webmaster, who managed the online platform used for drafting and reviewing.

Panel members were divided into nine working groups, each tasked with developing key clinical questions framed according to the PICO structure (Population, Intervention, Comparator, Outcomes) considered relevant to clinical practice (see **Supplementary Table 1**). A systematic review of the literature was performed by a medical librarian, covering studies published between 1 January 2018 and 27 October 2024, using MEDLINE, EMBASE, and the Cochrane Central databases. To ensure the inclusion of the most current evidence, additional targeted searches were conducted up to 1 June 2025.

Two independent reviewers from each working group screened titles and abstracts based on predefined eligibility criteria. Randomized controlled trials (RCTs), cohort and case-control studies involving paediatric patients with CD, as well as systematic reviews (SR) and meta-analyses (MA) for adult patients, were considered eligible. In cases where both reviewers agreed, full-text manuscripts were retrieved; discrepancies were resolved through discussion. The level of evidence was graded using the Oxford Centre for Evidence-Based Medicine criteria (available at https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf). Studies were downgraded if they did not directly address the predefined PICO question, except when observational paediatric data complemented adult RCT findings.

Each working group synthesized the evidence into summary tables (**Supplementary Table 2**) and drafted preliminary recommendation statements. These were uploaded to a secure online

platform for structured review. Using a Delphi consensus methodology, two online voting rounds were carried out to prioritize statements deemed clinically significant. The first round included all members of the guideline panel (n = 27), while the second round expanded participation to ECCO National Representatives and an international sounding board consisting of experts who had expressed interest in contributing but were not selected as core panelists (n = 57).

A final virtual consensus meeting was held in October 2025 to discuss and further refine statements. Statements achieving ≥80% agreement among the core panelists were adopted as final recommendations. Each final statement is presented with its corresponding evidence summary and discussion.

Results

3. Risk stratification of patients

3.1 Risk factors for a poor outcome include stricturing or penetrating disease, perianal involvement, extensive disease, deep ulcers, severe growth or pubertal delay, and failure to achieve clinical and biochemical remission after induction therapy. LoE: 3; 96% agreement.

Poor outcomes in paediatric CD, as defined by the Paediatric IBD Ahead program, include the need for surgery, development of complications (stricturing and/or penetrating disease), perianal disease, linear growth impairment, bone disease, and chronically active disease(7). Predictors for these poor outcomes (**Table 1**) can help inform treatment targets and guide the selection of appropriate therapies; however, their identification and interpretation vary across studies(8). The multicenter GROWTH CD study, involving 222 treatment-naïve paediatric CD patients, demonstrated that only steroid-free clinical remission with a normal C-reactive protein (CRP) level

at week 12 predicted sustained remission at 52 weeks (OR 3.6; 95% CI 1.4–9.39; p=0.008) (9). Additionally, in a subset of these patients followed for 104 weeks, active disease at week 12 and stricturing phenotype at diagnosis emerged as risk factors for early surgery (10). Similarly, in another cohort, reaching fecal calprotectin (FC) <250 µg/g within 12 weeks after induction therapy (steroids or exclusive enteral nutrition) was associated with a higher rate of relapse-free survival in the first year after diagnosis(11).

Other risk factors for poor outcomes reported in the PIBD-Ahead initiative (7) include CD diagnosis during adolescence, NOD2/CARD15 polymorphisms, stricturing or penetrating phenotype, and positive anti-Saccharomyces cerevisiae antibody (ASCA) status. Deep ulcerations at diagnosis were associated with increased rates of penetrating disease and relapse within 12 months, while isolated colonic disease was associated with fewer surgeries(12). Risk factors for stricturing (B2) and/or penetrating (B3) disease included older age at presentation for internal penetrating (B3) complications; small bowel disease for B2 complications; positive serology (ASCA, anti-flagellin, and anti-OmpC) for both, and Black ethnicity for B3(7). Several subsequent studies have shown that extensive disease (involving upper GI and/or jejunum)(13, 14) and perianal disease are associated with poor outcomes(15-17). Furthermore, B2 at diagnosis increased the need for surgery(10, 16) and was a risk factor for a more complicated disease course(14). Most studies on patients who have very early-onset (VEO)-IBD have analyzed IBD as a homogenous group rather than by diagnostic subtype, and the data on long-term complications remain inconclusive(18-21).

According to the prospective population-based EPIMAD registry, the presence of extra-intestinal manifestations (EIMs) at diagnosis independently increases the need for corticosteroid and immunosuppressive treatment in paediatric IBD patients (22). Specifically for CD patients, EIMs were associated with an increased relapse rate(23). A SR including adult patients showed that co-occurring immune-mediated inflammatory diseases are associated with an increased risk of

IBD-related surgeries(24). Other factors, such as delayed diagnosis, sarcopenia, and histologic granulomas, which were shown to be risk factors in adult studies, are not supported by conclusive evidence in paediatric studies.

4. Treatment targets and monitoring response

4.1 The short-term treatment target should be clinical response. Intermediate targets should include symptomatic remission, normalization of CRP, and a decrease in fecal calprotectin to an acceptable range. Long-term targets should be endoscopic remission, normalized quality of life, and normal growth. LoE 3; 93% agreement.

4.2 Disease activity and extent should be assessed before major treatment changes, to diagnose complications and to ensure endoscopic remission. LoE 3; 81% agreement.

The STRIDE-II update refined long-term targets for clinical remission and endoscopic healing, adding the absence of disability, QoL restoration, and normal growth in children (25). **Figure 1** and **Table 2** summarize these treatment targets and their respective surrogate markers. Clinical, systemic (CRP, ESR [erythrocyte sedimentation rate]) and mucosal (FC) inflammatory markers should be regularly monitored, even in clinically remitting patients, to detect disease flares at an early pre-symptomatic stage.

Clinical activity indexes

The PCDAI and its variations, including the weighted PCDAI (wPCDAI), short PCDAI, abbreviated PCDAI, and modified PCDAI, are the most widely utilized indices for assessing disease activity in paediatric CD. Unfortunately, the various versions of PCDAI are not reliable for evaluating mucosal inflammation(26-30). Studies showed that nearly half of patients whose scores indicated clinical remission may still exhibit residual mucosal ulceration. While the wPCDAI offers greater

diagnostic accuracy for determining clinical remission than other PCDAI versions (27), clinical assessment alone is therefore inadequate when ER is the treatment goal.

Fecal calprotectin

High-quality evidence supporting serial measurement of FC as a non-invasive tool for assessing inflammation resolution primarily comes from adult studies(31-33). Low FC levels (below 150–250 µg/g) correlated strongly with endoscopic remission (ER), while failure to reach these levels indicated persistent intestinal inflammation(11, 34-39). In a cross-sectional study, FC cut-off levels of 250 µg/g following induction therapy were shown to have the best area-under-the curve (AUC) of 0.95 for detecting inflammation compared with systemic inflammatory markers (36). The multicenter ImageKids study found that an FC cut-off of 300 µg/g best predicted ER, while levels <100 µg/g were associated with deep healing (endoscopic plus transmural healing)(40). Additional studies showed that FC on average rises 2 to 3 months before symptom recurrence(41, 42).

However, FC levels do not correlate linearly with the severity or extent of mucosal inflammation. Consequently, a significant reduction in FC without complete normalization during induction therapy may still reflect a favorable treatment response. A drop below 250 µg/g suggests treatment success in luminal disease, while values closer to 50 µg/g are more indicative of complete endoscopic and radiologic healing. Interpretation should be cautious in patients with isolated small bowel disease or upper GI involvement since lower FC values were reported for L1 compared to L2 and L3, and FC of 95 µg/g was identified as the best cut-off for the identification of active isolated ileal disease (sensitivity 77%, specificity 56%)(43). Importantly, healthy infants and toddlers have higher-than-normal FC levels, which typically reach typical adult levels by about 4-5 years of age (44-47). This should be taken into account when interpreting results.

Studies in adults and children showed that using composite endpoints that combine multiple measures improves accuracy. The MINI index is a weighted composite score of clinical items, FC, and CRP/ESR, and is currently considered a suitable non-invasive surrogate markers for ER in CD(48, 49). 78% of patients with a MINI score <8 achieved ER, and lowering the threshold to <6 increased the positive predictive value to 86%.

Endoscopy

Achieving ER after induction therapy is associated with better long-term outcomes. Endoscopic response is usually defined as at least a 50% reduction from baseline inflammation (50, 51), whereas ER is generally characterized by the absence of visible inflammation or an SES-CD score is ≤ 2(25).

Video-capsule endoscopy can enhance the assessment of disease extent by evaluating the small bowel mucosa. The Lewis score or the Capsule Endoscopy Crohn's Disease Activity Index was developed for adults(25). Knowing the limitations of both scores, a paediatric score was developed, the capsule endoscopy-CD index (55), which can predict the need for hospitalization, treatment escalation, steroid therapy, and clinical and endoscopic relapses over the next 24 months (52). A pan-enteric capsule endoscopy is another option that not only enables detailed characterization of CD phenotype and assessment of disease severity and extent (53) but also improves outcomes by reducing the need for steroids, treatment escalation, hospitalizations, and clinical relapses when used in a treat-to-target strategy (54).

Imaging

Cross-sectional imaging methods such as magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) are valuable for evaluating therapeutic effects on the bowel wall (25). Both MRE and IUS are non-invasive and avoid ionizing radiation. IUS is more affordable and accessible, but its accuracy relies heavily on the operator's skill and experience(55). There are 4

key IUS parameters: bowel wall thickness (BWT), color doppler signal, inflammatory fat, and bowel wall stratification. Among these, BWT is the most significant, with >3.0 mm considered pathological (56) while newer data for children suggest a threshold of 2.5 mm (57). Dolinger et al. performed a prospective paediatric study (n=44) and showed that a ≥18% decrease in terminal ileum BWT at week 8 predicted ER with an Area Under the Receiver Operating Characteristic (AUROC) of 0.99, superior to PCDAI and CRP (58). Bowel hyperemia (using the Limberg score) was shown to be the first sonographic variable with a significant reduction following anti-TNF therapy in children with CD(59, 60)

The International Bowel Ultrasound Group Segmental Activity Score (IBUS-SAS) standardizes IBUS reporting(56, 61). A retrospective paediatric study found that the IBUS-SAS significantly correlated with SES-CD, PCDAI, CRP, ESR, hemoglobin, and albumin levels(62). The most accurate cutoff for predicting endoscopic response was a 57.4% decrease in IBUS-SAS, with an optimal IBUS-SAS value of 26.0 to indicate ER (AUROC=0.686, p=0.017). Some scores were designed for children, including the Paediatric Crohn Disease Intestinal Ultrasound Score (PCD-US), where a cut-off of 1 resulted in a sensitivity of 82% (95% CI: 65%–93%) and 85% (95% CI: 80%–89%) and a cut-off of 3 in a specificity of 88% (72%–97%) and 92% (87%–96%) for TI and colon, respectively (63). The Simple Paediatric Activity Ultrasound Score (SPAUSS) was developed incorporating BWT, hyperemia and inflammatory fat, demonstrating a good predictive capacity to capture active disease with an AUC of 82.1% (64). The diagnostic accuracy of IUS can be improved with contrast enhancement (65, 66).

MRE effectively distinguishes active inflammation, shown by bowel wall enhancement, mucosal ulcers, and T2 hyperintensity, from structural damage, indicated by fibrotic strictures, abscesses, or fistulas(67). The Paediatric Inflammatory Crohn’s Magnetic Resonance Enterography Index (PICMI) score was developed specifically for children and correlated positively with Simple Endoscopic Score for Crohn's Disease (SES-CD) categories and scores(68). One limitation of

MRE is the need for adequate bowel preparation to ensure proper intestinal distension. While cooperative children can drink the oral contrast, others may require a temporary nasojejunal tube. Many centers now use a small-volume lactulose protocol, which significantly improves patient compliance(69). At the same time, growing evidence has highlighted potential concerns regarding contrast agent deposition in body tissues, particularly in the brain, following repeated intravenous administrations(70). It is possible to achieve sufficient accuracy with MRE even without gadolinium, as shown for the PICMI(68).

Patient-reported outcomes (PROs)

Discrepancies between patient and physician perspectives are common, leading to potential misalignment in disease evaluation. As a result, PROs are now emphasized as the standard for symptom assessment, with STRIDE II recommending their early and regular use throughout the disease course(25). The Patient-Reported Outcomes Measurement Information System, a system of PROs developed to assess physical, mental, and social health in chronic disease populations, has specifically designed paediatric domains for children aged 8-17 (71, 72). QoL is most commonly evaluated using the IMPACT-III questionnaire, which has been translated and validated in multiple languages(73).

5. Induction of remission in high-risk patients

5.1 In patients at high risk for a poor outcome, anti-TNF should be initiated as first-line therapy. LoE: 1; 93% agreement.

5.2 The choice between infliximab and adalimumab should be guided based on shared decision-making principles with no clear preference for one over the other. LoE: 2; 92% agreement.

5.3 In patients starting infliximab, combination therapy with an immunomodulator is recommended. LoE: 2; 96%.

5.4 Infliximab monotherapy with proactive drug monitoring during induction may be considered as an alternative to combination therapy. LoE: 3; 96% agreement.

5.5 When adalimumab is used as the first anti-TNF, it can be initiated as monotherapy (LOE: 2). When used as a second anti-TNF, combination therapy with an immunomodulator is suggested. LOE: 5; 96% agreement.

5.6 When anti-TNF is indicated and until therapy is initiated, nutritional therapy, such as the Exclusion Enteral Nutrition or the Crohn's Disease Exclusion Diet with Partial Enteral Nutrition, may be used as a bridge or adjunct. LoE: 4; 100% agreement.

Selection of medical therapy should be individualized, integrating disease phenotype and risk of poor outcome, presence of EIM, patient characteristics and preferences, safety profile, and prior treatment exposure. In addition, real-world considerations such as regulatory approval, access to therapies, cost, and feasibility of monitoring must be balanced against efficacy to support a pragmatic, patient-centered treatment strategy rather than a fixed stepwise sequence. The presence of EIMs should guide therapeutic selection toward agents with efficacy in both intestinal and extraintestinal disease, rather than gut-selective therapies alone. Specifically, anti-TNF agents are preferred when EIMs like axial spondyloarthritis, uveitis, pyoderma gangrenosum, or hidradenitis suppurativa are present, whereas gut-selective drugs (e.g. vedolizumab) may be insufficient or inappropriate for several EIMs.(74)

Identification of predictors of poor outcome (**Table 1**) should guide health-care professionals in choosing a therapeutic strategy for the child with CD (**Figure 2**). Early Infliximab or adalimumab should be considered as the treatment of choice in children with a high risk for a poor disease outcome in order to reduce risks of complications(75, 76). Moreover, data from an individual-patient MA of randomized trials and large population-based cohorts demonstrate that initiation of

anti-TNF therapy early in the course of CD in adults is associated with higher absolute rates of remission and, importantly, with reduced long-term hospitalizations and surgical interventions compared with delayed treatment, supporting a disease-modifying benefit of early intervention(77, 78). The decision to use infliximab or adalimumab should be based on shared decision-making principles, with no clear preference for one over the other with respect to major clinical outcomes or safety for most patients(79-81). Until anti-TNF are initiated, nutritional therapy is recommended, especially in cases where a delay in initiation of medical therapy is expected (e.g. in order to provide live vaccines, or due to insurance coverage). EEN was also shown to be effective in some cases of internal penetrating disease, with 70% avoiding surgery in a case series(82). A SR of five studies in adults showed that EEN alleviated symptoms in 60% of patients with stenotic CD(83).

Screening for latent tuberculosis with a combination of patient history, chest X-ray, tuberculin skin test or interferon-gamma release assays (IGRA or Quantiferon) is essential before initiating anti-TNF. The Quantiferon test is preferred in patients on immunosuppressive therapy and BCG-immunized patients. Screening for hepatitis B and C viruses, EBV and varicella zoster antibodies, and HIV is also recommended. Vaccination status should be reviewed and all indicated vaccines, particularly live vaccines, should be completed, if possible, prior to initiation of immunosuppressive therapy, as immunosuppression reduces vaccine efficacy and contraindicates live vaccines.

Infliximab

The efficacy of infliximab in inducing remission in paediatric CD has been well documented in several clinical studies. The REACH registration trial demonstrated that 59% of participants achieved clinical remission on infliximab at week 10 (84). Likewise, in the TISKIDS trial, the clinical remission rate at week 10 in infliximab-treated participants was 59%(85). Further evidence comes

from observational studies with a similar induction regimen, with clinical remission rates ranging from 33 to 79% at approximately 3 months after initiation(30, 86-90).

Intravenous infusions of infliximab are traditionally dosed 5 mg/kg at Weeks 0-2-6, followed by maintenance therapy of 5 mg/kg every 8 weeks. However, there is ample evidence that children <30 kg, those with extensive disease and low serum albumin levels and those with perianal disease require higher induction doses up to 10 mg/kg, shorter dosing intervals, or both to reach target trough concentrations (TC) (91). Infliximab is recommended to be used preferably in combination with an immunomodulator (thiopurine or methotrexate) to mitigate the formation of anti-drug antibodies (ADA) and enhance its effectiveness. To prevent immunogenicity, lower doses of azathioprine (1-1.5 mg/kg) may be sufficient (92, 93), although the PANTS study supports using a standard dose of 2-2.5mg/kg(94). Data on methotrexate dose in this setting are scarce, but low total doses of 7.5-12.5 mg weekly are reported(95). In the presence of high-range infliximab TC, combination therapy with an immunomodulator may have limited added value on ADAs formation(96).

Adalimumab

Multiple studies demonstrated efficacy of adalimumab in inducing remission in paediatric CD (97-101). In the IMAgINE-1 RCT, over 80% of children responded to adalimumab, with a >50% decrease in PCDAI by 4 weeks (98). Dose escalation in the maintenance phase is common(102, 103). In patients naive to anti-TNF agents, combination therapy with an immunomodulator is generally not warranted unless the patient is at particularly high risk of disease progression(104). When adalimumab is used as a second anti-TNF agent due to intolerance or secondary loss of response to infliximab, especially in the setting of high ADAs, combination therapy is recommended to improve treatment durability(105).

For patients weighing ≥ 40 kg, the initial induction dose is 160 mg subcutaneously, followed by 80 mg at Week 2, then 40 mg every other week. For patients <40 kg, the drug label recommends 80 mg at Week 0, 40 mg at Week 2, and 20 mg from Week 4 onwards. However, in view of the evidence on underdosing of anti-TNF in young children(106), higher doses are usually required and calculated based on body surface area (BSA) rather than weight (90mg/BSA followed by 45mg/BSA two weeks later and then 23mg/BSA every other week). Administration of weekly 40 mg injections or 80 every 2 weeks should be considered in patients losing response or with low drug levels. Higher dosing (80 mg weekly) can be implemented when inadequate serum drug levels are identified despite increased dosing and in the absence of ADA.

Comparison of infliximab vs. adalimumab and combination therapy

There are no direct, prospective, head-to-head studies comparing infliximab and adalimumab. A MA of 14 cohort studies, each comparing adalimumab to infliximab in adults with CD, found that both had similar clinical benefits, but patients treated with infliximab had higher adverse events(107). However, this MA did not differentiate between those treated in combination with immunomodulators and those treated as monotherapy. Two propensity-adjusted analyses on prospectively collected paediatric cohorts of 63 (108) and 296 (109) children showed similar outcomes of adalimumab and infliximab. Of note, in the first cohort, the vast majority of both groups were treated as combination treatment with an immunomodulator(108), and in the second, the infliximab-treated children had more often dose intensification and had combination therapy with immunomodulators practiced more often (67%) than adalimumab to reach the same outcomes(109). A propensity score analysis from the epi-IIRN nationwide cohort of paediatric IBD supported using adalimumab monotherapy as a first-line biologic in children with CD, as it was comparable in effectiveness to infliximab combo-therapy. This study also showed the superiority of infliximab combination therapy over monotherapy when infliximab is used(110). QoL has been

assessed infrequently for both drugs, and meaningful comparisons have not yet been possible(84, 85, 111).

Regarding biosimilars, a systematic review of nine studies showed that infliximab biosimilars or the originator have similar effectiveness even after switching from the originator in paediatric IBD(112). Concomitant corticosteroids did not improve the effectiveness of anti-TNF as induction treatment for CD, and, therefore, steroids should be rapidly weaned as soon as possible after initiating anti-TNF(113).

There is real-world experience of using both products in children with very-early onset IBD, with theoretical advantages for the flexible-dosing of infliximab, but both have been shown to be effective(20, 114-116). Finally, a systematic review of 268 adult patients showed no difference in clinical or endoscopic recurrence after surgery between the two therapies(117).

6. Induction of remission in low-risk patients

6.1 In patients at low risk for a poor outcome, exclusive enteral nutrition is recommended as a first-line nutritional therapy for the induction of remission (LoE 1). The Crohn's disease Exclusion Diet with Partial Enteral Nutrition is an alternative to exclusive enteral nutrition for the induction of remission. LoE 1; 93% agreement.

6.2 When nutritional therapy is not an option or not tolerated, corticosteroids could be considered to induce remission. [LoE: 1] Prednisone or prednisolone should be administered once a day (1mg/kg, not exceeding 40 mg) and should be tapered and stopped within 8-10 weeks. Oral budesonide can also be considered. LoE:1 85% agreement

6.3 In patients who do not respond to dietary or corticosteroid therapy, anti-TNF therapy is recommended. LoE:2. 89% agreement.

6.4 Dietary therapies should be initiated, monitored, and adjusted by a dietitian to ensure nutritional adequacy, adherence, and minimize the risk of developing or exacerbating disordered eating behaviors. LoE:5; 100%.

Exclusive Enteral Nutrition

Numerous studies have demonstrated that a 6-8-week course of EEN is effective in achieving clinical remission and is superior to steroids in promoting ER(118-122). A Cochrane review summarized RCTs on EEN as induction therapy in 1,011 patients with CD(123). The authors concluded that the overall treatment response of EEN parallels that of corticosteroids. However, the comparison between EEN and corticosteroids included only 57 paediatric patients and was considered of very low quality. There is no benefit of one formula over another for EEN, as reported in a SR(123). Older age (>15 years) and higher baseline PCDAI scores were associated with lower response to EEN(124). In another study of 241 adults, colonic involvement was associated with a lower remission rate (52% vs. 68%, p=0.029)(125).

Crohn's Disease Exclusion Diet (CDED) with Partial Enteral Nutrition (PEN)

The CDED is a whole-food diet designed to reduce exposure to potentially pro-inflammatory ingredients and is combined with PEN(126). The CDED induction protocol comprises two phases over 12 weeks. Phase 1 lasts 6 weeks and includes 50% of energy from PEN. Patients who obtained clinical remission will generally transition to phase 2, introducing more foods and reducing PEN to 25%. Two SRs concluded that CDED is an effective and well-tolerated strategy, with clinical remission rates ranging from 62% to 81% in both children and adults(127, 128). In the index trial, CDED combined with PEN was better tolerated than EEN and achieved similar remission rates in children with mild-to-moderate CD, with comparable reductions in CRP and FC. By week 12, patients who transitioned from EEN to PEN with a free diet showed a rebound in inflammation, with increased FC and microbiome shifts, unlike those on CDED phase 2 with

PEN (129). A recent RCT compared 2 weeks of EEN followed by the CDED (up to 24 weeks) to 8 weeks of EEN followed by PEN with a liberal diet. At week 14, no difference in remission rates was found in the two groups. By week 24, remission persisted in 60% on CDED vs. 42% on PEN (p=0.18). All EEN-treated patients received immunomodulators, compared with 56% in the CDED group. Notably, 5 patients maintained clinical remission with CDED alone(130). Several prospective and retrospective studies have replicated these findings(131, 132), and also showed improvement in body mass index (BMI) compared to EEN (133). In another prospective study among 39 children, ER was observed in 7/13 (54%) of PEN with modified CDED vs. 8/16 (50%) with EEN by week 6(134). Additional studies demonstrated the efficacy of CDED+PEN combined with anti-TNFs(134, 135).

Tasty and Healthy exclusive whole food diet

Tasty&Healthy is a whole food diet that excludes pro-inflammatory components, similar to the CDED, but without the need for PEN or recommended foods. It was effective in inducing clinical and inflammatory remission in several recent clinical trials. In the TASTI-MM RCT of 83 children and young adults with mild-moderate CD, Tasty&Healthy was better tolerated than EEN and similarly effective in inducing clinical and biochemical remission (56% [66% among completers] vs. 38% [76% among completers], P=0.1)(136). Another RCT of 46 children and young adults in symptomatic remission but with persistent intestinal inflammation showed higher FC response rates in the Tasty&Healthy vs. the habitual diet (37% vs. 15%; p=0.028) within 8 weeks (137). A prospective case series supported these findings(138).

Medical and nutritional treatment effects on linear growth

Growth impairment affects 15–40% of children with CD and may result in reduced adult height if uncorrected(139, 140). EEN supports catch-up growth and improves bone mineral density (BMD) (120, 121), although long-term effects on height may be limited (141). Anti-TNF therapy has been

associated with significant improvements in weight, height, and BMI within 12–24 months(139). Comparative studies suggest that EEN and anti-TNF offer similar short-term outcomes (133, 134), but anti-TNF may lead to superior linear growth (142). Early anti-TNF monotherapy shows higher remission rates and greater catch-up growth in height and weight compared to other strategies(142-144).

Corticosteroids

A MA focusing on the induction of clinical remission in adults with CD confirmed the effectiveness of corticosteroids(145). In children, up to 90% of paediatric patients have a rapid symptomatic response with prednisone equivalent of 1 to 2 mg/kg per day (maximum, 40 to 60 mg)(146). In a paediatric randomized open-label trial, budesonide 9 mg/d (all children >20kg) and prednisone 40 mg daily were equally effective in inducing clinical remission (47% vs. 50% at week 12); adverse events occurred in 32% and 71% of patients, respectively. Response to therapy occurred independently of disease location (147). In the randomized paediatric trial, higher exposure to budesonide was associated with a decrease in CRP, but the proportion of patients with normal CRP values was not reported (148). Prednisone/prednisolone should be administered once a day (1 mg/kg, not exceeding 40 mg) in the morning and should be tapered off within 8-10 weeks. For patients >40 kg, the initial dose of budesonide is 9 mg once daily for one month, then 6 mg for the second month, and 3 mg in the third month, depending on the response. Children 20-40 kg may start with 6 mg/day.

Glucocorticoids can cause immunosuppression, impaired growth, osteoporosis, muscle weakness, and disturbances in glucose regulation, with less common effects including cataracts, pancreatitis, and increased ocular pressure after prolonged use. High-dose or long-term therapy followed by abrupt withdrawal may suppress the hypothalamic–pituitary–adrenal axis, leading to adrenal insufficiency with nonspecific symptoms or, rarely, life-threatening adrenal crisis.

EEN vs. corticosteroids in children

An RCT of 19 children with CD showed a much higher rate of ER with EEN (89%) than steroids (17%)(149). In contrast, in an uncontrolled post-hoc analysis of the azathioprine arm of the TISKids RCT, the effectiveness of induction therapy in 47 children treated with either EEN or steroids was broadly similar by week 10, including in achieving ER(150). Finally, propensity-score matching of 274 children from the nationwide epi-IIRN cohort showed that long-term outcomes at 5 years were better in children treated with EEN vs. steroids, likely due to the tendency to repeat the induction intervention during the disease course when needed (151).

Other induction therapies

The CD-TREAT is a food-based diet designed to mimic the dietary profile and effects of EEN on the gut microbiome. It demonstrated 60% clinical remission with significant reductions in FC in five children with active disease(152). These results were supported by a subsequent uncontrolled study involving 25 children and 32 adults, where 78% achieved clinical remission, and 30% of those completing the intervention experienced a >50% reduction in FC(153) . Notably, these studies used pre-prepared chef-made meals, which may have affected the outcomes. It remains to be assessed whether the observed benefits persist when the diet is implemented with family-prepared meals.

Although numerous studies demonstrated the benefit of antibiotics in inducing remission in CD, the large heterogeneity of drugs, dosing, population, design, and outcomes across the studies prevent recommending antibiotics routinely(154). In the AZCRO RCT, azithromycin with metronidazole were more effective than metronidazole for inducing clinical remission (p=0.025)(155). Median FC remained high in both groups. Azithromycin (7.5 mg/kg/day, up to 500 mg once a day) was given 5 days per week, for the first 4 weeks, followed by 3 days per week in the subsequent 4 weeks. Metronidazole (20 mg/kg/day, up to 1000 mg) was divided into two daily doses and administered for 8 weeks. In another retrospective cohort of 38 patients, the

azithromycin-metronidazole combination led to clinical remission in 64% after 8 weeks of therapy, and FC levels declined from baseline to a median of 190 ug/g(156).

A MA found that a mesalamine dose >2.4 g/day was effective in adults with CD but less effective than corticosteroids; sulfasalazine was not superior to any therapy or placebo (145). Another MA of RCTs conducted in adults on methotrexate showed no significant effect on inducing clinical remission(157).

7. Maintenance therapy

7.1 Patients who responded to anti-TNF for induction should be treated with the same drug for maintaining remission. LOE: 2; agreement 100%.

7.2 In patients with luminal disease treated with combined anti-TNF-immunomodulator therapy, discontinuing immunomodulator should be considered within 6-12 months after a period of sustained clinical and biochemical remission. LOE: 3; agreement 96%.

7.3 Thiopurines or methotrexate may be used as sole maintenance therapy in uncomplicated, low-risk Crohn's disease. LOE: 2; agreement 93%.

7.4 There is insufficient evidence to support the use of 5-ASA or sulfasalazine for maintenance of remission. LOE: 2; agreement 89%.

7.5 We recommend against the use of corticosteroids in the maintenance of remission. LOE: 3; agreement 100%.

Anti-TNF therapy maintenance therapy

Anti-TNF medications initiated to induce remission should be continued, as infliximab and adalimumab have well-characterized efficacy in the maintenance treatment of paediatric CD (158-160). Most patients starting infliximab, and some starting adalimumab, will receive combination therapy with an immunomodulator, either a thiopurine or methotrexate, for 6-12 months. If patients

remain in remission, the most employed strategy is to de-escalate to anti-TNF monotherapy (this recommendation is for patients with luminal CD and the considerations for perianal disease may be different (see Chapter 10)(161).

In studies that have assessed immunomodulator withdrawal and anti-TNF continuation, a lower risk of relapse was observed when immunomodulators were withdrawn and anti-TNF therapy was continued, compared with withdrawing the anti-TNF agent (162). In a multicenter retrospective cohort study of 89 children who de-escalated to anti-TNF monotherapy after having received combination therapy for at least 6 months, 11% had a relapse at one year(163). In another single-center retrospective cohort study of 126 children with CD who de-escalated from combination therapy to anti-TNF monotherapy, after a median of 1.7 years, there was no significant effect on disease relapse(164). During one year of follow-up, 23 (18%) of patients required anti-TNF dose escalation after immunomodulator withdrawal.

The effect of withdrawing infliximab from combination therapy was analyzed retrospectively in 63 paediatric patients with CD, while continuing azathioprine monotherapy after at least one year of clinical remission(165). The median time to relapse was 3.3 years; infliximab levels of <2.5 mg/L and incomplete mucosal healing were associated with higher clinical relapse rates. This was replicated in a retrospective cohort of 24 patients who had anti-TNF therapy withdrawn (after endoscopic and histological healing) and subsequently treated with an immunomodulator (166). Relapse-free survival rates at 12, 24, and 36 months were 83.3%, 71.1%, and 23.7%, respectively. Conversely, a small paediatric prospective cohort study (n=17) showed no difference in sustained remission at one-year follow-up between the two strategies (167). Data from the seven-year extension study of STORI, the original prospective adult de-escalation study published in 2012, highlighted that one-fifth of patients who discontinued anti-TNF did not need to restart biologic therapy and did not develop major complications (168).

Sustained clinical and biochemical remission should be verified, and anti-TNF drug and antibody concentrations measured, before considering de-escalation of immunomodulator to anti-TNF monotherapy. For patients receiving combination therapy with anti-TNF and immunomodulator, we recommend stopping the immunomodulator rather than the anti-TNF. However, stopping anti-TNF therapy can be considered in selected cases, such as when significant anti-TNF-related adverse events occur. In a SR and MA in patients of all ages de-escalating from combination therapy to monotherapy, there was no significant difference in risk of relapse when withdrawing immunomodulator (Relative Risk (RR) 1.15; 95% CI, 0.75-1.76), but there was a significantly increased risk when anti-TNF was withdrawn (RR, 2.35; 95% CI, 1.38-4.01)(169). These findings were supported by the recent adult SPARE RCT, which demonstrated that de-escalating to immunomodulator monotherapy was associated with higher relapse within 2 years compared to continuing combination therapy or de-escalating to anti-TNF monotherapy (170). Similarly, in the only uncontrolled paediatric retrospective cohort study in which continuing, withdrawal of one, or both therapies was assessed, relapse was associated with anti-TNF, but not immunomodulator, withdrawal(171).

FC is a valuable biomarker in predicting relapses after anti-TNF therapy withdrawal(172), particularly when used adjunctively with other clinical, biochemical, and endoscopic parameters. In an RCT of 140 adults with IBD, a FC >250µg/g before anti-TNF withdrawal was associated with a lower likelihood of sustained clinical remission and a higher risk of loss of clinical remission at the end of one year(173). However, paediatric data remain limited.

In conclusion, criteria for de-escalation should include a disease activity score suggestive of remission; a normal CBC, CRP, ESR, and albumin. A FC in keeping with remission, and appropriate anti-TNF drug level and absence of ADA are factors associated with better outcomes following withdrawal of therapy. In patients who are de-escalated to anti-TNF monotherapy,

regular reassessment of clinical and biochemical markers of inflammation, for example, every 3 months for at least 12 months, is recommended.

Thiopurines

Thiopurines (azathioprine, mercaptopurine) are prodrugs that are metabolized into active metabolites, thioguanine nucleotides (TGNs) and methyl mercaptopurine (MMP), under pharmacogenomic regulation, particularly Thiopurine S-methyltransferase (TPMT) and Nudix Hydrolase 15 (NUDT15). Low-grade evidence from a Cochrane SR involving adult patients found that thiopurine monotherapy was superior to placebo for maintenance of disease remission in low-risk CD(174). However, it had a greater adverse event profile, including leukopenia, pancreatitis, gastrointestinal intolerance, and infections that led to withdrawal. In the same MA, it was inferior to maintenance anti-TNF therapy in RCTs. A single paediatric RCT published in 2000, albeit with methodological limitations, reported lower cumulative steroid exposure and relapse rates in children treated early with 6-mercaptopurine as maintenance therapy(146).

Thiopurine monotherapy dosing should be approximately 2.5 to 3 mg/kg/day of azathioprine or 1 to 1.5 mg/kg/day of mercaptopurine, in a single daily dose. The full therapeutic effect of thiopurines may not be evident until 10-14 weeks of treatment. Optimization of thiopurine dosing should be undertaken based on individual TPMT activity/genotype, 6-TGN, and MMP results. Observational studies support dose optimization of thiopurines in IBD and real-world retrospective analyses of the benefits of measuring TGN and MMP further support the use of metabolite level testing during thiopurines therapy. Only two studies have assessed the use of dose optimization in a prospective, controlled manner(175, 176). Neither demonstrated a benefit from dose optimization, yet both had methodologic issues that limited their findings. Apart from the possibility of adjusting doses to balance efficacy and toxicity, thiopurine TDM is also useful for monitoring treatment adherence.

Testing for TPMT genotype or activity before starting thiopurines helps to identify patients at greater risk of profound myelosuppression and should be based on local availability and variant frequency. Dosing should be reduced in heterozygous patients or those with reduced TPMT activity. Thiopurines should not be used in patients with homozygous mutations or those with very low TPMT activity. High TPMT activity can lead to increased MMP production (associated with an increased risk of hepatotoxicity) and lower levels of TGNs, resulting in subsequent lack of efficacy. In such cases, adding allopurinol may be an appropriate treatment option in experienced centers, with close monitoring given increased risk of toxicity(177). Conversely, low TPMT activity favors increased TGN and an increased risk of myelotoxicity.

Drug monitoring using thiopurine metabolite measurement should be considered in all patients treated with thiopurine monotherapy, in patients with an incomplete response on a stable thiopurine dosage, in patients who present with leukopenia or elevated transaminases, or in patients with suspected poor adherence. A MA confirmed the association between TGN concentration and therapeutic effect, with one study reporting a 3-fold increase in the rate of clinical remission in patients with levels >230 pmol/8 x 10^8 erythrocytes, and another identifying a cutoff of 397 pmol/8 x 10^8 erythrocytes for ER in CD (178-180). As combination therapy with infliximab, lower levels (>125 pmol/8x10^8 erythrocytes) may be sufficient to prevent immunogenicity and assist in achieving higher infliximab trough concentrations, but other data support standard thiopurine dosing(181).

Methotrexate

The therapeutic dose of methotrexate is 15 mg/m^2 once weekly, up to a maximum dose of 25 mg once weekly. The time taken to have a therapeutic effect is at least 6-8 weeks. Subcutaneous administration is preferable initially in order to optimize steady-state absorption. Switching to the oral formulation can be considered after 4-6 months of sustained remission. Dose reduction to 10mg/m^2 (maximum 15 mg per week) is optional after prolonged sustained remission. Low-grade

evidence suggests that adjunctive lower-dose methotrexate may be an alternative to thiopurines for co-immunomodulation(95). In a study in 65 newly diagnosed children, methotrexate monotherapy, ER at one year was observed in 22% of all starters and 39% of those still on therapy(182). Prophylactic ondansetron and regular folate supplementation (5 mg per week) may help to ameliorate methotrexate-associated gastrointestinal intolerance and side effects. Adolescents should be counseled regarding its teratogenic potential and the necessity of effective contraception,

Maintenance nutritional therapy

Epidemiologic, mechanistic, and therapeutic data support the idea that altering diet can impact disease outcomes(183). Most studies focus on inducing remission, and only a few on maintaining it, but using diet to maintain remission is an attractive option(184). Use of EEN is supported by strong evidence for induction, but is generally impractical for maintenance due to cost, taste fatigue, and psychological impact(185).

Maintenance enteral nutrition (MEN), defined as continued, long-term administration of PEN, usually alongside a normal diet, has been investigated as monotherapy with limited support, showing feasibility and improved clinical and growth outcomes(186). A MA demonstrated reduced disease relapse with up to 1 year of MEN, compared to no diet therapy, with benefits detectable at dosages of at least 35% of daily kcal (35%-50% EN: OR 0.42 [0.27-0.65], P = 0.0001; > 50% EN: OR 0.27 [0.08-0.88], P = 0.03)(187). Another MA also reported on maintenance of remission up to 0.5-1 year in 76% vs 48% in controls (RR: 1.32, 95% CI: 1.07-1.64, P= 0.01)(188). However, many of the supporting studies are small, and in a retrospective study, only 16/105 who started MEN maintained this therapy to 12 months, most of whom required additional therapies(189).

In general, some evidence supports the benefits of a healthy diet, low in processed and ultra-processed foods and high in fruits and vegetables, tailored to patient tolerance, for maintaining remission, particularly in patients using medical therapies. In selected cases with low-risk,

uncomplicated disease, patients may maintain remission for up to 6 months with an extended food-based exclusion diet, with or without additional medications, under extensive appropriate monitoring and guidance. Emerging evidence suggests that CDED may be used as a sole maintenance strategy in very selected cases (190), provided that patients are closely monitored by a dietitian to ensure that no disordered eating patterns develop. In an adult RCT, 80% of those who achieved remission at week 6 maintained it to week 24 on CDED(190). Some real-life studies further support the feasibility and efficacy of CDED maintenance(127, 191, 192). In addition, preliminary data suggest that Tasty&Healthy may be suitable for maintenance. In a 16-week open-label trial, 86% maintained clinical remission and 79% achieved MINI <8 without other interventions while reintroducing gluten and dairy, as assessed by monthly FC monitoring in approximately half of participants(138).

The Mediterranean diet appears to be feasible for long-term use and offers additional benefits, but data are limited (193). Finally, several studies have assessed the benefits of a low FODMAP diet in quiescent CD with irritable bowel syndrome (IBS)-like symptoms, showing some symptomatic improvement, although many patients also had underlying IBS (194). Other diets have been explored with mostly inconclusive results(194, 195). Other studies have looked at low red meat and low refined carbohydrate diets for the prevention of flare CD with no benefits observed (RR 0.99 and 1.04, respectively)(196). In conclusion, exclusive dietary therapy without medical treatment for maintenance is a therapeutic option only for a minority of paediatric CD patients with low-risk, uncomplicated phenotype, and, if considered, should warrant close clinical, biochemical, endoscopic and radiologic monitoring.

Aminosalicylates

Adult and paediatric guidelines recommend against the use of aminosalicylates in CD, with MA showing no benefit for induction or maintenance of remission (4, 5, 197). Nevertheless, 5-ASA preparations have been widely used in adult patients with CD(198), but their use appears to be

dropping (from 21% in 2005 to 11% in 2019 in a nationwide analysis from Israel)(199). This study also showed that 5-ASA as sole maintenance therapy was not superior to no treatment over 5 years and was associated with more adverse events, including renal injury and pancreatitis(199). However, 5-ASA or sulfasalazine can be considered in very selected cases, although evidence remains poor. A MA of studies focused on Crohn's colitis did show superiority to placebo for sulfasalazine at 18 weeks (45% vs. 29% remission; RR 1.38, 95% CI 1.00-1.89)(200). 5-ASA was suggested to be effective in preventing recurrence of CD after surgery (number needed to treat: 13), in older studies, before the year 2000(201). Chemoprotection from developing colorectal cancer using 5-ASA has been established in ulcerative colitis, but there is no evidence to support that this is the case in CD, including in adults(202). Although very few studies provide details, there is some data describing higher use of 5-ASA in VEO-IBD, with the additional advantage of the availability of liquid formulation(203). This is likely related to the very high colonic involvement in VEO-IBD (203).

Corticosteroids

While prednisone and budesonide have a proven role in inducing remission, they should not be used for maintaining it, given the significant side effects associated with long-term use. Furthermore, induction therapy with corticosteroids has not been shown to improve maintenance of remission on biologic treatment in adults with CD(204).

8. Therapeutic drug monitoring of anti-TNF drugs

8.1 Proactive therapeutic drug monitoring is recommended for both infliximab and adalimumab, particularly at the end of induction (before the 4th infliximab infusion and after 3 adalimumab injections), before de-escalation of both drugs and before withdrawal of an immunomodulator. LOE: 2; agreement 100%.

8.2 Reactive therapeutic drug monitoring is recommended in all children who experience either clinical, biomarker or endoscopic loss-of-response, or incomplete response to infliximab or adalimumab. Primary non-response should prompt reactive Trough Drug Monitoring during induction. LOE: 2; agreement 96%.

Drug clearance of anti-TNFs has been found to be specifically increased in young children, leading to lower TC and a higher rate of ADAs (91, 205). High BMI was also associated with increased clearance of monoclonal antibodies (206, 207). In a large cohort of children with IBD on anti-TNF (n=637), overweight was associated with the risk of relapse and treatment intensification(208). Conversely, weight-based dosing of patients with low weight can result in underdosing and lower TC(206, 209). In children with VEO-IBD, higher infliximab doses may be required to achieve adequate drug exposure, supporting the potential use of body surface area (BSA)-based dosing, typically 200mg/m^2 for infliximab(210). Infliximab TC should be measured before the next infusion, whereas adalimumab levels may be measured at any time point during the treatment cycle, except in the first 48 hours following injection(211). Higher trough adalimumab levels, compared to infliximab, may be required to achieve the same exposure-response relationship(212). Indications for more frequent anti-TNF TDM (e.g., during early induction and throughout maintenance) include conditions with increased anti-TNF clearance: body weight <30 kg, low serum albumin, high inflammatory burden, and high BMI.

TDM of infliximab during induction and maintenance

Figure 3 depicts an algorithm on TDM of anti-TNF therapy during induction and maintenance phases in paediatric patients with CD. Achievement and maintenance of clinical, biochemical, and more stringent outcomes, such as ER and transmural healing, have been correlated with higher infliximab TCs, with an exposure-response relationship (213). Minimal infliximab TCs prior to the second, third, and fourth infusions (TC before the fourth infusion represents maintenance TC) are approximately ≥25 µg/ml, ≥15 µg/mL, and ≥7 µg/mL, respectively. In the PANTS study(94), drug

TC at week 14 was the only independent predictor of clinical outcomes at week 54, with an optimal cut-off of 7 μg/ml. Similar findings were observed in paediatric cohorts, where infliximab TC>7 μg/mL before the fourth infusion was associated with sustained clinical remission(214, 215).

In general, the more stringent the target, the higher the required optimal maintenance TC cut-off (212). Infliximab trough concentrations ranging from 3-9.7 μg/ml (and more commonly >8 μg/mL) have been reported in adult studies to be associated with ER (216-219). TC>10 μg/mL during maintenance are often required in cases of high inflammatory burden, complicated disease, and fistulizing perianal disease(220-222). Based on these findings, in order to achieve deep remission, target infliximab TC during maintenance should be ≥8 μg/mL.

For patients switching from intravenous to subcutaneous infliximab, the suggested optimal cutoff concentration for clinical and biochemical remissions was 12.2 μg/mL and 13.2 μg/mL at weeks 12 and 52 following the switch, respectively (223), whereas the thresholds for ER and transmural healing were 17.5 μg/mL and 30.3 μg/mL, respectively (224).

TDM of adalimumab during induction and maintenance

Adalimumab TC was shown to respond almost linearly to escalation and de-escalation (225). Data on desirable adalimumab TC during induction or immediately post-induction (week 4) are scarce. Retrospective paediatric cohorts reported different week 4 TCs (22.5 and 13.8 μg/mL) that were associated with clinical and biochemical outcomes(102, 226). The reported optimal adalimumab cutoff for clinical outcomes during maintenance treatment varies across studies (94, 212, 227). In a large cohort of 213 children, TCs consistently >7.5 μg/mL were associated with durable clinical remission(228). In the PAILOT RCT, a threshold of 10 μg/mL performed better than lower thresholds in terms of clinical and biological remission(103). To achieve ER, higher TCs are required, ranging between 8-12 μg/ml in adult studies(229-232). In paediatric studies, optimal TC were reported as 8.2 μg/ml (n=28)(233), and 10 μg/mL (n=62)(228). Based on these findings, in order to achieve deep remission target adalimumab TC during maintenance should

be ≥10 μg/mL. Perianal fistula healing may require even higher adalimumab TC, as described in adult cohorts (233, 234).

Proactive vs Reactive TDM

The utility of reactive TDM is based on data demonstrating a clear association between loss-of-response and either low TC or high ADAs during induction and maintenance (94, 235, 236). Reactive TDM of anti-TNF drugs has shown superiority over empiric optimization in terms of clinical response, immunogenicity, ER (237), and drug retention(238) as well as in terms of cost-effectiveness (239-241). A recent MA of 9 studies concluded that proactive anti-TNF TDM is not more effective than clinical-based treatment in patients with IBD, but could improve drug durability, prevent acute infusion reactions, decrease adverse events and reduce the probability of surgery, at a lower economic expenditure(242).

Most retrospective adult(243-245) and paediatric cohorts 246-249) assessing the benefits of a proactive approach reported superiority of proactive over reactive/no TDM. In the PAILOT RCT assessing proactive vs. reactive strategies in adalimumab-treated children with CD, the primary endpoint of sustained corticosteroid-free clinical remission at all visits was achieved by a greater proportion in the proactive arm (82% vs 48%, p=0.02), with the proactive group also demonstrating superiority in terms of a composite outcome of sustained clinical, CRP and FC remission(103). Recently, a non-blinded RCT from South Korea involving 112 children following infliximab induction demonstrated that those allocated to a proactive approach achieved superior ER and sustained corticosteroid-free clinical remission rates at week 54 compared with those managed by a clinical-based approach (80% vs 57%, p=0.02 and 89% vs 70%, p=0.019, respectively)(250). Clinical relapse following immunomodulator withdrawal from infliximab combination therapy was associated with lower infliximab TC (163, 251), whereas sustained remission was associated with a minimal threshold of 5 μg/ml before withdrawal. It was also demonstrated that TC-based infliximab de-escalation was associated with decreased risk of relapse in both adults and children with IBD(165, 252).

9. Advanced therapies beyond anti-TNF

9.1 In patients who have failed to respond satisfactorily, have secondarily lost response, or have been intolerant to anti-TNF, ustekinumab or an anti-interleukin23p19 are recommended (LOE: 3), with some adult data suggesting a benefit of interleukin23p19 over ustekinumab. 96% agreement.

9.2 In patients who have failed to respond satisfactorily, have secondarily lost response, or have been intolerant to anti-TNF, upadacitinib may be considered. LOE:4; 93% agreement.

9.3 In patients who have failed to respond, have secondarily lost response, or have been intolerant to anti-TNF, vedolizumab may be considered in selected cases. LOE: 3; 89% agreement.

9.4 In patients with highly refractory disease, a combination of two biologic agents or a biologic agent with a small molecule as advanced combination therapy can be considered as a possible therapeutic option, on a case-by-case basis. To enhance safety, one of the agents should preferably be ustekinumab, an anti-IL23p19 agent, or vedolizumab. LOE: 4; 93% agreement.

Ustekinumab

Ustekinumab, a monoclonal antibody targeting the shared subunit p40 of IL-12 and IL-23, effectively induces and maintains remission in adults with active CD, with better responses among anti-TNF naïve patients with shorter disease duration than among anti-TNF-experienced patients(253). Phase 1 and 2 paediatric trials demonstrated that efficacy, pharmacokinetics (up to one year), safety, and immunogenicity (up to four years) in paediatric patients were broadly comparable to outcomes reported in adults(254-256). The Phase 3 UNITI-Jr one-year outcomes

in 48 patients weighing >40 kg, 60% of whom were bio-naïve, supported the spring 2025 European Medical Association approval of ustekinumab for children and adolescents with CD in this weight range who have failed conventional or anti-TNF therapy. Following open-label IV induction and randomization to q 8 weekly versus q 12 weekly maintenance, 25 of 48 patients [52.1%; 95% CI: 38.3%-65.5%] achieved steroid-free clinical remission at week 52. The lighter/younger patients enrolled in UNITI-Jr, who received 250 mg/m^2 induction dose, exhibited similar results; 84% of the overall cohort (43% bio-naive) achieved clinical response at week 8, and 54% of these responders were in clinical remission at week 54.

Real-world retrospective paediatric observational data reinforce the safety and efficacy of ustekinumab as a treatment option for paediatric CD patients resistant or intolerant to anti-TNF therapies, with clinical remission rates ranging from 40% to 60% at 32 and 52 weeks(257-260). In a retrospective report of 69 children whose maintenance interval was shortened to less than eight weeks or who underwent intravenous re-induction, 67% and 42% were able to achieve, respectively, clinical response and remission following treatment escalations(261). The usefulness of switching to ustekinumab in the setting of psoriasiform skin lesions induced by anti-TNF has been documented specifically in paediatric patients(262).

Data concerning ustekinumab in bio-naïve children and adolescents are just emerging. In a recently presented prospective multicentre Canadian study, 39/61 (64%) achieved the primary outcome of steroid-free clinical and biochemical remission at one year with continued ustekinumab(263). Overall, the body of evidence concerning efficacy of ustekinumab monotherapy in achieving and maintaining clinical remission in CD, combined with low immunogenicity, good durability and safety, may support its use as an alternative to anti-TNF as first-line biologic in paediatric CD(264-268). This is particularly relevant given that biosimilars are already available for patients weighing >40 kg in some countries, with broader availability expected in the near future. For all patients treated with ustekinumab, the rate of ADA formation

in long-term follow-up is very low (2.3% in IM-UNITI)(255), indicating considerably less immunogenicity compared to TNF antagonists. A similarly low rate of ADA was seen in the long-term extension study in paediatric CD(255). Therefore, monotherapy of ustekinumab is common practice.

Anti-IL23p19

Three selective IL-23 inhibitors (risankizimab, mirikizumab, guselkumab), which block the p19 subunit unique to IL-23, have demonstrated efficacy in phase 3 placebo-controlled trials of IV induction and subcutaneous maintenance in adults with moderate to severe CD, who had failed either conventional or prior biologic therapy(269-272). The efficacy of the three agents is similar(273). A few adolescents were included in the risankizumab trials, leading to approval also for paediatric patients >16 years in the UK, Japan and Israel. Risankizumab 600 mg IV at weeks 0, 4 and 8 resulted in clinical remission at week 12 in 35-43%, with no additional benefit observed with the 1200 mg dose(274). Patients who responded to intravenous risankizumab induction (weeks 0,4,8) were then re-randomized to subcutaneous treatment with 180 mg or 360 mg Risankizumab starting at week 12, or placebo, every 8 weeks(275). The proportion of responders to induction achieving the co-primary endpoint of clinical remission and endoscopic response at 52 weeks was significantly higher compared with placebo in the risankizumab 360-mg group (CDAI remission: 52% versus 41% for placebo)(275).

In the open-label, randomized phase 3b SEQUENCE trial of 520 adults with prior anti-TNF failure, risankizumab was non-inferior to ustekinumab at week 24 for clinical remission (CDAI <150: 58.6% vs 39.5%; adjusted difference 18.4%; 95% CI, 6.6–30.3%) and superior at week 48 for ER (31.8% vs 16.2%; adjusted difference 15.6%; 95% CI, 8.4–22.9%; P<0.001)(271).

The phase 3 RCTs of mirikizumab and guselkumab, which included bio-naive and bio-experienced patients, also had a ustekinumab comparator arm, which the risankizumab placebo-

controlled trial did not. A MA of these head-to-head ustekinumab versus anti-IL23p19 RCTs and the SEQUENCE trial concluded that IL-23p19 antagonists are likely more effective than ustekinumab in achieving clinical and ER in patients with prior anti-TNF exposure, though superiority in biologic-naive patients remains unproven(272).

Data concerning paediatric CD patients treated with risankizumab are limited. In the first retrospective study of 96 patients with CD who started risankizumab, 68 with active disease, corticosteroid-free clinical remission was achieved in 41%, 54% and 48% at end-of-induction, week 26 and week 54, respectively. Mirikizumab and guselkumab are being studied in a paediatric platform trial, but results are awaited.

Upadacitinib

Janus Kinase (JAK) inhibitors are small molecules and can therefore be administered orally. Upadacitinib, a selective JAK inhibitor, preferentially inhibits JAK1, a key enzyme in inflammatory cytokine signaling. Upadacitinib is the first JAK inhibitor to have shown efficacy and is now approved for the treatment of CD in adults. In two Phase 3 induction trials, clinical remission rates after 12 weeks of daily 45 mg upadacitinib were 49.5% and 38.9%, compared to 13.1% and 3.5% treated with placebo(276). Prior anti-TNF exposure did not significantly affect these clinical and endoscopic outcomes(277). Clinical response was observed within a few days(278). Patients who had a clinical response to upadacitinib induction therapy were re-randomized to receive 15 mg of upadacitinib, 30 mg of upadacitinib, or placebo (1:1:1 ratio) once daily for 52 weeks(276). Week 52 clinical remission rates among induction responders treated with 15 mg/30 mg/placebo were, respectively, 37.3%, 47.6% and 15.1%. The most significant adverse events were increased herpes zoster infections in patients receiving upadacitinib, and increased neutropenia among patients receiving 30 mg upadacitinib. Gastrointestinal perforations were observed in a total of 6 patients treated with upadacitinib in either the induction trial or the maintenance trial.

The largest paediatric study on upadacitinib therapy included 100 children and adolescents with refractory CD(279). At the end of the 8-week induction period, clinical response, clinical remission and corticosteroid- and exclusive enteral nutrition-free clinical remission were observed in 75%, 56% and 52% of the children, respectively. Most of the patients achieved biomarker remission as well. Adverse events were recorded in 24 children; the most frequent was acne (n=12), and 2 adverse events (severe acne and hypertriglyceridemia) led to discontinuation of therapy (279).

Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody, which binds to α4β7 integrin and therefore inhibits lymphocyte trafficking, specifically in the intestinal tract. In the registration trials, vedolizumab 300 mg IV at weeks 0 and 2 led to 14.5% clinical remission and 31.4% clinical response at week 6, versus 6.8% and 25.7% with placebo(280, 281). Vedolizumab shows modest benefit in patients with prior anti-TNF failure, explaining its lower ranking in network MA(282). A Cochrane review confirmed superiority over placebo for induction and maintenance of clinical remission (RR 1.61, 95% CI 1.20–2.17 and 1.52, 95% CI 1.24–1.87, respectively)(283). The Phase 2 paediatric HUBBLE trial included 45 children with CD, 47% of whom were weighing <30 kg. Participants were randomized based on weight to receive either low- or high-dose vedolizumab (150 mg or 300 mg for those weighing ≥30 kg; 100 mg or 200 mg for those <30 kg). At week 14, clinical response was observed with the higher of the two doses in 4 of 11 (33.3%) and 4 of 10 (40%), respectively, of those weighing ≥30 kg versus <30 kg. 25% of the older/heavier children and 50% of the younger/lighter children were bio-naive. Vedolizumab exposure increased approximately dose-proportionally, but no dose–response relationship was observed(284). VEDOKIDS was a paediatric, multicentre, prospective open-label cohort study wherein vedolizumab was administered intravenously at the suggested dose of 177 mg/m^2 (up to 300 mg maximum). Among 65 patients with CD (31% bio-naïve), 21 (32% [23–45]) were in steroid-free and EEN-free remission at 14 weeks(285). Steroid-free and EEN-free clinical remission at week

14 was significantly more common in children with isolated colonic CD (L2) than in those with L1 or L3 location. In children who weighed <30 kg, the dose required to reach the optimal drug concentration at week 6 was 200 mg/m² BSA(285). Analysis up to week 54 revealed that the median wPCDAI score decreased from 35 (IQR 18-49) at baseline to 13 (0-25), with 16 (25%) children in complete remission(286).

These two prospective paediatric studies are supported by retrospective data also predominantly involving anti-TNF experienced patients (280-283, 287-290). In these studies, steroid-free clinical remission rates at one year were up to 45%. Jossen et al included endoscopic outcomes, reporting ER in 66% of 10 anti-TNF naïve children and in 40% of 23 who were anti-TNF experienced (291).

Therapeutic drug monitoring of non-anti-TNF biologics

Data for the exposure-efficacy relationships for other biologics are less consistent than those for anti-TNF drugs. Despite previous studies showing that even at very low vedolizumab levels, the α4β7 receptor occupancy on both peripheral and lamina propria T cells is almost universal (292-295), a post hoc analysis of the GEMINI trials showed that higher vedolizumab concentrations at week 6 were associated with higher clinical remission rates in adult patients with IBD(296). In a prospective multicenter study in a combined population of patients with CD and UC, a vedolizumab trough level >18 µg/ml at week 6 was the only independent variable associated with ER within the first year of treatment (297). The LOVE-CD trial demonstrated that serum concentrations >10 µg/ml at week 22 were associated with ER at week 26 (298). Recently, findings from a retrospective cohort (n=94) reported that proactive TDM-guided therapy with vedolizumab yielded better outcomes than reactive TDM in terms of drug persistence (299). Nevertheless, in a study of 161 patients with IBD who underwent vedolizumab intensification, pre-intensification trough levels were comparable or higher among those subsequently attaining post-

optimization clinical, biomarker, and ER, compared with non-remitting patients, implying that TDM-based intensification is not superior to clinical-based intensification (300).

An exposure-response relationship was also observed for ustekinumab in registration trials (253, 301). Higher serum ustekinumab concentrations were associated with clinical remission both after induction and during maintenance in the UNITI pivotal studies, with optimal thresholds of 3.3 μg/ml at week 8 and 0.8- 1.4 μg/ml during maintenance (253). In a prospective single-centre study of patients with refractory CD, a minimal ustekinumab exposure of 4.2 μg/ml was needed at week 8 to achieve a 50% decrease in FC, which was also an independent predictor of endoscopic response at week 24 (302). A single retrospective study (n=83, proactive=46) reported better outcomes of proactive ustekinumab TDM vs. reactive TDM in terms of drug survival and hospitalizations (303). Nevertheless, in a cross-sectional study of 110 adult patients with CD, the addition of TDM into routine clinical practice did not significantly impact clinical decisions (304).

Few studies have investigated the pharmacokinetics of both vedolizumab and ustekinumab in paediatric patients (254, 261, 265, 284, 305). Although all of them showed exposure-response relationships similar to those found in adults, specific target levels for those drugs in children have not frequently been described. A recent prospective multi-center Canadian paediatric study, however, reported median week 8 ustekinumab levels to be significantly higher in patients with favorable clinical outcomes. ROC analysis identified week 8 level cut-offs of 6.3 and 6.7 for 1-year corticosteroid-free remission and intestinal healing, respectively (305).

A preliminary report of 28 patients with CD treated with risankizumab (n=28) found that patients in clinical and biochemical remission at week 12 had higher TC than those without remission (21.6±13.3 vs 7.4±6.4 μg/ml, respectively; P=0.001). ROC curve analysis identified a week 12 threshold of 11.5 μg/mL associated with clinical and biochemical remission (306).

Therapeutic sequencing after failure of anti-TNF therapy

The optimal second-line advanced therapy for the induction of remission in active CD following anti-TNF failure remains uncertain. Three network MA reported on the efficacy of second-line

treatments in biologic-experienced adult patients with luminal CD, but these analyses are limited and should be interpreted with caution. Attauabi et al (n=7,414) observed that upadacitinib and risankizumab induced the highest clinical responses in patients who have failed biologics, except infliximab (307). Barberio et al (n=8,720) showed that risankizumab ranked first for clinical remission in biologic-exposed patients (308). Singh et al (n=2,479) reported that adalimumab (in patients who had lost response to infliximab) and risankizumab were associated with higher odds of inducing remission (309). A comparative study (n=2,539) found that non-anti-TNF agents as a second line were superior to a second-line anti-TNF, although the absolute differences were small (310). Ustekinumab had superior persistence compared with an alternative anti-TNF agent or vedolizumab as second-line therapy in adults with CD in a propensity score-matched analysis from the Australian national IBD cohort (311). Similarly, a real-world propensity score-weighted analysis has shown that the likelihood of treatment failure was lower with ustekinumab compared with vedolizumab after failure of anti-TNF therapy (adjusted HR=0.66; 95% CI, 0.54-0.82)(312). Comparable results were reported in other real-world studies (313).

To conclude, data regarding the optimal therapeutic sequencing after anti-TNF therapy failure are limited due to the inherent limitations of network MA, the scarce data in the adult population, and the absence of paediatric data. Based on available data, ustekinumab or selective anti-IL23 agents are recommended as second-line therapy after failure of anti-TNF therapy (314), with adult data suggesting superiority of risankizumab over ustekinumab (271). In patients with CD who have failed to respond to two classes of biologics, upadacitinib may be considered. Vedolizumab therapy for induction and maintenance of remission can also be considered in selected cases, especially in patients with isolated CD colitis (286).

Advanced combination therapy

While advanced combination therapy (ACT) exhibits a relatively high efficacy in patients with refractory IBD, with high rates of clinical and biomarker remission, the rates of deep healing were reportedly low(314). The largest paediatric series on ACT reported on 62 children (35 CD) with

highly resistant IBD(315). The most frequent combinations were of an anti-TNF agent and vedolizumab or ustekinumab. Clinical remission was observed in 35%, 50%, and 63% of the children at 3, 6, and 12 months, respectively(315). Biomarker remission was achieved in most of the patients during the 12 months of follow-up. Eight serious adverse events were reported, including skin abscess and deep vein thrombosis (particularly when JAK inhibitors were combined). Comparable remission rates under ACT were reported in smaller paediatric case series(316-320).

In a MA that included predominantly an adult population (n=266, 29 children), the pooled clinical remission rates under ACT ranged from 40% to 80%, together with a generally favorable safety profile(321). The pooled endoscopic/radiologic remission rate ranged from 18% to 36% across the various combinations. The pooled rate of serious adverse events reached 12%, the most common were infections (75%). Another MA (n=279) reported clinical response and remission rates of 72% and 52%, respectively, in adults treated with ACT(322). The endoscopic response and remission rates were 58% and 33%, respectively. While ACT may be effective in children with highly refractory CD, the efficacy should be carefully weighed against the potential risk of serious adverse events. To enhance safety, one of the agents should preferably be ustekinumab, an anti-IL23 agent, or vedolizumab.

10. Management of patients with perianal Crohn's disease

10.1 A multidisciplinary approach for the care of children with perianal Crohn's disease, integrating both medical and surgical management, should be implemented. LOE: 3; 100% agreement.

10.2 Anti-TNF is recommended as first-line medical therapy for the management of perianal fistulizing disease. Infliximab LOE: 2; adalimumab LOE:3. 100% agreement.

10.3 Surgical care for patients with perianal fistulae should be performed by a surgeon experienced in these techniques and should largely follow the schema outlined for adults. LOE: 4; 96% agreement.

10.4 Seton placement is recommended with drainage of perianal abscess, especially in complex or recurrent perianal fistulae, and should be used in conjunction with medical therapy, typically anti-TNF. Subsequent surgical interventions may aim at fistula closure once proctitis is well-controlled. LOE: 4; 93% agreement.

10.5 Antibiotics can be used along with seton placement and/or anti-TNF therapy in the management of perianal CD. Although antibiotics have an important role in controlling fistula-associated infection, they should not be used as monotherapy for induction or maintenance of remission of perianal fistula. LOE: 4; 96% agreement.

10.6 Diversion of faecal stream with temporary stoma may be considered for management of refractory perianal fistulae. LOE; 4. When symptoms persist despite defunctioning, or when restoration of continuity is impossible, proctectomy may be considered. LOE: 5; 93% agreement.

Perianal CD (pCD) is associated with a high need for immunosuppressive therapy, surgery, hospitalization, and impaired QoL, with specific challenges arising from its impact on continence and body image(323, 324). Inception cohort analysis has demonstrated that pCD is more common in paediatric-onset compared to adult-onset CD (308/2186 [14%]) vs. 433/1222 [11%], p<0.001)(325). A MA of 12 population studies comprising patients with CD of all ages demonstrated that 18.9% (95% CI, 15.0-23.4%) have developed pCD by 10 years following diagnosis(326).

The cornerstone of successful pCD management is a combined medical and surgical approach, in both decision-making and treatment strategy(327). It is important that perianal disease be systematically classified. Geldof et al. described a fistula classification system, subsequently

adopted by ECCO in the adult CD treatment guidelines, which emphasizes whether the therapeutic object is fistula repair, symptomatic control in a currently irreparable fistula, or to determine if disease is rapidly progressive or gradually debilitating to an extent that defunctioning may be the best option (**Supplementary Figure 1**, adapted from Geldof et al)(6, 328). Although not explicitly designed for a paediatric population, we advocate using this classification system to determine clear treatment targets.

Anti-TNF therapy for perianal Crohn's disease

Infliximab has the strongest RCT data in perianal disease. A SR of the efficacy of anti-TNF therapy in paediatric pCD demonstrated that 326/565 (60%) patients achieved clinical remission, and 310 (55%) demonstrated clinical response of pCD(329). Another SR identified 197 paediatric patients across 4 studies who received infliximab therapy for pCD; 110 (55%) and 33 (17%) achieved complete remission and partial response, respectively(330). The same SR also identified 41 patients who received combination therapy with infliximab and an immunomodulator for pCD; 71% had resolution of their perianal disease at 1 year, though many of the patients included within this cohort also underwent surgery within the study period(330).

A multicenter inception cohort managing pCD with infliximab demonstrated that higher postinduction infliximab TCs are associated with improved outcomes in perianal fistulising disease(331). The median TC pre-fourth infliximab infusion was 12.7 (6.6–15.5 ug/ml) in responders compared with 5.4 (2.7–8.4 ug/ml) in non-responders. There was also a significant correlation between TC and healing at week 24(331).

When considering paediatric data supporting adalimumab in pCD, a sub-analysis of the IMAgINE 1 and IMAgINE 2 studies reported short- and long-term outcomes(332). Thirty-six patients were included in the week 12 analysis, which showed fistula closure and response rates to be 44.4% and 52.8%, respectively. The majority of patients who entered IMAgINE 2 with a healed fistula

maintained fistula healing at 2 years (64% hybrid non-responder imputation, 100% as observed)(342). In adult literature, although no placebo-controlled RCTs have been specifically designed to evaluate adalimumab use in pCD, multiple studies have nonetheless demonstrated its efficacy and safety in this context(6, 333-336). There is no evidence that adding an immunomodulator to adalimumab yields higher rates of fistula healing(337). However, there may be a benefit in persistence on therapy and higher drug levels(94).

Advanced therapies beyond anti-TNF for perianal Crohn' disease

There has been no RCT to specifically address ustekinumab in pCD in adults or children specifically. In the paediatric population, a GETAID study identified 20 anti-TNF-refractory patients who received ustekinumab for pCD, 9 of whom also underwent surgery; 50% showed improvement with ustekinumab(338). Kim et al also retrospectively evaluated outcomes of 13 children with pCD who received ustekinumab, all of whom were anti-TNF experienced. At end of follow-up, 5 patients were in remission, with a statistically significant decrease in PCDAI across the cohort (256).

In adults, a SR and MA identified 396 patients within 9 studies (7 of which were observational) treated with ustekinumab for pCD and found a pooled proportion of fistula response and remission to be 41.0% (95% CI 23.9–60.6%) and 17.1% (95% CI 8.1–32.7%) at 8 weeks, respectively(339). At 52 weeks, rates were 55.9% (95% CI 40.8–69.9%) and 16.7% (95% CI 3.0–56.5%), although by this time point, there were small sample sizes (N=44) and significant heterogeneity. It is worth noting that many of those included were refractory patients with prior anti-TNF failure(339). However, this study did not provide a clear placebo comparator.

Upadacitinib demonstrated superiority over placebo in fistula response and remission (RR 2.56, 95% CI: 1.18–5.53 and RR 2.92, 95% CI: 1.21–7.05, respectively)(340). During maintenance, upadacitinib was associated with significantly greater rates of fistula closure at week 52 compared

with placebo (delta 18.8%, 95% CI: 5.2–32.3, p=0.024)(341). There is no published RCT of upadacitinib in children in CD; as such, a recommendation has been softened to consideration in the paediatric population.

There have been no studies specifically powered to evaluate vedolizumab as a treatment of pCD in children or adults. A SR and MA with the primary outcome of fistula healing with vedolizumab identified 198 adult patients with active perianal fistulas across 4 studies, 87% of whom had failed previous anti-TNF therapy(342). The pooled complete healing rate was 27.6% (95% CI, 18.9–37.3%) with moderate heterogeneity (I^2=49.4%) and the pooled partial healing rate was 34.9% (95% CI, 23.2–47.7%) with high heterogeneity (I^2=67.1%).

Surgical care of perianal Crohn's disease

The choice of surgical technique for pCD, (depending upon fistula characteristics), is outlined in the adult CD treatment guidelines(6). Broadly, paediatric patient guidance should follow these guidelines when possible, taking into account the patient's size and age and local surgical expertise. An exam under anesthesia with seton insertion is widely accepted as the first step in the surgical approach for complex or recurrent perianal fistulae in adults and children alike. However, seton placement alone is associated with low rates of remission at 1-year post-intervention: 28.6% in the paediatric population (6, 330, 343). Of note, seton placement prior to anti-TNF therapy is associated with better fistula response (100% vs 82.6%; *p*=0.014), lower recurrence rates (44% vs 79%; *p*=0.001), and longer time to recurrence than with anti-TNF therapy alone (13.5 vs 3.6 months; *p*=0.0001)(344). Following seton placement and once proctitis is well controlled, further surgical interventions aiming at fistula closure should be considered. In brief, there is some adult evidence to support consideration of fistulotomy (6, 345-349), advancement flap(6, 350-355), and ligation of the intersphincteric tract (355-358) in patients with no active proctitis. There is insufficient evidence to recommend fibrin glue (359), video-assisted

anal fistula closure(360, 361), or fistula laser closure(362, 363). Anal fistula plugs are not recommended(6, 364-366).

Although there are some data that ciprofloxacin may improve outcomes with anti-TNF in the short term, there is no evidence that antibiotics improve long-term fistula outcomes(367-369). As such, we do not recommend antibiotics alone for fistula closure, although we recognize their importance in controlling infection associated with perianal disease.

In children, the outcomes of faecal diversion in the management of refractory perianal disease have been studied in small numbers. Dharmaraj et al evaluated outcomes in children who underwent diversion for refractory colonic or perianal disease (n=28); however, the majority included in the analysis had predominantly colonic phenotype (n=21). This study demonstrated that clinical remission was achieved in 46% (13/28), with intestinal continuity restored in 50% (14/28), although 3/14 cases ultimately required a permanent stoma within a median follow-up of 2.26 years (range 0.79–10.2 years). In univariate analysis, perianal disease was predictive of a lower likelihood of restored continuity (p = 0.023)(370). Johnston et al identified 109 paediatric patients with perianal disease, 12 of whom underwent diversion for refractory disease(371). Only 3 of these (25%) had their ostomies successfully reversed. In the adult literature, there is also a relatively high proportion of patients who ultimately require proctectomy following diversion, either due to failure to control symptoms or failure to maintain remission following restoration of continuity(372).

11. Management of stricturing or fistulizing Crohn´s disease

11.1 Bowel resection is recommended in patients with penetrating or stricturing disease refractory to medical therapy. LOE: 3; 88% agreement.

11.2 Endoscopic balloon dilatation could be used in patients with short (up to 5 cm) strictures accessible by endoscopy. LOE: 4; 93% agreement.

11.3 Strictureplasty should be the preferred option in strictures inaccessible by endoscopy and should be preferred in patients at risk for short bowel syndrome (LOE: 3). Bowel resection should be preferred in strictures with associated abscesses, phlegmons, penetrating disease, dysplasia, or malignancy. LOE: 3; 85% agreement

11.4 Anti-TNF therapy is recommended as first-line prevention of disease recurrence in most patients after bowel resection. LOE: 4; 93% agreement.

11.5 Endoscopic monitoring is recommended 6 to 9 months after intestinal resection to identify early endoscopic recurrence. LOE: 4; 89% agreement.

11.6 Pre-operative optimization should be initiated, including infection control, decision on perioperative medical therapy, and optimization of nutritional status. Exclusive enteral nutrition for at least 2 weeks might be considered as a preoperative approach to help reduce intestinal inflammation, improve nutritional status, and potentially enhance surgical outcomes. LOE: 4; 93% agreement.

Typical indications for surgery in CD include strictures, fistulas, abscesses, or refractory disease course(373-375). Along with medical treatment, endoscopic balloon dilatation (EBD), strictureplasty, and surgical bowel resection (BR) should be used in B2 or B3 (376, 377). However, paediatric evidence in the field is scarce. In a SR reviewing therapies used in paediatric stricturing CD, recurrence rates following interventions were 9%, 38% and 47 for BR, strictureplasty, and EBD, while complications occurred in 11%, 15% and 6%, respectively(377). A retrospective study that analyzed 88 EBD in 53 patients revealed that 12 patients underwent surgery and 7 had subsequent unplanned EBD over the following year. Adverse event rates were low and consistent with adult data(378). A recent SR and MA of invasive treatment techniques in children demonstrated combined stricture recurrence rates requiring surgical intervention of 0.171, 0.100

and 0.347 for EBD, BR and strictureplasty, respectively. Adverse events occurred most frequently after BR(376).

Another SR revealed that in 50% of patients with stricturing disease, surgery could be avoided by anti-TNF during a 4-year follow-up period and that EBD was effective for strictures ≤5 cm(379). Focusing on nutritional interventions in stricutring CD, a SR concluded that EEN led to clinical improvement in approximately 60% of patients and total parenteral nutrition in 75% while a liquid diet resulted in no improvement(83). According to recent RAND/UCLA consensus statement with SR, patients with confirmed intestinal obstruction should be hospitalized and treated by a multi-disciplinary team. Anti-inflammatory medical therapy in the acute setting should only be considered if an active inflammatory component was confirmed (**Supplementary Table 3**)(375).

General considerations on therapeutic strategy

We recommend upfront anti-TNF therapy in B2 CD if pre-stenotic dilatation is absent (**Figure 2**)(6). In patients refractory to anti-TNF, who have symptomatic pre-stenotic dilatation, obstructive signs or symptoms, or both, BR is recommended followed by postoperative anti-TNF therapy. Surgery and postoperative anti-TNF are recommended for B3 disease(4). The laparoscopic approach is preferred as first-line, and stapled side-to-side anastomoses are suggested(6). Therapeutic options based on RAND/UCLA consensus are listed in **Supplementary Table 4**(385).

Medical prevention of disease recurrence after ileocaecal resection

Paediatric evidence is also very scarce in the field of postoperative medical prevention. According to a recent SR, paediatric CD patients should not be left untreated post-resection(380), and anti-TNF seems to be an optimal medical prevention of disease recurrence(6). Azathioprine may be an exceptional alternative in very low-risk patients(381). In adult patients, a MA demonstrated superior efficacy for anti-TNF compared with thiopurine prophylaxis (382). Moreover, a recent

adult RCT has shown superiority of vedolizumab over placebo in the prevention of disease recurrence(383). Regular endoscopic monitoring starting at 6-9 months after surgery and supported by FC evaluation should be used to identify early endoscopic recurrence(381, 384, 385). A SR and MA show that MRE and CTE are effective initial screening tools for postoperative disease recurrence(386).

Peri-operative optimization

There are limited paediatric data available on the topic. In 21 paediatric patients with B3 CD, anti-TNF therapy, prior to complication resolution, reduced infectious adverse events, while CD-related surgeries and hospitalizations occurred with similar frequency(387). In adults, ECCO guidelines recommend elective BR over emergency surgery, and surgery should be performed in high-volume IBD centers(6). For intra-abdominal abscesses, intravenous antibiotics and percutaneous image-guided drainage should be used as the first-line treatment, and a low threshold for surgery is recommended. A temporary stoma formation is suggested in patients with CD if they are not sufficiently optimized for surgery(6). According to a SR, anti-TNF does not increase postoperative complications, and more data are needed for other biologics and small molecules (388). Another SR shows that corticosteroids are independent predictors of morbidity, and vedolizumab was associated with increased rates of superficial skin infections and small bowel obstruction(389).

ECCO guidelines recommend tapering corticosteroids but not biologics before surgery(6). Malnutrition is a risk factor for adverse postoperative outcomes. The benefits of preoperative EEN for at least 2 weeks on postoperative morbidity have been consistently reported(390-392). Thus, when feasible, enteral nutrition should be part of a pre-operative optimization strategy, based on nutritional assessment by an IBD-dedicated dietitian as part of a multidisciplinary team(6).

12. Additional health-care related issues

12.1 25-OH vitamin D serum level should be monitored at least once a year, and adequate supplementation is recommended to achieve a satisfactory concentration (at least >50 nmol/L or 20 ng/ml). LOE: 2; 96% agreement.

12.2 Hemoglobin and iron status should be monitored regularly, at least every 6-12 months, and following an iron treatment course. Oral iron is suggested to treat mild iron-deficiency anemia (Hb>10 g/dL, or 6.2 mmol/L) in patients with mild CD activity. Intravenous iron should be preferred when hemoglobin levels are lower, in moderate-severe CD activity, or in case of intolerance or refractoriness to oral iron supplements. LOE: 3; 89% agreement.

12.3 The risk of venous thromboembolism should be assessed in all inpatients and prophylaxis started accordingly. LOE:2; 92% agreement.

Vitamin D

Bone mineral accrual during childhood is critical, yet over one-third of children with IBD present with osteopenia at diagnosis(393). Low BMD has been linked to lower BMI z-scores and higher disease activity(394, 395). Vitamin D plays a key role in bone health and is commonly deficient in children with IBD, with prevalence rates up to 98%, particularly among African American patients(396-398). Supplementation may reduce disease activity and inflammation(399-405). In a randomized trial, vitamin D supplementation improved PCDAI scores, inflammatory markers, and QoL(406).

Preventative supplementation dosing of vitamin D is 600 IU (15 mcg) daily. The following dosing of 25-OH vitamin D3 (cholecalciferol) should be used to treat vitamin D deficiency (<50 nmol/L): 2,000-3,000 IU (50-75 mcg) a day for children <4 years; 3,000-5,000 IU (75-125 mcg) a day for children 4-18 years, with treatment duration of 1-3 months depending on the level achieved. A single high-dose of oral vit D3 (stoss dose: 200,000-600,000 IU) can be equally safe and effective(407-409).

Dual-energy X-ray absorptiometry (DEXA) is recommended at diagnosis and follow-up for high-risk patients, though interpretation may require bone specialist input due to growth-related limitations(410). Based on the evidence available, bone health should be monitored through DEXA at diagnosis in children presenting with suboptimal growth (BMI z-score <1). Children with low BMI z-score (<-0.5), decreased physical activity, ongoing chronic inflammation, delayed puberty, and prolonged steroid exposure have a higher risk of low BMD. In children with BMD z-score ≤-1 at diagnosis, DEXA should be performed every 1-2 years during follow-up.

Iron deficiency anemia

Iron deficiency anemia (IDA) is common in IBD, affecting up to 90% of patients, yet often remains underestimated in clinical practice(411-420). In children with CD, factors like young age at diagnosis increase the risk of severe anemia, while higher albumin levels offer protection(421). Management options include oral and intravenous iron, each with advantages and limitations; oral iron often has poor absorption and side effects, whereas intravenous iron is more costly and carries an increased side effect profile(416,419, 422).

A Cochrane systematic review showed that intravenous ferric carboxymaltose (FCM) tends to be more effective than intravenous iron sucrose, with a higher likelihood of resolving IDA(411). The POPEYE trial in children with IBD found that intravenous FCM is superior to oral iron in improving physical fitness more rapidly, though by 3-6 months, both methods yielded similar hemoglobin increases(423). Overall, oral iron can be used in mild iron-deficiency anemia in patients with mild CD activity, while intravenous should be preferred when hemoglobin levels are lower (Hb<10 g/dL), in moderate-severe CD activity, and/or when oral iron is not effective or tolerated. An important side effect of FCM is hypophosphatemia: A retrospective study in 94 children that received FCM, 25 (94.4%) developed hypophosphatemia, which was severe in two(424). Nevertheless, in the POPEYE trial that included 33 paediatric IBD patients treated with FCM, no

case of hypophosphatemia was reported. Follow-up phosphate checks in symptomatic patients receiving FCM is advised (423).

Venous thromboembolism prophylaxis

Thrombotic events are more common in IBD patients than in the general population, with venous thromboembolism (VTE) incidence in children ranging from 4-30 per 10,000 patient-years(425-435). A large, prospective, international paediatric study (PIBD-SET Quality Safety Registry) reported an incidence of 3.72 per 100,000 person-years, significantly higher than in healthy children (434). Risk factors for VTE are presented in **Supplementary Table 5**. Whereas acute severe colitis in hospitalized patients with ulcerative colitis is a well-established indication for initiating VTE prophylaxis, the recommendations for hospitalized patients with CD are more nuanced and less definitive(234). Current evidence supports considering prophylaxis with low molecular weight heparin (s.c. enoxaparin 1 mg/Kg up to 40mg, once daily) in at-risk hospitalized children (i.e. at least one additional risk factor as in **Supplementary Table 5**), often combined with mechanical methods(436). The use of direct oral anticoagulants for the treatment or prevention of VTE has not been studied in the paediatric population yet(433).

13. Monitoring of patient-related outcomes

13.1 Patient disease-related concerns and expectations, psychosocial status, and general functioning should be consistently and routinely assessed, regardless of disease control, with particular attention to diagnosis, relapses, transition phases, and major surgeries. LOE: 5; 96% agreement.

13.2 Fatigue should be addressed at every visit, with consideration of potential causes, including active inflammation, adverse drug effects, sleep and/or psychological

disorders, anemia, micronutrient deficiency, or endocrine disorders. LOE: 3; 96% agreement.

13.3 Multidisciplinary IBD teams are vital and should provide integrated psychosocial care and facilitate interventions as needed. LOE: 5; 96% agreement.

Health-related QoL is a multidimensional construct encompassing physical, psychological, and social well-being(437, 438). Psychological and social dimensions have emerged as key priorities in IBD (439-443), driven by the recognition that remission does not guarantee psychosocial well-being (441, 444, 445).

Psychosocial disorders

Patients with CD are at an increased risk of psychological disorders(446-448). In a recent paediatric IBD MA, pooled prevalence estimates were 16% (95%CI: 7-27%) for anxiety symptoms and 15% (95%CI: 6-25%) for depressive symptoms, irrespective of disease type(449). Paediatric nationwide studies reinforce these findings(450-453): for example, Cooney et al reported increased risks of anxiety/depression in paediatric CD in the UK (aHR 1.39, 95%CI:1.11-1.74 for anxiety; aHR 1.41, 95%CI: 1.15-1.74 for depression)(452). The true extent of the association between CD and psychological disorders remains unclear due to biases, including the paucity of studies with appropriate comparators, challenges in controlling disease severity, variability in assessment tools for psychological disorders, and cross-national differences in mental health awareness. Moreover, beyond anxiety and depression, eating, body image disorders, and other mood and personality disorders have been suggested as more prevalent, with further research needed to confirm these associations(447, 451, 462, 454-456).

Studies of bi-directional brain-gut interaction highlight a complex interplay between depression and both IBD activity and diagnosis, predominantly in adults(446, 454, 457-468). Disentangling the temporal relationships between both conditions is challenging; nevertheless, it remains

undeniable that a chronic and unpredictable disease, characterized by potentially embarrassing symptoms and a source of stigma, can impact psychosocial well-being and overall functioning(469). Therefore, maintaining awareness and continuously monitoring patients' psychosocial status is essential.

A notable gap exists in the availability of tailored tools to assess psychological health in paediatric IBD. While IMPACT III and IMPACT III-P are available for QoL, no paediatric scores exist to assess specific psychosocial domains(470-474). A dedicated psychosocial team available to ensure integrated care is fundamental; various non-pharmacologic interventions, including educational programs, cognitive-behavioral therapy, and mindfulness-based interventions, have been described with insufficient evidence to draw definitive, rigorous conclusions(475-489)

Fatigue and Disability

Fatigue, the most troublesome and widely reported symptom in IBD, was the top priority for IBD research in patient-focused initiatives by the James Lind Alliance (490-492). Its burden is notable with a prevalence of 50% in adult IBD patients(493). A recent SR identified only 14 paediatric IBD studies on fatigue, of which 2 reported severe fatigue rates; these authors' single-center paediatric IBD cohort experience showed 33% of patients with moderate/severe fatigue versus 9% of healthy controls, with 11% and 0% for severe fatigue(494). Unlike in adults, where the IBD-fatigue scale is widely used, no equivalent tool exists in paediatric IBD, although the PROMIS paediatric fatigue score has been used without validation (471, 495). An adult Cochrane SR and the paediatric IBD SR, which updated adult IBD interventions for fatigue to 19, failed to identify successful interventions(496). A high-dose oral thiamine RCT reported improvement in fatigue among adults with quiescent IBD(497), while a feasibility RCT is underway following a case series on modafinil for severe fatigue(498).

Disability is underexplored in paediatric IBD(480). While the IBD Disability Index and IBD Disk are available for adults, there is no paediatric equivalent. Development of specific tools like the

Paediatric IBD Fatigue Index (PIFI) and Paediatric IBD Disability Index (PIDI) is underway, offering hope for targeted assessments in the future(499, 500). While research is awaited, clinical teams should systematically evaluate daily functioning and psychosocial status, including school engagement, social participation, physical activity, sleep, and dietary habits, along with patients' disease-related concerns and expectations, to identify underlying challenges that may require further evaluation or intervention(501). When disease-specific tools are unavailable, validated, age-appropriate paediatric tools can support well-being monitoring (**Supplementary Table 6**). Addressing these psychosocial challenges may help improve QoL, pain management, illness perception, and even influence disease outcomes (**Figure 4**)(458, 477, 483, 489, 502-504).

Conclusion

These updated ECCO–ESPGHAN guidelines provide evidence-based, multidisciplinary recommendations for the management of paediatric CD, reflecting the advances in diagnostics, therapeutic strategies, and treatment targets since the previous edition. Early risk stratification, proactive monitoring, and a treat-to-target approach, with short (clinical response and remission), medium (biochemical response), and long-term outcomes (ER, and, when possible, transmural healing), remain crucial to prevent long-term bowel damage and optimize growth, development, and QoL.

Nutritional therapy continues to play a key role in achieving remission in low-risk patients. At the same time, anti-TNF agents represent the most effective first-line option for children at high risk of poor outcomes and should be prescribed for most newly diagnosed patients with CD. TDM, both proactive and reactive, is now an essential component of biologic optimization. For patients who fail or lose response to anti-TNF therapy, emerging biologics targeting IL-12/23 or IL-23p19, and JAK inhibitors, offer valuable alternatives. However, paediatric data remain limited, and most

of these agents can be prescribed only off-label in many countries. The selective use of combination therapies, including dual-targeted approaches, in highly refractory disease is increasingly supported by real-world evidence.

Diet-based strategies for maintenance show promise for low-risk patients but require close monitoring and dietitian involvement and should currently be reserved only for highly selected patients. Treatment de-intensification should be carefully individualized once deep remission is achieved and objective markers confirm a stable disease remission. In parallel, patient-reported outcomes and quality-of-life measures are essential components of disease assessment, helping ensure that treatment strategies align not only with biological targets but also with the daily functioning, well-being, and psychosocial needs of children and adolescents.

Surgical management remains an integral component of paediatric CD management, particularly in cases of stricturing, penetrating, or perianal complications, or when medical therapy fails to control inflammation or restore growth. Early surgical consultation is recommended as part of a multidisciplinary approach, as timely, well-planned surgery can improve symptoms, reduce corticosteroid exposure, and prevent further bowel damage. Surgery should not be viewed as a last resort but as a complementary treatment option within a personalized therapeutic approach, often followed by optimized medical therapy to prevent postoperative recurrence.

A persistent challenge in the optimal management of children with CD is the significant delay between the approval of novel therapies for adults and their availability for paediatric use (505). This therapeutic gap restricts access to effective advanced treatments for children with refractory disease and may contribute to disease progression and long-term poor outcomes. Close collaboration among regulators, industry, and academic networks is essential to facilitate earlier inclusion of children and adolescents in drug development, to enable appropriate extrapolation of adult data to paediatric populations, and to ensure timely and equitable access to innovative therapies.

Legend to Figures

Figure 1: Treatment targets based on STRIDE II.

Figure 2: Treatment algorithm of a newly-diagnosed patient with Crohn's disease.

Figure 3: Anti-TNF therapeutic drug monitoring in induction and maintenance phases in paediatric patients with Crohn's disease. IFX, infliximab; ADA, adalimumab, TDM, therapeutic drug monitoring; TC, trough concentration; IMM, immunomodulator.

Figure 4: Addressing psychosocial challenges in paediatric patients with Crohn's disease.

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