Journal of Crohn's and Colitis, 2026, **20**(**8**), jjag084
https://doi.org/10.1093/ecco-jcc/jjag084
ECCO Guideline

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

Dror S. Shouval[1,2,*,†], Iva Hojsak[3,†], Erasmo Miele[4,†], Christiane Sokollik[5,†], Dan Turner[6,†], Kaija-Leena Kolho[7,†], Rotem Sigall-Boneh[8,†], Patrick F. van Rheenen[9,†], Eytan Wine[10,†], Richard K. Russell[11,12,†], Seamus Hussey[13,†], Neil Chanchlani[14,†], Amit Assa[15,16,†], Javier Martin de Carpi[17,†], Luca Scarallo[18,†], Anne M. Griffiths[10,†], Anat Yerushalmy-Feler[2,19,†], Caterina Strisciuglio[20,†], Lissy de Ridder[21,†], Jiri Bronsky[22,†], Hannah Gordon[23,†], Michel Adamina[24,25,†], Johanna C. Escher[26,†], Marco Gasparetto[27,28,†], Laura Gianolio[29,†], David C. Wilson[11,12,†], Marina Aloi[30,31,*,†]

[1]Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petah Tikva, Israel
[2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[3]Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, University of Zagreb Medical School, Zagreb, Croatia
[4]Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Naples, Italy
[5]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[6]The Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Eisenberg R&D Authority, Shaare Zedek Medical Centre, The Hebrew University, Jerusalem, Israel
[7]Department of Pediatric Gastroenterology, Children's Hospital, University of Helsinki and HUS, Helsinki, Finland
[8]Pediatric Gastroenterology and Nutrition Unit, The E. Wolfson Medical Center, Holon, Israel
[9]Department of Paediatric Gastroenterology, University of Groningen, University Medical Centre Groningen, Beatrix Children's Hospital, Groningen, The Netherlands
[10]Division of Gastroenterology, Hepatology, and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
[11]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Royal Hospital for Children and Young People, Edinburgh, United Kingdom
[12]Child Life and Health, Centre for Inflammation Research, University of Edinburgh, Scotland, United Kingdom
[13]DOCHAS Group, Children's Health Ireland, University College Dublin, Dublin, Ireland
[14]Department of Paediatric Gastroenterology, Bristol Royal Hospital for Children, Bristol, United Kingdom
[15]The Pediatric Gastroenterology Unit, Kaplan Medical Center, Rehovot, Israel
[16]The Hebrew University, Jerusalem, Israel
[17]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Hospital Sant Joan de Déu, Barcelona, Spain
[18]Gastroenterology and Nutrition Unit, Meyer Children's Hospital IRCCS, Florence, Italy
[19]Pediatric Gastroenterology Institute, "Dana-Dwek" Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[20]Department of Woman, Child and General and Specialistic Surgery, University of Campania Vanvitelli, Naples, Italy
[21]Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands
[22]Department of Paediatrics, Motol and Homolka University Hospital, Prague, Czech Republic
[23]Translational Gastroenterology and Liver Unit, University of Oxford, Oxford, United Kingdom
[24]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[25]Faculty of Medicine, University of Basel, Basel, Switzerland
[26]Department of Paediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
[27]Jenny Lind Children's Hospital, Norfolk and Norwich University Hospitals, Norwich, United Kingdom
[28]Norwich Medical School, University of East Anglia, Norwich, United Kingdom
[29]Department of Paediatrics, Vittore Buzzi Children's Hospital, University of Milan, Milan, Italy
[30]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
[31]Pediatric Gastroenterology, Hepatology and Cystic Fibrosis Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy

*Corresponding authors: Dror S. Shouval, Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petah Tikva, 4920235 Israel; Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, 6997801, Israel (Dror.shouval@gmail.com) and Marina Aloi, Department of Pathophysiology and Transplantation, Università degli Studi di Milano—Pediatric Gastroenterology, Hepatology and Cystic Fibrosis Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Via della Commenda 9, 20122 Milan, Italy (Marina.aloi@unimi.it).

†These authors contributed equally to this work.

Abstract

Objective: To provide an updated, evidence-based European Crohn's and Colitis Organisation [ECCO]–European Society for Paediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN] guideline for the management, monitoring, and long-term care of pediatric 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: This guideline provides updated recommendations across major domains of pediatric 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. This guideline also reviews emerging advanced therapies, including biologics and small molecules, which are increasingly used in practice but generally not yet approved for pediatric CD, to inform clinicians about their potential role.

Conclusions: This updated ECCO–ESPGHAN guideline integrates new pediatric 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 in pediatric CD.

Key words: therapeutic drug monitoring

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 pediatric-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 European Crohn's and Colitis Organisation [ECCO]–European Society for Paediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN] guidelines on the medical management of pediatric 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 pediatric patients with CD. The 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. Consistent 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 pediatric 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 9 working groups, each tasked with developing key clinical questions framed according to the Population, Intervention, Comparator, Outcomes [PICO] structure considered relevant to clinical practice (see Table S1). A systematic review of the literature was performed by a medical librarian, covering studies published between January 1, 2018, and October 27, 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 June 1, 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 pediatric patients with CD, and 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 [LoE] 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 pediatric data complemented adult RCT findings.

Each working group synthesized the evidence into summary tables (Table S2) 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 pediatric CD, as defined by the Pediatric IBD Ahead program, include the need for surgery, development of complications [stricturing or penetrating disease, or both], 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, which included 222 treatment-naive pediatric patients with CD, demonstrated that only steroid-free clinical remission with a normal C-reactive protein [CRP] level at week 12 predicted sustained remission at 52 weeks (odds ratio [OR]: 3.6; 95% confidence interval [CI]: 1.4-9.39; $P = .008$).[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, achieving fecal calprotectin [FC] <250 µg/g within 12 weeks after induction therapy (steroids or exclusive enteral nutrition [EEN]) 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] or penetrating [B3] disease [or both] 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, jejunum, or both][13,14] and perianal disease are associated with poor outcomes.[2,15,16] Furthermore, B2 at diagnosis increased the need for surgery[10,15] and was a risk factor for a more complicated disease course.[14] Diagnostic delay, not surprisingly, is associated with such complicated diseases at the time of CD recognition.[17] 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 extraintestinal manifestations [EIM] at diagnosis independently increases the need for corticosteroid and immunosuppressive treatment in pediatric patients with IBD.[22] For patients with CD specifically, 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 surgery.[24] Other factors, such as sarcopenia and histologic granulomas, which were shown to be risk factors in adult studies, are not supported by conclusive evidence in pediatric studies.[17]

Table 1. Risk factors associated with poor outcome.

Growth or pubertal delay
Perianal disease
Extensive disease
Deep ulcers
Failure to achieve clinical and biochemical remission after induction therapy
Stricturing disease (B2)
Penetrating disease (B3)

The absence of the above-mentioned risk factors suggests a low risk for poor outcomes.

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 or 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, erythrocyte sedimentation rate [ESR]), and mucosal [FC] inflammatory markers should be regularly monitored, even in patients in clinical remission, to detect disease flares at an early pre-symptomatic stage.

Clinical activity indices

The pediatric Crohn's disease activity index [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 pediatric CD. Unfortunately, the various versions of PCDAI are not reliable for evaluating mucosal inflammation.[26–29] Studies showed that nearly half of patients whose scores indicated clinical remission may still exhibit residual mucosal inflammation. While the wPCDAI offers greater diagnostic accuracy for determining clinical remission than other PCDAI versions,[27] clinical assessment alone is inadequate when endoscopic remission [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.[30–32] Low FC levels [<150-250 µg/g] correlated strongly with ER, while failure to

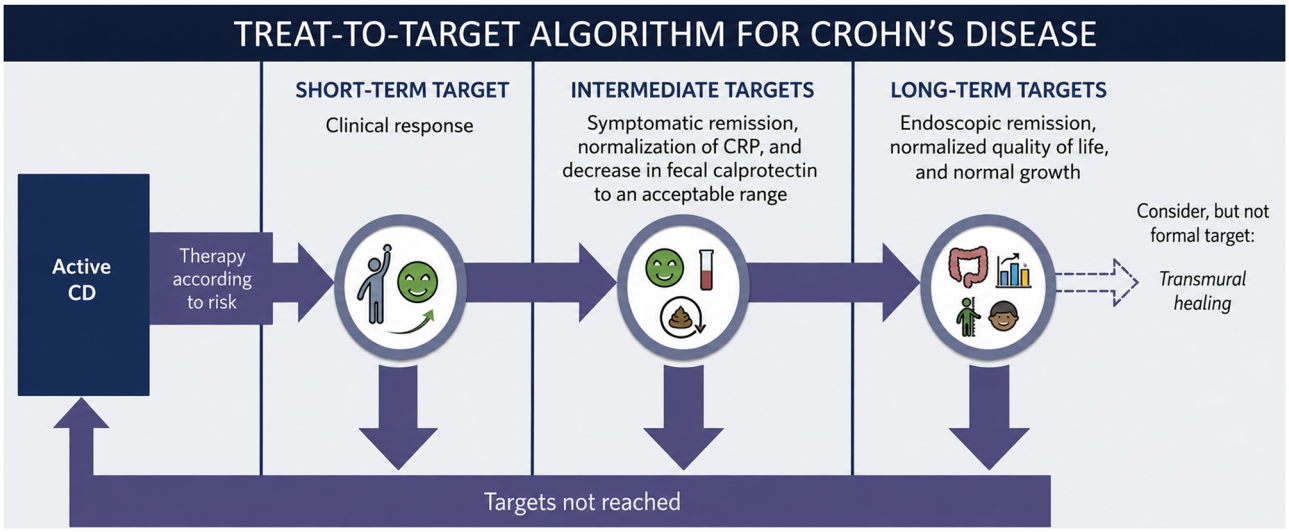

Figure 1. Treatment targets based on STRIDE II. Adapted from Turner et al.[25]

Table 2. Treatment targets with values that correlate with response and remission.

Treatment target	Tools	Response	Remission
Clinical	PCDAI	Decrease of at least 12.5 points	PCDAI ≤10 points or <7.5 excluding the height item
	wPCDAI	Decrease of at least 17.5 points	wPCDAI <12.5 points
Biochemical	CRP		<ULN
	Fecal calprotectin	<250 µg/g	<100 µg/g
Endoscopic	SES-CD	Reduction of at least 50%	≤2
Endoscopic surrogate markers	MINI index		<8
	Fecal calprotectin	Reduction of at least 50%	<100 µg/g
Transmural	MRI – PICMI	Decrease >20 points	≤10 points
	IUS – bowel wall thickness		<2.5-3 mm

Abbreviations: CRP, C-reactive protein; IUS, intestinal ultrasound; MINI, mucosal inflammation non-invasive index; PCDAI, pediatric Crohn's disease activity index; PICMI, pediatric inflammatory Crohn's magnetic resonance enterography index; SES-CD, Simple Endoscopic Score for Crohn's Disease; ULN, upper limit of normal; wPCDAI, weighted pediatric Crohn's disease activity index.

achieve these levels indicated persistent intestinal inflammation.[11,33–38] In a cross-sectional study, FC cut-off levels of 250 µg/g following induction therapy had the best area under the curve [AUC] of 0.95 for detecting inflammation compared with systemic inflammatory markers.[35] 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].[39] Additional studies showed that FC, on average, increases 2-3 months before symptom recurrence.[40,41]

However, FC levels do not correlate linearly with the severity or extent of mucosal inflammation.[42] Consequently, a significant reduction in FC without complete normalization during induction therapy may still reflect a favorable treatment response. A decrease to <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.[42] Interpretation should be made with caution in patients with isolated small-bowel disease or upper GI involvement, since lower FC values were reported for L1 compared with L2 and L3, and FC of 95 µg/g was identified as the best cut-off for 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 adult levels in the first years of life.[44–47] This should be considered when interpreting results.

Studies in adults and children showed that using composite endpoints that combine multiple measures improves accuracy. The Mucosal Inflammation Non-invasive Index [MINI] index is a weighted composite score of stool consistency and frequency, FC, and CRP/ESR, and is currently considered a suitable non-invasive surrogate marker for ER in CD.[48,49] Seventy-eight percent 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.[25] Endoscopic response is usually defined as at least a 50% reduction in simple endoscopic score for Crohn's disease [SES-CD] from baseline inflammation,[50,51] whereas ER is generally characterized by the absence of visible inflammation or an SES-CD score ≤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 pediatric score was developed, the capsule endoscopy-CD index,[52] which can predict the need for hospitalization, treatment escalation, steroid therapy, and clinical and endoscopic relapses over the next 24 months.[51] 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. Although IUS is more affordable and accessible, 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]; newer data in children suggest a threshold of 2.5 mm.[57] Dolinger et al. performed a prospective pediatric 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, which was superior to PCDAI and CRP.[58] Bowel hyperemia [using the Limberg score] was the first sonographic variable to show a significant reduction following anti-TNF therapy in children with CD.[59,60]

The International Bowel Ultrasound Group Segmental Activity Score [IBUS-SAS] standardizes IUS reporting.[56,61] A retrospective pediatric 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% decrease in IBUS-SAS, with an optimal IBUS-SAS value of 26 to indicate ER [AUROC = 0.686; $P = .017$]. Some scores were designed for children, including the Pediatric Crohn's Disease Intestinal Ultrasound Score, 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 resulted in a specificity of 88% [95% CI: 72%-97%] and 92% [95% CI: 87%-96%] for defining ER in the terminal ileum and colon, respectively.[63] The Simple Pediatric Activity Ultrasound Score was developed and incorporates BWT, hyperemia, and inflammatory fat, demonstrating a good predictive ability 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, diffusion restriction, and T2 hyperintensity] from structural damage [indicated by fibrotic strictures, abscesses, or fistulae].[67] The Pediatric Inflammatory Crohn's Magnetic Resonance Enterography Index [PICMI] score was developed specifically for children and correlates positively with the 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

Discrepancies between patient and physician perspectives are common and may lead to potential misalignment in disease management. Consequently, patient-reported outcomes [PRO] are now emphasized as the standard for symptom assessment, and STRIDE II recommends their early and regular use throughout the disease course.[25] The Patient-Reported Outcomes Measurement Information System (PROMIS), a PRO framework developed to assess physical, mental, and social health in chronic disease populations, includes pediatric domains specifically designed for children aged 8-17 years.[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 agents should be initiated as first-line therapy (LoE: 1) (93% agreement)

5.2. The choice between adalimumab and infliximab 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% agreement)

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 agent, it can be initiated as monotherapy (LoE: 2). When used as a second anti-TNF agent, combination therapy with an immunomodulator is suggested (LoE: 5) (96% agreement)

5.6. When an anti-TNF agent is indicated and until therapy is initiated, nutritional therapy, such as exclusive 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 EIMs, patient characteristics and preferences, safety profile, and prior treatment exposure. In addition, real-world considerations, such as regulatory approval, access to therapies, cost, and the feasibility of monitoring, must be balanced with

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 such as 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 healthcare professionals in choosing a therapeutic strategy for a child with CD (Figure 2). Most newly diagnosed pediatric patients with CD exhibit at least one item indicating high risk for poor outcome, and therefore should start anti-TNF as first line treatment, in order to reduce risk of future complications.[75,76] Moreover, a MA of data from a systematic review and individual-patient data of randomized trials and large population-based cohorts demonstrated 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 therapy is initiated, nutritional therapy is recommended, especially when a delay in medical therapy is expected [e.g., to provide live vaccines or due to insurance coverage]. EEN is also effective in some cases of internal penetrating disease, with 70% avoiding surgery in a case series.[82] A SR of 5 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 agents. 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, before initiation of immunosuppressive therapy, as immunosuppression reduces vaccine efficacy and contraindicates the use of live vaccines.

Infliximab

The efficacy of infliximab in inducing remission in pediatric 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.[29,86–90]

Intravenous infusions of infliximab are traditionally dosed 5 mg/kg at weeks 0, 2, and 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, or 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] It is recommended to use infliximab preferably in combination with an immunomodulator [thiopurine or methotrexate], for 6-12 months, to mitigate the formation of anti-drug antibodies [ADA] and enhance infliximab effectiveness.[92,93] To prevent immunogenicity, lower doses of azathioprine [1-1.5 mg/kg] may be sufficient,[92,93] although the PANTS study supports the use of a standard dose of 2-2.5 mg/kg.[94] Data on methotrexate dosing in this setting are scarce, but low total doses of 7.5-12.5 mg weekly have been reported.[95] In the presence of high-range infliximab TCs, combination therapy with an immunomodulator may have limited added value in decreasing ADA formation.[96]

Adalimumab

Multiple studies demonstrated the efficacy of adalimumab in inducing remission in pediatric 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] In patients naive to anti-TNF agents, the lower immunogenicity of adalimumab relative to infliximab supports the use of monotherapy.[103] However, the PANTS study clearly demonstrated a benefit of combination therapy with an immunomodulator.[94] 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.[104]

For patients ≥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 onward. However, considering the evidence on underdosing of anti-TNF agents in young children,[105] higher doses are usually required and calculated based on body surface area [BSA] rather than weight [90 mg/BSA followed by 45 mg/BSA 2 weeks later and then 23 mg/BSA every other week]. Administration of weekly 40-mg injections or 80 mg 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.[106]

Comparison of infliximab versus 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 a higher rate of 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 pediatric 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 received combination treatment with an immunomodulator.[108] In the second cohort, the infliximab-treated children more often had dose intensification and combination therapy with immunomodulators [67%] than adalimumab to achieve the same

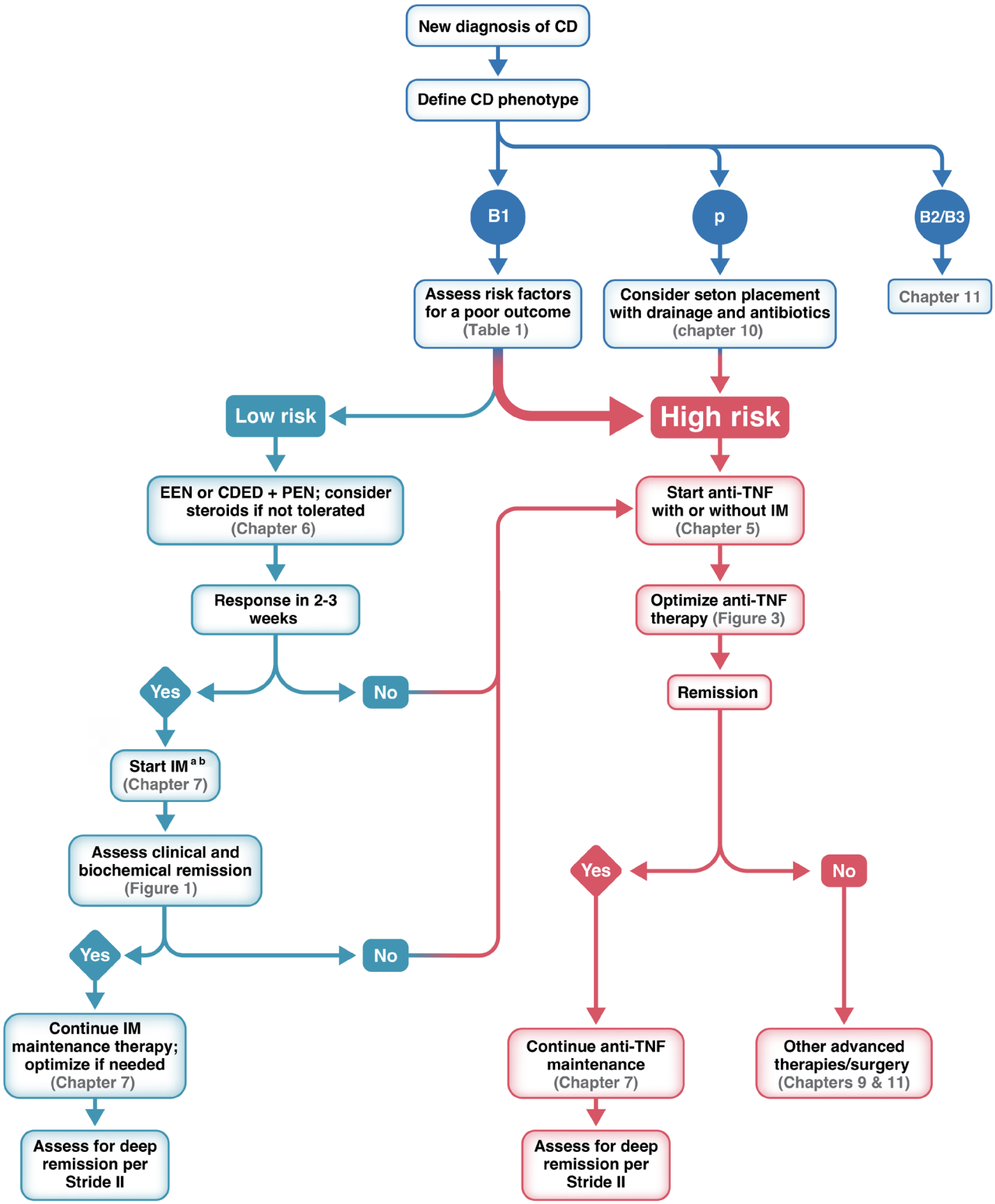

Figure 2. Treatment algorithm of a newly diagnosed patient with Crohn's disease. [a]Given the long duration until full effect of immunomodulator monotherapy in low-risk uncomplicated CD [6-12 weeks], azathioprine or methotrexate should be started within the first few weeks after induction of nutritional or steroid therapy. [b]In low-risk uncomplicated scenarios, exclusive dietary maintenance therapy without medical treatment is a therapeutic option only for highly selected CD patients, and if considered, should warrant close monitoring. CD, Crohn's disease; CDED, Crohn's disease exclusion diet; EEN, exclusive enteral nutrition; IM, immunomodulator; PEN, partial enteral nutrition.

outcomes.[109] A propensity score analysis of the epi-IIRN nationwide cohort of pediatric IBD supported the use of adalimumab monotherapy as a first-line biologic in children with CD, as it was comparable in effectiveness to infliximab combination 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.[85,111]

Regarding biosimilars, a systematic review of 9 studies showed that infliximab biosimilars or the originator have similar effectiveness even after switching from the originator in pediatric IBD.[112] Concomitant corticosteroids did not improve the effectiveness of anti-TNF agents as induction treatment for CD, and, therefore, steroids should be rapidly weaned as soon as possible after initiating the anti-TNF agent.[113]

There is real-world experience of using both anti-TNF agents in children with VEO-IBD, with theoretical advantages for the flexible dosing of infliximab, but both have been shown to be effective.[19,114–116] 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 (1 mg/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 to minimize the risk of developing or exacerbating disordered eating behaviors (LoE: 5) (100% agreement)

Exclusive enteral nutrition

Numerous studies have demonstrated that a 6- to 8-week course of EEN is effective in achieving clinical remission and is superior to steroids in promoting ER.[118–123] In a prospective, 10-week, open-label trial comparing induction with EEN versus corticosteroids, the proportion of children showing mucosal healing was significantly higher in the EEN group (14/19; 74%; 95% CI, 51%-89%) than the corticosteroid group (6/18 [33%; 95% CI, 16%-57%]; $P < .05$), with similar rates of clinical remission.[122] A Cochrane review summarized RCTs on EEN as induction therapy in 1011 patients with CD.[118] The authors concluded that the overall treatment response of EEN parallels that of corticosteroids. However, the comparison between EEN and corticosteroids included only 57 pediatric patients and was considered of very low quality. There is no benefit of one formula over another for EEN, as reported in a SR.[124] Older age [>15 years] and higher baseline PCDAI scores were associated with lower response to EEN.[121] In another study of 241 adults, colonic involvement was associated with a lower remission rate [52% vs. 68%; $P = .029$].[125]

Crohn's disease exclusion diet with partial enteral nutrition

The Crohn's Disease Exclusion Diet [CDED] is a whole-food diet designed to reduce exposure to potentially pro-inflammatory ingredients and is combined with partial enteral nutrition [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 achieve clinical remission will generally transition to phase 2, which introduces more foods and reduces 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 resulted in 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 clinical remission rates was found in the two groups. By week 24, remission persisted in 60% on CDED versus 42% on PEN [$P = .18$]. 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 with EEN.[133] In another prospective study among 39 children, ER was observed in 7/13 [54%] children receiving PEN with modified CDED versus 8/16 [50%] receiving EEN by week 6.[134] Additional studies demonstrated the efficacy of CDED + PEN combined with anti-TNF agents.[134,135]

Tasty&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. Tasty&Healthy was effective in inducing clinical and inflammatory remission in several recent clinical trials: In the TASTI-MM RCT on 83 children and young adults with mild-to-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]; $P = .1$).[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 versus habitual diet [37% vs. 15%; $P = .028$] 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],[121,123] although long-term effects on height may be limited.[141] Anti-TNF therapy is associated with significant improvements in weight, height, and BMI within 12-24 months.[139] Comparative studies suggest that EEN and anti-TNF agents offer similar short-term outcomes,[133,134] but anti-TNF agents may lead to superior linear growth.[141] Early anti-TNF monotherapy shows higher remission rates and greater catch-up growth in height and weight compared with other strategies.[142–144]

Corticosteroids

A MA on the induction of clinical remission in adults with CD confirmed the effectiveness of corticosteroids.[145] In children, up to 90% of pediatric patients have a rapid symptomatic response with prednisone equivalent of 1-2 mg/kg per day [maximum, 40-60 mg].[146] In a pediatric randomized open-label trial, budesonide 9 mg/d [all children > 20 kg] 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 pediatric trial, higher exposure to budesonide was associated with decreased CRP; the proportion of patients with normal CRP values was not reported.[148] Prednisone/prednisolone should be administered once daily [1 mg/kg, not exceeding 40 mg] in the morning and should be tapered and stopped within 8-10 weeks. For patients > 40 kg, the initial dose of budesonide is 9 mg once daily for 1 month, then 6 mg for the second month, and 3 mg in the third month, depending on clinical response. Children weighing 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.[149]

EEN versus corticosteroids in children

An RCT of 19 children with CD showed a much higher rate of ER with EEN [89%] than with steroids [17%].[150] 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.[151] 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 versus steroids, likely due to the tendency to repeat the induction intervention during the disease course when needed.[152]

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. Among 5 children with active CD treated with CD-TREAT, 3 achieved clinical remission with significant reductions in FC.[153] 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.[154] 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 have demonstrated the benefit of antibiotics in inducing remission in CD, the large heterogeneity of drugs, dosing, population, design, and outcomes across the studies prevents recommending antibiotics routinely.[155] In the AZCRO RCT, azithromycin with metronidazole were more effective than metronidazole for inducing clinical remission [$P = .025$].[156] 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 administered twice daily 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 decreased from baseline to a median of 190 µg/g.[157]

A MA revealed that a mesalamine dose > 2.4 g/day was effective in adults with CD, but less effective than corticosteroids. Another MA of RCTs conducted in adults on methotrexate showed no significant effect on inducing clinical remission.[158]

7. Maintenance therapy

7.1. Patients who respond to anti-TNF agents during induction should be treated with the same drug to maintain remission (LoE: 2) (100% agreement)

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

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

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

7.5. We recommend against the use of corticosteroids in the maintenance of remission (LoE: 3) (100% agreement)

Anti-TNF maintenance therapy

Anti-TNF therapy initiated to induce remission should be continued, as infliximab and adalimumab have well-characterized efficacy as maintenance treatment for pediatric CD.[159–161] 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 commonly employed strategy is to de-escalate to anti-TNF monotherapy. Note that this recommendation is for patients with luminal CD, and the considerations for perianal disease may be different [see Section 10].[162]

In studies that have assessed immunomodulator withdrawal and anti-TNF agent continuation, a lower risk of relapse was observed when immunomodulators were withdrawn and anti-TNF therapy was continued when compared with withdrawing the anti-TNF agent.[163] 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 1 year.[164] In another single-center retrospective cohort study of 126 children with CD who de-escalated from combination therapy to anti-TNF monotherapy, there was no significant effect on disease relapse after a median of 1.7 years.[165] During 1 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 pediatric patients with CD, while continuing azathioprine monotherapy after at least 1 year of clinical remission.[166] The median time to relapse was 3.3 years; infliximab levels < 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 were subsequently treated with an immunomodulator.[167] Relapse-free survival rates at 12, 24, and 36 months were 83.3%, 71.1%, and 23.7%, respectively. Conversely, a small pediatric prospective cohort study [$n = 17$] showed no difference in sustained remission at 1-year follow-up between the two strategies.[168] Data from the 7-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 agents did not need to restart biologic therapy and did not develop major complications.[169]

Sustained clinical and biochemical remission should be verified and anti-TNF TCs and ADAs should be measured before considering de-escalation of immunomodulator to anti-TNF monotherapy. For patients receiving combination therapy with an anti-TNF agent and an immunomodulator, we recommend stopping the immunomodulator rather than the anti-TNF agent. 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 the immunomodulator (Relative Risk [RR]: 1.15; 95% CI: 0.75-1.76), but there was a significantly increased risk when the anti-TNF agent was withdrawn [RR: 2.35; 95% CI: 1.38-4.01].[170] 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 with continuing combination therapy or de-escalating to anti-TNF monotherapy.[171] Similarly, in the only uncontrolled pediatric retrospective cohort study in which continuation or withdrawal of one or both therapies were assessed, relapse was associated with anti-TNF agent but not immunomodulator withdrawal.[172]

FC is a valuable biomarker in predicting relapse after anti-TNF withdrawal,[173] particularly when used adjunctively with other clinical, biochemical, and endoscopic parameters. In an RCT of 140 adults with IBD, FC > 250 µg/g before anti-TNF agent withdrawal was associated with a lower likelihood of sustained clinical remission and a higher risk of loss of clinical remission at the end of 1 year.[174] However, pediatric data remain limited.

In conclusion, criteria for de-escalation should include a disease activity score suggestive of remission and normal complete blood count, CRP, ESR, and albumin. A FC level consistent with remission and appropriate anti-TNF TCs and absence of ADAs are factors associated with better outcomes following withdrawal of therapy. In patients who are de-escalated to anti-TNF agent monotherapy, regular reassessment of clinical and biochemical markers of inflammation [e.g., every 3 months for at least 12 months] along with imaging (e.g., IUS) is recommended.

Thiopurines

Thiopurines [azathioprine, mercaptopurine] are prodrugs that are metabolized into the active metabolites thioguanine nucleotides [TGN] and methyl mercaptopurine [MMP] under pharmacogenomic regulation, particularly Thiopurine S-methyltransferase [TPMT] and Nudix Hydrolase 15 [NUDT15]. Low-grade evidence from a Cochrane SR in adult patients found that thiopurine monotherapy was superior to placebo for maintenance of disease remission in low-risk CD.[175] However, thiopurine monotherapy had a greater adverse event profile, including leukopenia, pancreatitis, gastrointestinal intolerance, and infections that led to withdrawal.[175] In the same MA, thiopurine monotherapy was inferior to maintenance anti-TNF therapy in RCTs. A single pediatric 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 2.5-3 mg/kg/day of azathioprine or 1-1.5 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. Thiopurine dosing should be optimized based on individual TPMT activity/genotype, 6-TGN, and MMP results.[176] 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 testing metabolite levels during thiopurine therapy. Only two studies assessed the use of dose optimization in a prospective, controlled manner.[177,178] Although neither study demonstrated a benefit from dose optimization, both had methodologic issues that limited their findings. In addition to adjusting doses to balance efficacy and toxicity, thiopurine TDM is useful for monitoring treatment adherence.

Testing for TPMT and NUDT15 [particularly in non-Caucasian populations] genotype or activity[179] before starting thiopurines helps 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 TGN levels, resulting in subsequent lack of efficacy. In such cases, adding allopurinol may be an appropriate treatment option in experienced centers, with close monitoring given the increased risk of toxicity.[180] 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,[176] 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 × 10^8 erythrocytes and another identifying a cutoff of 397 pmol/8 × 10^8 erythrocytes for ER in CD.[181–183] As combination therapy with infliximab, lower levels [>125 pmol/8 × 10^8 erythrocytes] may be sufficient to prevent immunogenicity and assist in achieving higher infliximab TCs, although other data support standard thiopurine dosing.[184]

Methotrexate

The therapeutic methotrexate dose for maintenance of remission is 15 mg/m^2 once weekly up to a maximum dose of 25 mg once weekly. The time required for a therapeutic effect is at least 6-8 weeks. Subcutaneous administration is preferable initially to optimize steady-state absorption. Switching to the oral formulation can be considered after 4-6 months of sustained remission. Dose reduction to 10 mg/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.[96] In a study on 65 newly diagnosed children on methotrexate monotherapy, ER at 1 year was observed in 22% of all starters and 39% of those still on therapy.[185] Prophylactic ondansetron and regular folate supplementation [5 mg per week] may help to ameliorate methotrexate-associated gastrointestinal intolerance and side effects. Adolescents should be counselled 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.[186] Although most studies have focused on inducing remission and only a few on maintaining remission, using diet to maintain remission is an attractive option.[187] While use of EEN is supported by strong evidence for induction, it is generally impractical for maintenance due to cost, taste fatigue, and psychological impact.[188]

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.[189] A MA demonstrated reduced disease relapse with up to 1 year of MEN compared with no diet therapy, with benefits detectable at dosages of at least 35% of daily kcal [35%-50% enteric nutrition, OR: 0.42; 95% CI: 0.27-0.65; $P = .0001$; >50% enteric nutrition, OR: 0.27; 95% CI: 0.08-0.88; $P = .03$].[190] Another MA also reported on maintenance of remission up to 0.5-1 year in 76% versus 48% in controls [RR: 1.32; 95% CI: 1.07-1.64; $P = .01$].[191] However, many of the supporting studies were small, and in a retrospective study, only 16/105 who started MEN maintained this therapy to 12 months, most of whom required additional therapies.[192]

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,[193] 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 clinical remission at week 6 maintained it to week 24 on CDED.[193] Some real-life studies further support the feasibility and efficacy of CDED maintenance.[128,194,195] In addition, preliminary data suggest that Tasty&Healthy may be suitable for maintenance in selected patients. 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.[137]

The Mediterranean diet appears to be feasible for long-term use and offers additional benefits, but data are limited.[196] 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.[197] Other diets have been explored with mostly inconclusive results.[197,198] Other studies have examined low red meat and low refined carbohydrate diets for the prevention of CD flares with no benefits observed [RR: 0.99 and RR: 1.04, respectively].[199] In conclusion, dietary therapy without medical treatment for maintenance is a therapeutic option only for a minority of pediatric CD patients with low-risk, uncomplicated phenotype, and, if considered, should warrant close clinical, biochemical, endoscopic, and radiologic monitoring.

Aminosalicylates

Adult and pediatric guidelines recommend against the use of aminosalicylates in CD, with a MA showing no benefit for induction or maintenance of remission.[4,5,200] Nevertheless, 5-ASA preparations have been widely used in adult patients with CD,[201] but their use appears to be dropping [21% in 2005 to 11% in 2019 in a nationwide analysis from Israel].[202] 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.[202] 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].[203] In older studies before the year 2000, 5-ASA was suggested to be effective in preventing recurrence of CD after surgery [number needed to treat: 13].[204] Chemoprotection from developing colorectal cancer using 5-ASA has been established in ulcerative colitis [UC], but there

is no evidence to support this in CD, including in adults.[205] Although very few studies provide details, there are some data describing higher use of 5-ASA in VEO-IBD, with the additional advantage of the availability of liquid formulation.[206] This is likely related to the very high colonic involvement in VEO-IBD.[206]

Corticosteroids

While prednisone and budesonide have a proven role in inducing remission, they should not be used for maintenance, 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.[207]

8. Therapeutic drug monitoring of anti-TNF agents

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

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 therapeutic drug monitoring during induction (LoE: 2) (96% agreement)

Drug clearance of anti-TNF agents is specifically increased in young children, leading to lower TCs and a higher rate of ADAs.[91] A high BMI is also associated with increased clearance of monoclonal antibodies.[208,209] In a large cohort of children with IBD treated with anti-TNF agents [$n = 637$], overweight was associated with risk of relapse and need for treatment intensification.[210] Conversely, weight-based dosing of patients with low weight can result in underdosing and lower TCs.[210,211] In children with VEO-IBD, higher infliximab doses may be required to achieve adequate drug exposure, supporting the potential use of BSA-based dosing, typically 200 mg/m^2 for infliximab.[212] Infliximab TCs 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.[213] Compared with infliximab, higher adalimumab TCs may be required to achieve the same exposure-response relationship.[214] Indications for more frequent anti-TNF TDM [e.g., during early induction and throughout maintenance] include conditions with increased anti-TNF agent clearance, such as 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 for TDM with anti-TNF agents during induction and maintenance in pediatric patients with CD. Achievement and maintenance of clinical, biochemical, and more stringent outcomes, such as ER and transmural healing, correlate with higher infliximab TCs and have an exposure-response relationship.[215] Minimum infliximab TCs before the second, third, and fourth infusions [TC before the fourth infusion represents maintenance TC] should ideally be 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 pediatric cohorts, where an infliximab TC > 7 µg/mL before the fourth infusion is associated with sustained clinical remission.[216,217]

In general, the more stringent the target, the higher the required optimal maintenance TC cut-off.[214] Infliximab TCs from 3 to 9.7 µg/mL [and more commonly > 8µg/mL] are associated with ER in adult studies.[218–221] Based on these findings, target infliximab TC during maintenance should be ≥ 8 µg/mL to achieve deep remission. TCs > 10 µg/mL during maintenance are often required in cases of high inflammatory burden, complicated disease, and fistulizing perianal disease.[222–224]

For patients switching from intravenous to subcutaneous infliximab, the suggested optimal cut-off concentration for clinical and biochemical remission was 12.2 and 13.2 µg/mL at weeks 12 and 52 following the switch, respectively,[225] whereas the thresholds for ER and transmural healing were 17.5 and 30.3 µg/mL, respectively.[226]

TDM of adalimumab during induction and maintenance

Adalimumab TCs respond almost linearly to escalation and de-escalation.[227] Data on desirable adalimumab TCs during induction or immediately post-induction [week 4] are scarce. Prospective and retrospective pediatric cohorts reported different week 4 TCs [22.5 and 13.8 µg/mL] that were associated with clinical and biochemical outcomes.[103,228] The reported optimal adalimumab cutoff for clinical outcomes during maintenance treatment varies across studies.[95,214,229] In a large cohort of 213 children, TCs consistently >7.5 µg/mL were associated with durable clinical remission.[230] In the PAILOT RCT, a threshold of 5 µg/mL was better than lower thresholds in achieving clinical and biological remission.[103] In adult studies, higher TCs [8-12 µg/mL] are required to achieve ER.[231–235] In pediatric studies, optimal TCs are 8.2 µg/mL [$n = 28$][231] and 10 µg/mL [$n = 62$].[230] Based on these findings, adalimumab TCs during maintenance should be ≥ 10 µg/mL to achieve deep remission. Perianal fistula healing may require an even higher adalimumab TC, as described in adult cohorts.[236,237]

Proactive versus reactive TDM

The utility of reactive TDM is based on data demonstrating a clear association between loss-of-response and either low TCs or high ADAs during induction and maintenance.[95,237,238] Reactive TDM of anti-TNF agents is superior to empiric optimization in terms of clinical response, immunogenicity, ER,[239] drug retention,[240] and cost-effectiveness.[241–243] A recent MA of 9 studies concluded that proactive anti-TNF TDM is not more effective than clinically based dosing 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.[244]

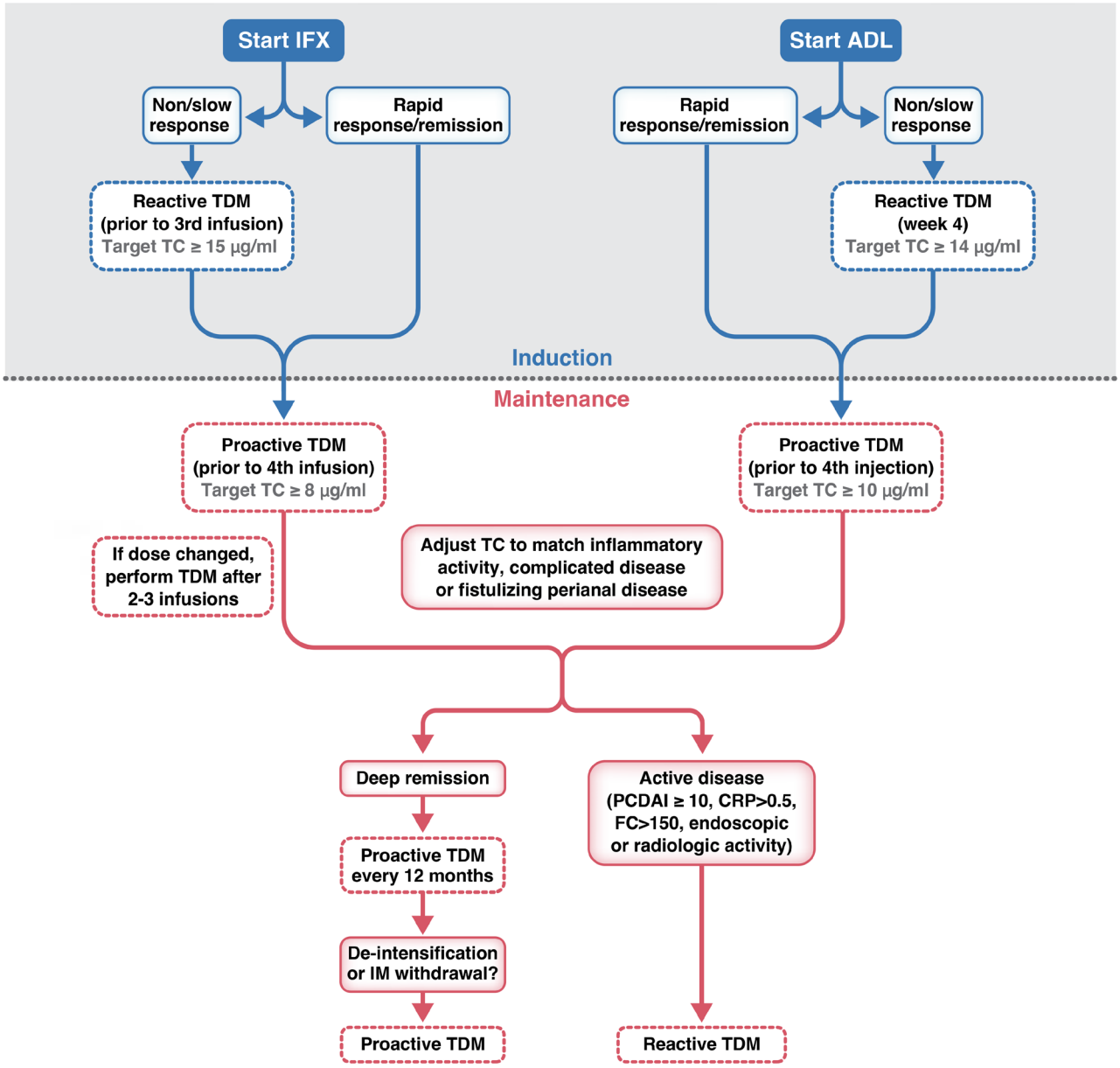

Figure 3. Therapeutic drug monitoring of anti-TNF agents in induction and maintenance phases in pediatric patients with Crohn's disease. ADA, adalimumab; IFX, infliximab; IM, immunomodulator; TC, trough concentration; TDM, therapeutic drug monitoring.

Most retrospective adult[245–247] and pediatric cohorts[248–253] assessing the benefits of a proactive approach reported superiority of proactive over reactive or no TDM. In the PAILOT RCT assessing proactive versus 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%; $P = .02$], 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 clinically based dosing [80% vs. 57%; $P = .02$ and 89% vs. 70%; $P = .019$, respectively].[252] Clinical relapse following immunomodulator withdrawal from infliximab combination therapy was associated with lower infliximab TC,[165,253] whereas sustained remission was associated with a minimal threshold of 5 µg/mL before withdrawal. TC-based infliximab de-escalation is also associated with decreased risk of relapse in both adults and children with IBD.[166,254]

9. Advanced therapies beyond anti-TNF agents

9.1. In patients who have failed to respond satisfactorily, have secondary loss of response, or are intolerant to anti-TNF agents, ustekinumab or an anti-IL23p19 agent are recommended (LoE: 3), with some adult data suggesting a benefit of anti-IL23p19 agents over ustekinumab (96% agreement)

9.2. In patients who have failed to respond satisfactorily, have secondary loss of response, or are intolerant to anti-TNF agents, upadacitinib may be considered (LoE: 4) (93% agreement)

9.3. In patients who have failed to respond satisfactorily, have secondary loss of response, or are intolerant to anti-TNF agents, 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 p40 subunit of IL-12 and IL-23, induces and maintains remission in adults with active CD, with better responses among anti-TNF-naive patients with shorter disease duration than among anti-TNF-experienced patients.[255] Phase 1 and 2 pediatric trials demonstrated that efficacy, pharmacokinetics [up to 1 year], safety, and immunogenicity [up to 4 years] were broadly comparable with outcomes reported in adults.[256–258] The Phase 3 UNITI-Jr 1-year outcomes in 48 patients weighing > 40 kg [60% bio-naive] supported the spring 2025 European Medicines Agency approval of ustekinumab for children and adolescents with CD in this weight range who have failed conventional or anti-TNF therapy.[257] Following open-label intravenous induction and randomization to q 8 weekly versus q 12 weekly maintenance, 25/48 patients [52.1%; 95% CI: 38.3%-65.5%] achieved steroid-free clinical remission at week 52. The lighter and younger patients enrolled in UNITI-Jr, who received a 250 mg/m^2 induction dose, had 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.[259]

Real-world retrospective pediatric observational data support the safety and efficacy of ustekinumab as a treatment option for pediatric patients who are intolerant to or have CD refractory to anti-TNF agents, with clinical remission rates ranging from 40% to 60% at 32 and 52 weeks.[260–263] In a retrospective report of 69 children whose maintenance interval was shortened to less than 8 weeks or who underwent intravenous re-induction, 67% and 42% achieved clinical response and remission following treatment escalation, respectively.[264] The usefulness of switching to ustekinumab in the setting of psoriasiform skin lesions induced by anti-TNF agents has been documented specifically in pediatric patients.[265]

Data on ustekinumab in bio-naive children and adolescents are emerging. A recent prospective multicenter Canadian study revealed that 39/61 [64%] patients achieved the primary outcome of steroid-free clinical and biochemical remission at 1 year with continued ustekinumab.[266] Overall, the body of evidence on the efficacy of ustekinumab monotherapy in achieving and maintaining clinical remission in CD, combined with low immunogenicity and good durability and safety may support its use as an alternative to anti-TNF agents as a first-line biologic in pediatric CD.[267–271] This is particularly relevant given that biosimilars are already available for patients > 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],[257] indicating considerably less immunogenicity than anti-TNF agents. A similarly low rate of ADAs was observed in the long-term extension study in pediatric CD.[257] Therefore, monotherapy of ustekinumab is common practice.

Anti-IL23p19 agents

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 intravenous induction and subcutaneous maintenance in adults with moderate-to-severe CD who failed either conventional or prior biologic therapy.[272–275] The efficacy of these 3 agents is similar.[276] Some adolescents were included in the risankizumab trials, leading to approval for pediatric patients aged > 16 years in the U.K., Japan, and Israel. Risankizumab 600 mg intravenously at weeks 0, 4, and 8 resulted in clinical remission at week 12 in 35%-43% of patients, with no additional benefit observed with the 1200 mg dose.[277] 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.[278] 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% vs. 41% for placebo].[278]

In the open-label, randomized Phase 3 b 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%; $P < .001$].[274]

In contrast to the risankizumab placebo-controlled trial, the Phase 3 RCTs of mirikizumab and guselkumab, which included bio-naive and bio-experienced patients, also had a ustekinumab comparator arm. A MA of these head-to-head ustekinumab versus anti-IL23p19 RCTs and the SEQUENCE trial concluded that IL-23p19 antagonists may be more effective than ustekinumab in achieving clinical and ER in patients with prior anti-TNF exposure, although superiority in biologic-naive patients remains unproven.[274,275]

Data on pediatric patients with CD treated with risankizumab are limited. In the first retrospective study of 103 patients with CD who started risankizumab, corticosteroid-free clinical remission was achieved in 51%, 62%, and 65% at end-of-induction, week 26, and week 54, respectively.[279] Results are currently unavailable from studies of mirikizumab and guselkumab in a pediatric platform trial.

Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody that binds to the α4β7 integrin and therefore inhibits lymphocyte trafficking, specifically in the intestinal tract. In the

registration trials, 14.5% and 31.4% of patients treated with vedolizumab 300 mg intravenously at weeks 0 and 2 achieved clinical remission and clinical response at week 6, respectively, 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 of adult patients.[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 RR: 1.52; 95% CI: 1.24-1.87, respectively].[283]

The Phase 2 pediatric HUBBLE trial included 45 children with CD, 47% of whom were <30 kg. Participants were randomized based on weight to receive either low- or high-dose vedolizumab [150 mg or 300 mg for those ≥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 4/11 [33.3%] and 4/10 [40%] patients weighing ≥30 kg and <30 kg, respectively. Twenty-five percent of the older and heavier children and 50% of the younger and lighter children were bio-naive. No dose-response relationship was observed.[284] VEDOKIDS was a pediatric, multicenter, prospective open-label cohort study where vedolizumab was administered intravenously at the suggested dose of 177 mg/m^2 [up to 300 mg/m^2]. Among 65 patients with CD [31% bio-naive], 21 (32%) were in steroid-free and EEN-free remission at 14 weeks,[281] which was more common in children with isolated colonic CD [L2] than in those with L1 or L3 location. In children < 30 kg, the dose required to reach the optimal drug concentration at week 6 was 200 mg/m^2 BSA.[285] Analysis up to week 54 revealed that the median wPCDAI score decreased from 35 [interquartile range: 18-49] at baseline to 13 [interquartile range: 0-25], with 16 [25%] children in complete remission.[286]

These two prospective pediatric 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 1 year reached up to 45%. Jossen et al. included endoscopic outcomes, reporting ER in 80% of anti-TNF-naive children and in 54% of anti-TNF-experienced children.[291]

TDM of non-anti-TNF biologics

Data for the exposure-efficacy relationships for other biologics are less consistent than those for anti-TNF agents. An exposure-response relationship was observed for ustekinumab in registration trials.[256,292] 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.[256] In a prospective single-center study of patients with refractory CD, a minimal ustekinumab exposure of 4.2 µg/mL was required at week 8 to achieve a 50% decrease in FC, which was also an independent predictor of endoscopic response at week 24.[293] A single retrospective study [n = 83, proactive: n = 46] revealed better outcomes of proactive ustekinumab TDM versus reactive TDM regarding drug survival and hospitalizations.[293] Nevertheless, in a cross-sectional study of 110 adult patients with CD, the addition of TDM into routine clinical practice did not significantly affect clinical decisions.[294]

Few studies have investigated the pharmacokinetics of vedolizumab and ustekinumab in pediatric patients.[257,264,268,295] Although these studies showed exposure-response relationships similar to those in adults, specific target levels for these drugs in children have not frequently been described. However, a recent prospective multicenter Canadian pediatric study 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 µg/mL for 1-year corticosteroid-free remission and intestinal healing, respectively.[296]

A preliminary report on 28 patients with CD treated with risankizumab [n = 28] found that patients in clinical and biochemical remission at week 12 had higher TCs than those without remission [21.6 ± 13.3 vs. 7.4 ± 6.4 µg/mL, respectively; P = .001]. ROC curve analysis identified a week 12 threshold of 11.5 µg/mL associated with clinical and biochemical remission.[297]

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,[298–299] 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.[300] In a prospective multicenter study in a combined population of patients with CD and UC, a vedolizumab TC > 18 µg/mL at week 6 was the only independent variable associated with ER within the first year of treatment.[301] The LOVE-CD trial in adults demonstrated that TCs > 10 µg/mL at week 22 were associated with ER at week 26.[302] 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.[303] Nevertheless, in a study of 161 adult patients with IBD who underwent vedolizumab intensification, pre-intensification TCs were comparable or higher among those subsequently attaining post-optimization clinical, biomarker, and ER when compared with non-remitting patients, implying that TDM-based intensification is not superior to clinically based intensification.[304] This same observation was made in a pediatric study of 50 patients.[289]

Upadacitinib

Janus kinase [JAK] inhibitors are small molecules that can be administered orally. Upadacitinib, a selective JAK inhibitor, preferentially inhibits JAK1, a key enzyme in inflammatory cytokine signaling. Upadacitinib is the first JAK inhibitor shown to have efficacy in CD 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 with 13.1% and 3.5% in participants treated with placebo.[305] Prior anti-TNF exposure did not significantly affect these clinical and endoscopic outcomes.[306] Clinical response was observed within a few days.[307] 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.[306] Week 52 clinical remission rates among induction responders treated with 15 mg or 30 mg upadacitinib or placebo were 37.3%, 47.6%, and 15.1%, respectively. The most significant adverse events were increased rates of herpes zoster infections in patients receiving upadacitinib and increased neutropenia among patients receiving 30 mg upadacitinib. Gastrointestinal perforations were observed in 6 patients treated with upadacitinib in either the induction trial or the maintenance trial.

The largest pediatric study on upadacitinib therapy retrospectively included 100 children and adolescents with refractory CD.[308] At the end of the 8-week induction period, clinical response, clinical remission, and corticosteroid- and EEN-free clinical remission were observed in 75%, 56% and 52% of patients, respectively. Most of the patients also achieved biomarker remission. Adverse events were observed in 24 patients. The most frequent adverse event was acne [$n = 12$], and 2 adverse events [severe acne and hypertriglyceridemia] led to discontinuation of therapy.[308]

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 MAs reported on the efficacy of second-line treatments in biologic-experienced adult patients with luminal CD, but these analyses were limited and should be interpreted with caution. Attauabi et al. [$n = 7414$] observed that upadacitinib and risankizumab induced the highest clinical responses in patients who have failed biologics except infliximab.[309] Barberio et al. [$n = 8720$] showed that risankizumab ranked first for clinical remission in biologic-exposed patients.[310] Singh et al. [$n = 2479$] reported that adalimumab [in patients who had lost response to infliximab] and risankizumab were associated with higher odds of inducing remission.[311] A comparative study [$n = 2539$] found that non-anti-TNF agents as a second line were superior to a second-line anti-TNF agent, although the absolute differences were small.[312] 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.[313] 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 hazard ratio [HR]: 0.66; 95% CI: 0.54-0.82].[314] Comparable results were reported in other real-world studies.[315]

To conclude, data regarding the optimal therapeutic sequencing after anti-TNF agent failure are limited due to lack of head-to-head studies, the inherent limitations of network MAs, the limited data in the adult population, and the absence of pediatric data. Based on available data, ustekinumab or selective anti-IL23p19 agents are recommended as second-line therapy after failure of anti-TNF agents,[315] with adult data suggesting superiority of risankizumab over ustekinumab.[274] 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.[289]

Advanced combination therapy

While advanced combination therapy [ACT] leads to high rates of clinical and biomarker remission in patients with refractory IBD, the rates of deep healing were reportedly low.[316] The largest pediatric series on ACT reported on 62 children [35 with CD] with highly refractory IBD.[317] The most frequent combinations were 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.[317] 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 included in the combination]. Comparable remission rates with ACT were reported in smaller pediatric case series.[318–322]

In a MA that included predominantly an adult population [$n = 266$; 29 children], the pooled clinical remission rates with ACT ranged from 40% to 80%, together with a generally favorable safety profile.[323] The pooled endoscopic and 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.[324] 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-IL23p19 agent, or vedolizumab.

10. Management of patients with perianal CD

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 agents are 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 an anti-TNF agent. 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, anti-TNF agents, or both in the management of perianal Crohn's disease. 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 fistulae (LoE: 4) (96% agreement)

10.6. Diversion of fecal 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 Crohn's disease [pCD] is associated with a high need for immunosuppressive therapy, surgery, hospitalization, and impaired QoL, with specific challenges due to its effects on continence and body image.[325,326] Inception cohort analysis revealed that pCD is more common in pediatric-onset than in adult-onset CD (308/2186 [14%] vs. 433/1222 [11%]; $P < .001$).[327] A MA of 12 population studies that included patients with CD of all ages revealed that 18.9% [95% CI: 15.0-23.4%] developed pCD by 10 years after diagnosis.[328]

The cornerstone of successful pCD management is a combined medical and surgical approach, in both decision-making and treatment strategy.[329] 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 target is fistula repair, symptomatic control in a currently irreparable fistula, or to determine whether disease is rapidly progressive or gradually debilitating to the extent that defunctioning may be the best option (Figure S1 [see online supplementary material for a color version of this figure], adapted from Geldof et al.).[6,330] Although not explicitly designed for a pediatric population, we advocate using this classification system to determine clear treatment targets.

Anti-TNF agents for pCD

Infliximab has the strongest RCT data in perianal disease. A SR of the efficacy of anti-TNF agents in pediatric pCD demonstrated that 326/565 [58%] patients achieved clinical remission.[331] Another SR identified 197 pediatric patients across 4 studies who received infliximab therapy for pCD; 110 [55%] and 33 [17%] achieved complete remission and partial response, respectively.[332] 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, although many of the patients included within this cohort also underwent surgery within the study period.[332]

In a multicenter inception cohort where pCD was managed with infliximab, higher post-induction infliximab TCs were associated with improved outcomes in perianal fistulizing disease.[224] The median TC before the fourth infliximab infusion was 12.7 [6.6-15.5] μg/mL in responders compared with 5.4 [2.7-8.4] μg/mL in non-responders. There was also a significant correlation between TC and healing at week 24.[224]

When considering pediatric data supporting adalimumab in pCD, a sub-analysis of the IMAgINE 1 and IMAgINE 2 studies reported short- and long-term outcomes.[333] Thirty-six patients were included in the week 12 analysis, which showed fistula closure and response rates of 44.4% and 52.8%, respectively. Most patients who entered IMAgINE 2 with a healed fistula maintained fistula healing at 2 years [64% hybrid non-responder imputation, 100% as observed].[333] In adult patients, 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.[6,334–336] 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.[95]

Advanced therapies beyond anti-TNF agents for pCD

There has been no RCT to specifically address ustekinumab in pCD in adults or children. In the pediatric population, a GETAID study identified 20 patients with disease refractory to anti-TNF agents who received ustekinumab for pCD, 9 of whom also underwent surgery. Of these patients, 10 showed improvement with ustekinumab.[263] Kim et al. also retrospectively evaluated outcomes of 13 children with pCD who received ustekinumab, all of whom were anti-TNF experienced. At the end of follow-up, 5 patients were in remission, with a statistically significant decrease in PCDAI across the cohort.[260]

In adults, a SR and MA identified 396 adult patients within 9 studies 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.[338] At 52 weeks, rates were 55.9% [95% CI: 40.8%-69.9%] and 16.7% [95% CI: 3.0%-56.5%]. However, it should be noted that there were small sample sizes [$n = 44$] and significant heterogeneity, and many of those included were patients with refractory disease and 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 in adults [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, $P = .024$].[340] There are no published RCTs of upadacitinib in children with CD; as such, a recommendation has been softened for consideration in the pediatric population.

There have been no studies specifically powered to evaluate vedolizumab as a treatment for 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 fistulae across 4 studies, 87% of whom had failed previous anti-TNF therapy.[341] 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 pCD

The choice of surgical technique for pCD depends upon fistula characteristics and is outlined in the adult CD treatment guidelines.[6] Broadly, pediatric patient guidance should follow these guidelines when possible, considering 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. However, seton placement alone is associated with low rates of remission at 1 year post-intervention [28.6% in the pediatric population].[6,342] Of note, seton placement prior to anti-TNF therapy is associated with better fistula response [100% vs. 82.6%; $P = .014$], lower recurrence rates [44% vs. 79%; $P = .001$], and longer time to recurrence than with anti-TNF therapy alone [13.5 vs. 3.6 months; $P = .0001$].[343] 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,[6,344–348] advancement flap,[6,349–354] and ligation of the intersphincteric tract[355–357] in patients without active proctitis. There is insufficient evidence to recommend fibrin glue,[358] video-assisted anal fistula closure,[359,360] or fistula laser closure.[361,362] Anal fistula plugs are not recommended.[6,363–365]

Although there are some data that ciprofloxacin may improve outcomes with anti-TNF agents in the short term, there is no evidence that antibiotics improve long-term fistula outcomes.[366–368] As such, we do not recommend antibiotics alone for fistula closure, although we recognize their importance in controlling infection associated with perianal disease.

There are limited data on the outcomes of fecal diversion in the management of refractory perianal disease in children. Dharmaraj et al. evaluated outcomes in children who underwent diversion for refractory colonic or perianal disease [$n=28$]; however, most of these children included in the analysis had a 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 children ultimately required a permanent stoma within a median follow-up of 2.26 [range 0.79-10.2] years. In univariate analysis, perianal disease was predictive of a lower likelihood of restored continuity [$P=.023$].[369] Johnston et al. identified 109 pediatric patients with perianal disease, 12 of whom underwent diversion for refractory disease.[370] Only 3 of these patients [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.[371]

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, fistulae, abscesses, or a refractory disease course.[372–374] Along with medical treatment, endoscopic balloon dilatation [EBD], strictureplasty, and surgical bowel resection [BR] should be used for B2 or B3.[375,376] However, pediatric evidence is limited. In a SR on therapies used in pediatric stricturing CD, recurrence rates following interventions were 9%, 38%, and 47% for BR, strictureplasty, and EBD, respectively, while complications occurred in 11%, 15%, and 6%, respectively.[376] A retrospective study that analyzed 88 EBDs 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.[377] A recent SR and MA of invasive treatment techniques in children demonstrated combined stricture recurrence rates that required surgical intervention of 17.1%, 10%, and 34.7% for EBD, BR, and strictureplasty, respectively. Adverse events occurred most frequently after BR.[375]

Another SR revealed that surgery could be avoided in 50% of adult patients with stricturing disease treated with anti-TNF agents over a 4-year follow-up period, and that EBD was effective for strictures ≤5 cm.[378] A SR on nutritional interventions in stricturing CD concluded that EEN led to clinical improvement in approximately 60% of patients, while total parenteral nutrition was associated with improvement in 75%; in contrast, a liquid diet resulted in no improvement.[83] According to a recent RAND/UCLA consensus statement with SR, patients with confirmed intestinal obstruction should be hospitalized and managed by a multidisciplinary team. Anti-inflammatory medical therapy in the acute setting should only be considered if an active inflammatory component is confirmed (Table S3).[374]

General considerations on therapeutic strategy

We recommend upfront anti-TNF therapy in patients with B2 CD, unless prestenotic dilatation with features of obstruction are present.[6] In patients with disease refractory to anti-TNF agents, who have symptomatic pre-stenotic dilatation, obstructive signs or symptoms, or a combination of these, BR is recommended followed by postoperative anti-TNF therapy. Surgery and postoperative anti-TNF agents are recommended for B3 disease.[4] A 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 Table S4.[374]

Medical prevention of disease recurrence after ileocecal resection

Pediatric evidence is also very limited regarding postoperative medical prevention. According to a recent SR, pediatric patients with CD should receive medical therapy post-resection,[379] and anti-TNF agents seem to provide optimal medical prevention

of disease recurrence.[6] Azathioprine may be an exceptional alternative in very low-risk patients.[380] In adult patients, a MA demonstrated superior efficacy for anti-TNF agents compared with thiopurine prophylaxis.[380] Moreover, a recent adult RCT has shown superiority of vedolizumab over placebo in the prevention of disease recurrence.[381] Regular endoscopic monitoring starting at 6-9 months after surgery and supported by FC evaluation should be used to identify early endoscopic recurrence.[379,381,382] A SR and MA of adult patients revealed that MRE and computed tomography enterography are effective initial screening tools for postoperative disease recurrence.[383] However, computed tomography enterography should be avoided in children as a screening tool.[384]

Perioperative optimization

There are limited pediatric data on perioperative optimization. In 21 pediatric patients with internally penetrating CD complications, including abscesses and phlegmon, anti-TNF therapy prior to complication resolution reduced infectious adverse events, while CD-related surgeries and hospitalizations occurred with similar frequency.[385] 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 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 agents do not increase postoperative complications, and more data are needed for other biologics and small molecules.[386] Another SR revealed that corticosteroids are independent predictors of morbidity, and vedolizumab was associated with increased rates of superficial skin infections and small-bowel obstruction.[387]

ECCO guidelines recommend tapering corticosteroids but not biologics before surgery.[6] Malnutrition and low albumin levels are risk factors for adverse postoperative outcomes.[388] The benefits of preoperative EEN for at least 2 weeks on postoperative morbidity have been consistently reported.[389–391] Thus, when feasible, enteral nutrition should be part of a preoperative optimization strategy, based on nutritional assessment by an IBD-dedicated dietitian as part of a multidisciplinary team.[6]

12. Additional healthcare considerations

12.1. 25-OH vitamin D serum levels 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 Crohn's disease activity. Intravenous iron should be preferred when hemoglobin levels are lower, in moderate-to-severe Crohn's disease 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.[392] Low BMD has been linked to lower BMI z-scores and higher disease activity.[393,394] 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.[395–397] Supplementation may reduce disease activity and inflammation.[398–404] In a randomized trial, vitamin D supplementation improved PCDAI scores, inflammatory markers, and QoL.[405]

Preventative supplementation dosing of vitamin D is 600 IU [15 µg] daily. The following dosing of 25-OH vitamin D3 [cholecalciferol] should be used to treat vitamin D deficiency [<50 nmol/L]: 2000-3000 IU [50-75 µg] a day for children aged < 4 years or 3000-5000 IU [75-125 µg] a day for children aged 4-18 years, with treatment duration 1-3 months depending on the level achieved. A single high dose of oral vitamin D3 [stoss dose: 200 000-600 000 IU] can be equally safe and effective.[406,407]

Dual-energy X-ray absorptiometry [DEXA] is recommended at diagnosis and follow-up for high-risk patients, although interpretation may require bone specialist input due to growth-related limitations.[408] 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

Although iron-deficiency anemia [IDA] is common in IBD and affects up to 90% of patients, IDA often remains underestimated in clinical practice.[409–418] In children with CD, factors such as young age at diagnosis increase the risk of severe anemia, while higher albumin levels offer protection.[419] 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 has an increased side effect profile.[414,417,420]

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.[409] The POPEYE trial in children with IBD revealed that intravenous FCM is superior to oral iron in improving physical fitness more rapidly, although both approaches yielded similar hemoglobin increases by 3-6 months.[421] Overall, oral iron can be used in mild IDA in patients with mild CD activity, while intravenous iron should be preferred when hemoglobin levels are lower [Hb < 10 g/dL], in moderate-to-severe CD activity, or when oral iron is not effective or tolerated. An important side effect of FCM is hypophosphatemia; in a retrospective study of 94 children who received FCM, 25 [26.6%] developed hypophosphatemia, which was severe in 2 children.[422] Nevertheless,

in the POPEYE trial that included 33 pediatric patients with IBD treated with FCM, no case of hypophosphatemia was reported. Follow-up phosphate measurements in symptomatic patients receiving FCM are advised.[422]

Venous thromboembolism prophylaxis

Thrombotic events are more common in patients with IBD than in the general population, with the incidence of venous thromboembolism [VTE] in children ranging from 4 to 30 per 10 000 patient-years.[423–433] A large, prospective, international pediatric study [PIBD-SET Quality Safety Registry] reported an incidence of 3.72 per 100 000 person-years, which is significantly higher than in healthy children.[432] Risk factors for VTE are presented in Table S5. Whereas acute severe colitis in hospitalized patients with UC is a well-established indication for initiating VTE prophylaxis, the recommendations for hospitalized patients with CD are more nuanced and less definitive.[433] Current evidence supports considering prophylaxis with low molecular-weight heparin [s.c. enoxaparin 1 mg/kg up to 40 mg, once daily] in at-risk hospitalized children (i.e., at least one additional risk factor as in Table S5), often combined with mechanical methods.[434] The use of direct oral anticoagulants for the treatment or prevention of VTE has not yet been studied in the pediatric population.[431]

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, anaemia, 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.[435,436] Psychological and social dimensions have emerged as key priorities in IBD,[437–441] driven by the recognition that remission does not guarantee psychosocial well-being.[439,442,443]

Psychosocial disorders

Patients with CD are at an increased risk of psychological disorders.[444–446] In a recent pediatric 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.[447] Pediatric nationwide studies reinforce these findings.[448–450] For example, Cooney et al. reported increased risks of anxiety/depression in pediatric CD in the U.K. [adjusted HR: 1.39; 95% CI: 1.11-1.74 for anxiety and aHR: 1.41, 95% CI: 1.15-1.74 for depression].[450] 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.[445,449,451–453]

Studies on bi-directional brain-gut interactions highlight a complex interplay between depression and both IBD activity and diagnosis, predominantly in adults.[444,451,454–465] 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.[466] Therefore, maintaining awareness and continuously monitoring the patient's psychosocial status is essential.

A notable gap exists in the availability of tailored tools to assess psychological health in pediatric IBD. While IMPACT III and IMPACT III-P are available for QoL, no pediatric scores exist to assess specific psychosocial domains.[467–471] 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.[472–486]

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.[487–489] Its burden is notable, with a prevalence of 50% in adult patients with IBD.[490] A recent SR identified only 14 pediatric IBD studies on fatigue, of which 2 reported severe fatigue rates; a single-center pediatric IBD cohort experience revealed that 33% of patients had moderate/severe fatigue versus 9% of healthy controls, with 11% and 0% having for severe fatigue, respectively.[491] Unlike in adults, where the IBD-fatigue scale is widely used, no equivalent tool exists in pediatric IBD, although the PROMIS pediatric fatigue score has been used without validation.[468,492] A Cochrane review failed to identify successful pharmacological and non-pharmacological interventions for managing fatigue.[493] Anemia should be assessed as a potential cause of fatigue, and treated accordingly. Otherwise, a high-dose oral thiamine RCT revealed improvement in fatigue among adults with quiescent IBD,[494] while a feasibility RCT is underway following a case series on modafinil for severe fatigue.[495]

Disability is underexplored in pediatric IBD.[496] While the IBD Disability Index and IBD Disk are available for adults, there is no pediatric equivalent. Development of specific tools like the Pediatric IBD Fatigue Index and Pediatric IBD Disability Index is underway, offering hope for targeted assessments in the future.[496,497] While research is ongoing, clinical teams should systematically evaluate daily functioning and psychosocial status, including school engagement, social participation, physical

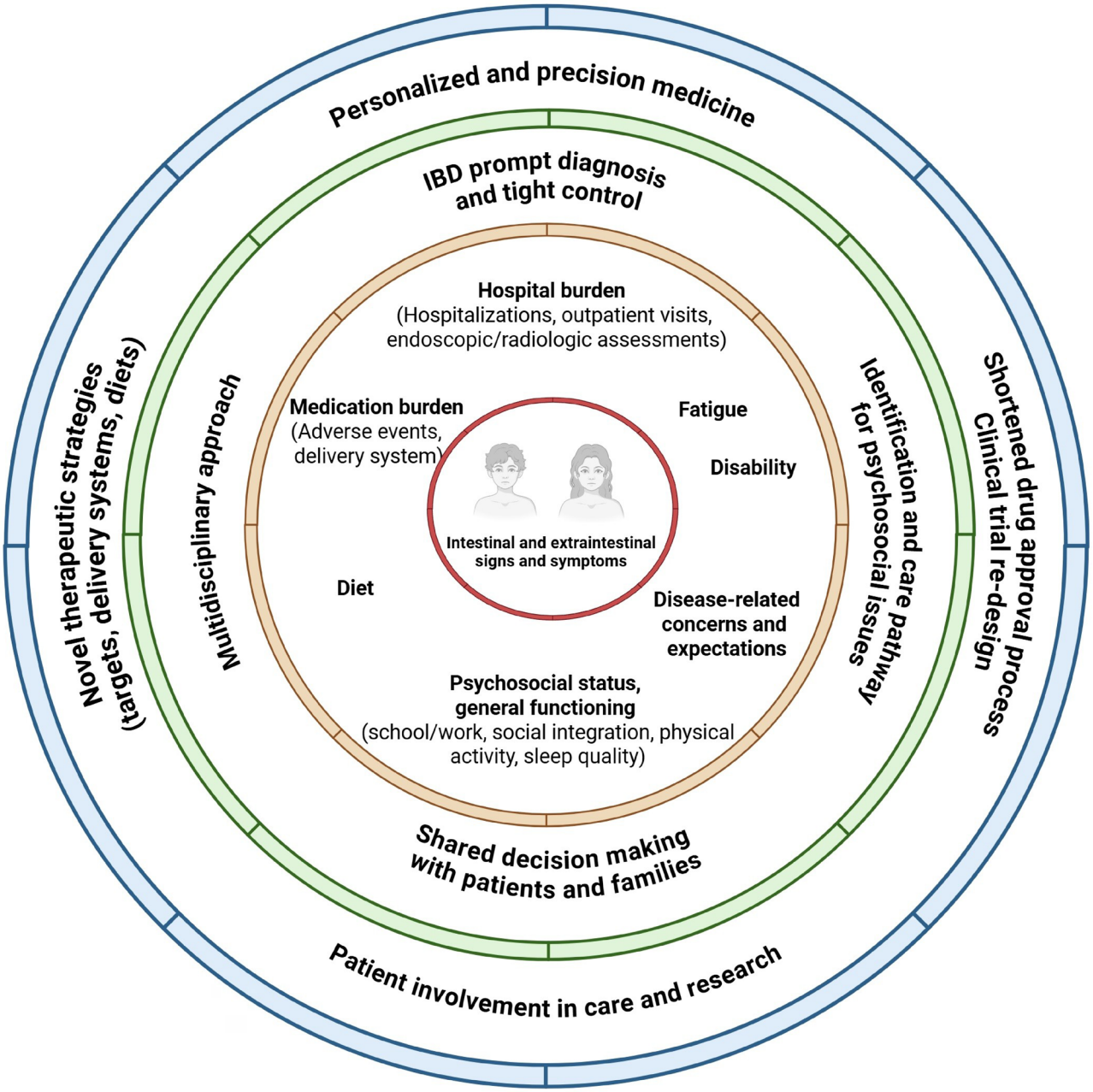

Figure 4. Addressing psychosocial challenges in pediatric patients with Crohn's disease.

activity, sleep, and dietary habits, along with the patient's disease-related concerns and expectations, to identify underlying challenges that may require further evaluation or intervention.[498] When disease-specific tools are unavailable, validated, age-appropriate pediatric tools can support monitoring of well-being (Table S6). Addressing these psychosocial challenges may help improve QoL, pain management, illness perception, and even influence disease outcomes (Figure 4).[455,474,480,486,499–501]

Conclusion

These 2026 updated ECCO–ESPGHAN guidelines provide evidence-based, multidisciplinary recommendations for the management of pediatric CD, reflecting 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 anti-TNF 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, pediatric 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 stable disease remission. In parallel, patient-reported outcomes and QoL 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 pediatric 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 pediatric use.[502] This therapeutic gap restricts access to effective advanced treatments for children with refractory disease and may contribute to disease progression and poor long-term outcomes. Close collaboration among regulators, scientific societies, 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 pediatric populations, and to ensure timely and equitable access to innovative therapies.

Acknowledgments

We would like to thank Houda Amiri for the literature search and Torsten Karge for support with informatics and the online platform. We would also like to acknowledge the following colleagues who shared their feedback in the second online voting round: ECCO National Representatives: Edmond Baghdasaryan, Ante Bogut, Aleksejs Derovs, Shahida Din, Piotr Eder, Ondrej Hradsky, Željko Krznarić, Lone Larsen, Diana Martins, Gregor Novak, Lieven Pouillon, Elisabeth Schnoy, Spyridon Siakavellas, Svetlana Turcan, Sophie Vieujean, Signe Wildt, and Yamile Zabana, ESPGHAN National Representatives: Antal Dezsofi-Gottl, Mariam Ghughunishvili, Anatoly Khavkin, Darius Lebensztejn, Ivan Milovanovic, Carsten Posovszky, and Claudio Romano, and Additional Reviewers: Michal Brzezinski, Giacomo Calini, Ruben Colman, Jan de Laffolie, Federica Furfaro, Sujin Gang, Simona Gatti, Ben Kang, Amelia Kellar, Paulina Krawiec, Sara Lega, Delphine Ley, Katalin Müller, Victor Manuel Navas-Lopez, Nurulamin Noor, Lorenzo Norsa, Ola Olen, Gianluca Pellino, Joseph Picoraro, Corina Pinar, Chen Sarbagili-Shabat, Raanan Shamir, Malgorzata Sladek, Alessandra Soriano, Helena Tavares de Sousa, Christos Tzivinikos, Karen Van Hoeve, and Aglaia Zellos.

Supplementary material

Supplementary material is available at *ECCO-JCC* online.

Funding

This project was initiated, funded, and supported by the European Crohn's and Colitis Organisation and the European Society for Paediatric Gastroenterology Hepatology and Nutrition.

Conflicts of interest

D.S.S.: Received lecture fees from Takeda and served on the scientific advisory board for Tracells. I.H.: Received lecture fees from Abbott, Takeda, Sandoz, and Nestlé. Ch.S.: President of the Swiss society of pediatric gastroenterology, hepatology and nutrition, Board member of IBDnet, Local PI AbbVie M16-194 and VedoSC-3003. E.M.: Received for the last 3 years consultation fees, research grants, royalties, or honorarium from Danone, Bioprojet, Dicofarm, Pfizer, Recordati, and Takeda. D.T.: Received for the last 3 years consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, AbbVie, Takeda, Lilly, SorrisoPharma, Galapagos, BMS, AlfaSigma, and Merck. K.L.K.: Received for the last 3 years consultation fees from AbbVie, Biocodex, and Ferring. R.S.B.: Received consultation or speaker funds from Nestlé Health Science, Takeda, Megapharm, and Janssen and served on advisory board for Evinature. R.K.R.: Received for the last 3 years consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, AbbVie, Lilly, AlfaSigma, Nestlé Health Sciences, and Ferring. J.C.E.: Received research support from Celltrion and AbbVie and consultancy fees from Janssen. J.M.-d.-C.: Received lecture fees and consultancy and scientific expenses from AbbVie, Adacyte, FAES, Johnson & Johnson, and Nestlé. M.G: Medical Adviser of Crohn's in Childhood Research Association (CICRA) and is principal investigator of commercial trials sponsored by AbbVie (M14-671 and M21-862). A.M.G.: Received for the last 3 years consultation fees, research grants, royalties, or honorarium from AbbVie, Alfasigma, Janssen, Lilly, Pfizer, Roche, Shaare Zedek Medical Center, SickKids Hospital, and Takeda. E.W.: Received consulting or speaker funds from AbbVie, BioJamp, Nestlé Health Science, and Pfizer. Ca.S.: Received for the last 3 years consultation fees, research grants, royalties, or honorarium from Alphasigma, Sanofi, AstraZeneca, Novalac, Takeda, Aboca, and Nestlé. Ld.R.: Served on advisory board for Celltrion and Data Monitoring Safety Board for Alvotech and received lecture fees from Takeda, Janssen, Medtronic, and Pfizer and a grant from Pfizer. J.B.: Received honoraria and consultation or speakers fees and served on an advisory board [all outside of the submitted work] for AbbVie, MSD, Nestlé, Nutricia, Sanofi, Pfizer, and Vitabalans. M.A.: Received lecture fees from Pfizer and Nestle. All other co-authors have no conflicts of interest to declare.

References

1. Kuenzig ME, Fung SG, Marderfeld L, et al. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. *Gastroenterology*. 2022;162:1147-1159.e4.

2. Fumery M, Pariente B, Sarter H, et al. Long-term outcome of pediatric-onset Crohn's disease: a population-based cohort study. *Dig Liver Dis*. 2019;51:496-502.
3. Alvisi P, Labriola F, Scarallo L, et al. Epidemiological trends of pediatric IBD in Italy: a 10-year analysis of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition registry. *Dig Liver Dis*. 2022;54:469-476.
4. van Rheenen PF, Aloi M, Assa A, et al. The medical management of paediatric Crohn's disease: an ECCO-ESPGHAN guideline update. *J Crohns Colitis*. 2021;15:jjaa161.
5. Gordon H, Minozzi S, Kopylov U, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2024;18:1531-1555.
6. Adamina M, Minozzi S, Warusavitarne J, et al. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis*. 2024;18:1556-1582.
7. Ricciuto A, Aardoom M, Orlanski-Meyer E, et al. Predicting outcomes in pediatric Crohn's disease for management optimization: systematic review and consensus statements from the pediatric inflammatory bowel disease-ahead program. *Gastroenterology*. 2021;160:403-436.e26.
8. Grover Z. Predicting and preventing complications in children with inflammatory bowel disease. *Transl Pediatr*. 2019;8:70-76.
9. Levine A, Turner D, Pfeffer Gik T, et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the Porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflamm Bowel Dis*. 2014;20:278-285.
10. Levine A, Chanchlani N, Hussey S, et al. Complicated disease and response to initial therapy predicts early surgery in paediatric Crohn's disease: results from the Porto group GROWTH study. *J Crohns Colitis*. 2020;14:71-78.
11. Haisma SM, Verkade HJ, Scheenstra R, van der Doef HPJ, Bodewes F, van Rheenen PF. Time-to-reach target calprotectin level in newly diagnosed patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2019;69:466-473.
12. Ronconi MS, Neuraz A, Payen E, et al. Long-term outcome of paediatric Crohn's disease patients with deep ulcerations at diagnosis. *Acta Paediatr*. 2025;114:2329-2336.
13. Tan ZV, Kosana K, Savarino J, et al. Histology at diagnostic gastroscopy predicts outcome after intestinal resection in pediatric Crohn's disease. *J Gastroenterol Hepatol*. 2020;35:2074-2079.
14. Yerushalmy-Feler A, Moran-Lev H, Galai T, Cohen S. Predictors for complicated disease course after stepping down from combination to antitumor necrosis factor alpha monotherapy in children with inflammatory bowel disease. *Digestion*. 2020;101:121-128.
15. Klamt J, de Laffolie J, Wirthgen E, Stricker S, Dabritz J, Group C-Gs. Predicting complications in pediatric Crohn's disease patients followed in CEDATA-GPGE registry. *Front Pediatr*. 2023;1511:1043067.
16. Akkelle BS, Sengul OK, Volkan B, et al. Outcomes of pediatric fistulising perianal Crohn's disease. *Turk J Gastroenterol*. 2021;32:240-247.
17. Ricciuto A, Mack DR, Huynh HQ, et al. Diagnostic delay is associated with complicated disease and growth impairment in paediatric Crohn's disease. *J Crohns Colitis*. 2021;15:419-431.
18. Guz-Mark A, Aloi M, Scarallo L, et al. Infantile and very early onset inflammatory bowel disease: a multicenter study. *Pediatrics*. 2024;1154:e2023064546.
19. Kelsen JR, Conrad MA, Dawany N, et al. The unique disease course of children with very early onset-inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:909-918.
20. Eindor-Abarbanel A, Meleady L, Lawrence S, et al. Progression to anti-TNF treatment in very early onset inflammatory bowel disease patients. *J Pediatr Gastroenterol Nutr*. 2022;75:473-479.
21. Weidner J, Zoch M, Kern I, et al. Predictors of improvement in disease activity in childhood and adolescent Crohn's disease: an analysis of age, localization, initial severity and drug therapy - data from the Saxon Registry for Inflammatory Bowel Disease in Children in Germany (2000-2014). *Eur J Pediatr*. 2024;183:4363-4377.
22. Duricova D, Sarter H, Savoye G, et al. Impact of extra-intestinal manifestations at diagnosis on disease outcome in pediatric- and elderly-onset Crohn's disease: a French population-based study. *Inflamm Bowel Dis*. 2019;25:394-402.
23. Jansson S, Malham M, Paerregaard A, Jakobsen C, Wewer V. Extraintestinal manifestations are associated with disease severity in pediatric onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;71:40-45.
24. Attauabi M, Zhao M, Bendtsen F, Burisch J. Systematic review with meta-analysis: the impact of co-occurring immune-mediated inflammatory diseases on the disease course of inflammatory bowel diseases. *Inflamm Bowel Dis*. 2021;27:927-939.
25. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160:1570-1583.
26. Zubin G, Peter L. Predicting endoscopic Crohn's disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin. *Inflamm Bowel Dis*. 2015;21:1386-1391.
27. Turner D, Levine A, Walters TD, et al. Which PCDAI version best reflects intestinal inflammation in pediatric Crohn disease? *J Pediatr Gastroenterol Nutr*. 2017;64:254-260.
28. Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn's disease: results from the GROWTH CD study. *J Crohns Colitis*. 2018;12:306-312.
29. D'Arcangelo G, Oliva S, Dilillo A, et al. Predictors of long-term clinical and endoscopic remission in children with Crohn disease treated with infliximab. *J Pediatr Gastroenterol Nutr*. 2019;68:841-846.
30. Sipponen T, Savilahti E, Kärkkäinen P, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis*. 2008;14:1392-1398.
31. D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology*. 2018;154:1343-1351.
32. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. 2017;390:2779-2789.
33. Diederen K, Hoekman DR, Leek A, et al. Raised faecal calprotectin is associated with subsequent symptomatic relapse in children and adolescents with inflammatory bowel disease in clinical remission. *Aliment Pharmacol Ther*. 2017;45:951-960.
34. Kostas A, Siakavellas SI, Kosmidis C, et al. Fecal calprotectin measurement is a marker of short-term clinical outcome and presence

of mucosal healing in patients with inflammatory bowel disease. *World J Gastroenterol*. 2017;23:7387-7396.
35. Akutko K, Iwańczak B. Evaluation of fecal calprotectin, serum C-reactive protein, erythrocyte sedimentation rate, seromucoid and procalcitonin in the diagnostics and monitoring of Crohn's disease in children. *J Clin Med*. 2022;11:6086.
36. Lerchova T, Hradsky O, Copova I, Potuznikova K, Gonsorcikova L, Bronsky J. The accuracy of a home-performed faecal calprotectin test in paediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2019;69:75-81.
37. Giugliano FP, Strisciuglio C, Martinelli M, et al. Does Azathioprine induce endoscopic and histologic healing in pediatric inflammatory bowel disease? A prospective, observational study. *Dig Liver Dis*. 2018;50:240-246.
38. Leach ST, Day AS, Messenger R, et al. Fecal markers of inflammation and disease activity in pediatric Crohn disease: results from the imagekids study. *J Pediatr Gastroenterol Nutr*. 2020;70:580-585.
39. Weinstein-Nakar I, Focht G, Church P, et al. Associations among mucosal and transmural healing and fecal level of calprotectin in children with Crohn's disease. *Clin Gastroenterol Hepatol*. 2018;16:1089-1097 e4.
40. Heida A, Park KT, van Rheenen PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis*. 2017;23:894-902.
41. Sassine S, Djani L, Cambron-Asselin C, et al. Risk factors of clinical relapses in pediatric luminal Crohn's disease: a retrospective cohort study. *Am J Gastroenterol*. 2022;117:637-646.
42. Ananthakrishnan AN, Adler J, Chachu KA, et al. AGA clinical practice guideline on the role of biomarkers for the management of Crohn's disease. *Gastroenterology*. 2023;165:1367-1399.
43. D'Arcangelo G, Imondi C, Terrin G, Catassi G, Aloi M. Is fecal calprotectin a useful marker for small bowel Crohn disease? *J Pediatr Gastroenterol Nutr*. 2021;73:242-246.
44. Roca M, Rodriguez Varela A, Carvajal E, et al. Fecal calprotectin in healthy children aged 4-16 years. *Sci Rep*. 2020;10:20565.
45. Roca M, Rodriguez Varela A, Donat E, et al. Fecal calprotectin and eosinophil-derived neurotoxin in healthy children between 0 and 12 years. *J Pediatr Gastroenterol Nutr*. 2017;65:394-398.
46. Oord T, Hornung N. Fecal calprotectin in healthy children. *Scand J Clin Lab Invest*. 2014;74:254-258.
47. Kolho KL, Alfthan H. Concentration of fecal calprotectin in 11,255 children aged 0-18 years. *Scand J Gastroenterol*. 2020;55:1024-1027.
48. Cozijnsen MA, Ben Shoham A, Kang B, et al. Development and validation of the mucosal inflammation noninvasive index for pediatric Crohn's disease. *Clin Gastroenterol Hepatol*. 2020;18:133-140.e1.
49. Yogev D, Verstockt B, Dignass A, et al. The modified mucosal inflammation noninvasive index and endoscopic remission in adults with Crohn's disease. *Inflamm Bowel Dis*. 2023;29:1170-1174.
50. Ferrante M, Colombel J-F, Sandborn WJ, et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. *Gastroenterology*. 2013;145:978-986.e5.
51. Oliva S, Thomson M, de Ridder L, et al. Endoscopy in pediatric inflammatory bowel disease: a position paper on behalf of the porto IBD group of the european society for pediatric gastroenterology, hepatology and nutrition. *J Pediatr Gastroenterol Nutr*. 2018;67:414-430.
52. Arcos-Machancoses JV, Kapoor A, Schluckebier D, Thomson M. Clinical validation and accuracy assessment of the Capsule Endoscopy-Crohn's Disease index (CE-CD). *J Pediatr Gastroenterol Nutr*. 2024;79:721-728.
53. Oliva S, Veraldi S, Russo G, et al. Pan-enteric capsule endoscopy to characterize Crohn's disease phenotypes and predict clinical outcomes in children and adults: the Bomiro study. *Inflamm Bowel Dis*. 2025;31:636-646.
54. D'Arcangelo G, Russo G, Aloi M, et al. A treat-to-target strategy guided by pan-enteric evaluation in children with Crohn's disease improves outcomes at 2 years. *Inflamm Bowel Dis*. 2024;30:1303-1308.
55. Calabrese E, Maaser C, Zorzi F, et al. Bowel ultrasonography in the management of Crohn's disease. a review with recommendations of an international panel of experts. *Inflamm Bowel Dis*. 2016;22:1168-1183.
56. Novak KL, Nylund K, Maaser C, et al. Expert consensus on optimal acquisition and development of the International Bowel Ultrasound Segmental Activity Score [IBUS-SAS]: a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's disease. *J Crohns Colitis*. 2021;15:609-616.
57. Kellar A, Chavannes M, Huynh HQ, et al. Defining normal bowel wall thickness in children with inflammatory bowel disease in deep remission: a multicenter study on behalf of the pediatric committee of the International Bowel Ultrasound Group (IBUS). *J Pediatr Gastroenterol Nutr*. 2025;81:53-61.
58. Dolinger MT, Aronskyy I, Kellar A, Spencer E, Pittman N, Dubinsky MC. Early intestinal ultrasound response to biologic therapy predicts endoscopic remission in children with ileal Crohn's disease: results from the prospective super sonic study. *J Crohns Colitis*. 2024;18:1002-1011.
59. Dolinger MT, Choi JJ, Phan BL, Rosenberg HK, Rowland J, Dubinsky MC. Use of small bowel ultrasound to predict response to infliximab induction in pediatric Crohn's disease. *J Clin Gastroenterol*. 2021;55:429-432.
60. Dillman JR, Dehkordy SF, Smith EA, et al. Defining the ultrasound longitudinal natural history of newly diagnosed pediatric small bowel Crohn disease treated with infliximab and infliximab-azathioprine combination therapy. *Pediatr Radiol*. 2017;47:924-934.
61. Yanai H, Feakins R, Allocca M, et al. ECCO-ESGAR-ESP-IBUS guideline on diagnostics and monitoring of patients with inflammatory bowel disease: part 2. *J Crohns Colitis*. 2025;19:jjaf106.
62. Wang L, Zhang Y, Wu H, Tang Z, Wang Y, Huang Y. Intestinal ultrasound score predicts therapeutic outcomes of infliximab in pediatric patients with Crohn's disease. *Scand J Gastroenterol*. 2024;59:156-163.
63. van Wassenaer EA, van Rijn RR, de Voogd FAE, et al. Assessing disease activity in pediatric Crohn's disease using ultrasound: the pediatric Crohn disease intestinal ultrasound score. *J Pediatr Gastroenterol Nutr*. 2023;76:582-589.
64. Kellar A, Wilson S, Kaplan G, DeBruyn J, Tanyingoh D, Novak KL. The simple pediatric activity ultrasound score (SPAUSS) for the accurate detection of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2019;69:e1-e6.
65. Yoon H, Kim J, Lim HJ, et al. Contrast-enhanced ultrasonography for the evaluation of Crohn's disease in pediatric patients. *J Korean Med Sci*. 2023;38:e219.
66. Ponorac S, Gosnak RD, Urlep D, Kljucevsek D. Contrast-enhanced ultrasonography in the evaluation of Crohn disease activity in children: comparison with histopathology. *Pediatr Radiol*. 2021;51:410-418.
67. Church PC, Turner D, Feldman BM, et al. Systematic review with meta-analysis: magnetic resonance enterography signs for the

detection of inflammation and intestinal damage in Crohn's disease. *Aliment Pharmacol Ther*. 2015;41:153-166.
68. Focht G, Cytter-Kuint R, Greer M-LC, et al. Development, validation, and evaluation of the pediatric inflammatory Crohn's Magnetic Resonance Enterography Index from the ImageKids study. *Gastroenterology*. 2022;163:1306-1320.
69. Giles E, Barclay AR, Chippington S, Wilson DC. Systematic review: MRI enterography for assessment of small bowel involvement in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2013;37:1121-1131.
70. Ramalho J, Ramalho M, Jay M, Burke LM, Semelka RC. Gadolinium toxicity and treatment. *Magn Reson Imaging*. 2016;34:1394-1398.
71. Cella D, Yount S, Rothrock N, et al. The patient-reported outcomes measurement information system (PROMIS): progress of an NIH roadmap cooperative group during its first two years. *Med Care*. 2007;45:S3-S11.
72. Forrest CB, Bevans KB, Tucker C, et al. Commentary: the patient-reported outcome measurement information system (PROMIS(R)) for children and youth: application to pediatric psychology. *J Pediatr Psychol*. 2012;37:614-621.
73. Chen X-L, Zhong L-H, Wen Y, et al. Inflammatory bowel disease-specific health-related quality of life instruments: a systematic review of measurement properties. *Health Qual Life Outcomes*. 2017;15:177.
74. Gordon H, Burisch J, Ellul P, et al. ECCO guidelines on extraintestinal manifestations in inflammatory bowel disease. *J Crohns Colitis*. 2024;18:1-37.
75. Geem D, Hercules D, Pelia RS, et al. Progression of pediatric Crohn's disease is associated with anti-tumor necrosis factor timing and body mass index z-score normalization. *Clin Gastroenterol Hepatol*. 2024;22:368-376.e4.
76. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389:1710-1718.
77. Ben-Horin S, Novack L, Mao R, et al. Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease: a systematic review and an individual-patient data meta-analysis of randomized controlled trials. *Gastroenterology*. 2022;162:482-494.
78. Targownik LE, Bernstein CN, Benchimol EI, et al. Earlier anti-TNF initiation leads to long-term lower health care utilization in Crohn's disease but not in ulcerative colitis. *Clin Gastroenterol Hepatol*. 2022;20:2607-2618.e14.
79. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:811-817.e3.
80. Doecke JD, Hartnell F, Bampton P, et al. Infliximab vs. adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study. *Aliment Pharmacol Ther*. 2017;45:542-552.
81. Fanous E, Marshanski T, Tal N, et al. Comparison of clinical outcomes in pediatric patients with ileocolonic Crohn disease treated with infliximab versus adalimumab. *J Pediatr Gastroenterol Nutr*. 2023;77:358-365.
82. Nixon C, Putrus E, Simpson E, et al. Benefits of exclusive enteral nutrition in adults with complex active Crohn's disease: a case series of 13 consecutive patients. *Crohn's & Colitis*. 2019;1:360.
83. Cooper JL, Rosentreter RE, Filyk A, et al. Nutritional interventions in adult fibrostenotic Crohn's disease: a systematic review. *Front Nutr*. 2023;10:1017382.
84. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863-873.
85. Jongsma MME, Aardoom MA, Cozijnsen MA, et al. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomised controlled trial. *Gut*. 2022;71:34-42.
86. Kierkus J, Dadalski M, Szymanska E, et al. The impact of infliximab induction therapy on mucosal healing and clinical remission in Polish pediatric patients with moderate-to-severe Crohn's disease. *Eur J Gastroenterol Hepatol*. 2012;24:495-500.
87. Kierkus J, Iwanczak B, Wegner A, et al. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60:580-585.
88. van Hoeve K, Seyed Tabib NS, Dreesen E, et al. Infliximab concentrations during induction are predictive for endoscopic remission in pediatric patients with inflammatory bowel disease under combination therapy. *J Pediatr*. 2022;240:150-157.e4.
89. Courbette O, Aupiais C, Viala J, et al. Trough levels of infliximab at week 6 are predictive of remission at week 14 in pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2020;70:310-317.
90. Chanchlani N, Mortier K, Williams LJ, et al. Use of infliximab biosimilar versus originator in a pediatric united kingdom inflammatory bowel disease induction cohort. *J Pediatr Gastroenterol Nutr*. 2018;67:513-519.
91. Winter DA, Joosse ME, de Wildt SN, Taminiau J, de Ridder L, Escher JC. Pharmacokinetics, pharmacodynamics, and immunogenicity of infliximab in pediatric inflammatory bowel disease: a systematic review and revised dosing considerations. *J Pediatr Gastroenterol Nutr*. 2020;70:763-776.
92. Arieira C, Dias de Castro F, Curdia Goncalves T, Moreira MJ, Cotter J. Combination therapy in inflammatory bowel disease patients: do we need to maximize the dose of azathioprine? *Scand J Gastroenterol*. 2020;55:920-923.
93. Roblin X, Boschetti G, Williet N, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther*. 2017;46:142-149.
94. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol*. 2019;4:341-353.
95. Kappelman MD, Wohl DA, Herfarth HH, et al. Comparative effectiveness of anti-TNF in combination with low-dose methotrexate vs anti-TNF monotherapy in pediatric Crohn's disease: a pragmatic randomized trial. *Gastroenterology*. 2023;165:149-161.e7.
96. Ungaro RC, Colombel JF, Dubinsky MC, Jain A, Dervieux T. Impact of thiopurine exposure on immunogenicity to infliximab is negligible in the setting of elevated infliximab concentrations. *Inflamm Bowel Dis*. 2022;28:649-651.
97. Cozijnsen M, Duif V, Kokke F, et al. Adalimumab therapy in children with Crohn's disease previously treated with infliximab. *J Pediatr Gastroenterol Nutr*. 2015;60:205-210.
98. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology*. 2012;143:365-374.e2.
99. Hyams JS, Dubinsky M, Rosh J, et al. The effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in paediatric patients with Crohn's disease: a post hoc analysis. *Aliment Pharmacol Ther*. 2019;49:155-164.

100. Rosh JR, Lerer T, Markowitz J, et al. Retrospective evaluation of the safety and effect of adalimumab therapy (RESEAT) in pediatric Crohn's disease. *Am J Gastroenterol*. 2009;104:3042-3049.
101. Viola F, Civitelli F, Di Nardo G, et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *Am J Gastroenterol*. 2009;104:2566-2571.
102. Rinawi F, Ricciuto A, Church PC, et al. Association of early postinduction adalimumab exposure with subsequent clinical and biomarker remission in children with Crohn's disease. *Inflamm Bowel Dis*. 2021;27:1079-1087.
103. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology*. 2019;157:985-996.e2.
104. Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut*. 2020;69:1206-1212.
105. Jongsma MME, Winter DA, Huynh HQ, et al. Infliximab in young paediatric IBD patients: it is all about the dosing. *Eur J Pediatr*. 2020;179:1935-1944.
106. Cohen-Sela E, Yerushalmy-Feler A, Rinawi F, et al. Safety and efficacy of weekly adalimumab 80 mg therapy in pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2026;82:1427-1434. Mar 25
107. Yang HH, Huang Y, Zhou XC, Wang RN. Efficacy and safety of adalimumab in comparison to infliximab for Crohn's disease: A systematic review and meta-analysis. *World J Clin Cases*. 2022;10:6091-6104.
108. Bronsky J, Copova I, Kazeka D, et al. Adalimumab vs infliximab in pediatric patients with Crohn's disease: a propensity score analysis and predictors of treatment escalation. *Clin Transl Gastroenterol*. 2022;13:e00490.
109. deBruyn JC, Huynh HQ, Griffiths AM, et al. Adalimumab vs infliximab in luminal pediatric Crohn's disease: comparable outcomes in a prospective multicenter cohort study. *Am J Gastroenterol*. 2024;119:565-575.
110. Atia O, Friss C, Focht G, et al. Durability of adalimumab and infliximab in children with Crohn's disease: a nationwide comparison from the epi-IIRN cohort. *Inflamm Bowel Dis*. 2024;30:2097-2104.
111. Hyams J, Damaraju L, Blank M, et al. T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2012;10:391-399.e1.
112. Dipasquale V, Cicala G, Spina E, Romano C. Biosimilars in pediatric inflammatory bowel diseases: a systematic review and real life-based evidence. *Front Pharmacol*. 2022;13:846151.
113. Faleck DM, Shmidt E, Huang R, et al. Effect of concomitant therapy with steroids and tumor necrosis factor antagonists for induction of remission in patients with Crohn's disease: a systematic review and pooled meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19:238-245.e4.
114. Luo Y, Cheng Q, Fang Y, Yu J, Lou J, Chen J. Infliximab therapy in very early onset Crohn's disease: real-world experience in China. *Dig Dis Sci*. 2021;66:3555-3562.
115. Weintraub Y, Collen LV, Hussey S, et al. Effectiveness and safety of adalimumab in patients with very early-onset inflammatory bowel disease: a retrospective study on Behalf of the Porto Inflammatory Bowel Disease Working Group of European Society for Pediatric Gastroenterology Hepatology and Nutrition. *Inflamm Bowel Dis*. 2025;31:2184-2194.
116. Bramuzzo M, Arrigo S, Romano C, et al. Efficacy and safety of infliximab in very early onset inflammatory bowel disease: a national comparative retrospective study. *United European Gastroenterol J*. 2019;7:759-766.
117. Gangwani MK, Nawras M, Aziz M, et al. Comparing adalimumab and infliximab in the prevention of postoperative recurrence of Crohn's disease: a systematic review and meta-analysis. *Ann Gastroenterol*. 2023;36:293-299.
118. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2018;4:CD000542.
119. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li Ferry S. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2017;46:645-656.
120. Yu Y, Chen KC, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World J Pediatr*. 2019;15:26-36.
121. Sohouli MH, Fatahi S, Farahmand F, Alimadadi H, Seraj SS, Rohani P. Meta-analysis: efficacy of exclusive enteral nutrition as induction therapy on disease activity index, inflammation and growth factors in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2022;56:384-395.
122. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol*. 2006;4:744-753.
123. Tang W, Hu W, Shi P, et al. The SES-CD could be a predictor of short- and long-term mucosal healing after exclusive enteral nutrition in pediatric Crohn's disease patients. *Front Pediatr*. 2022;10:874425.
124. Cuomo M, Carobbio A, Aloi M, et al. Induction of remission with exclusive enteral nutrition in children with Crohn's disease: determinants of higher adherence and response. *Inflamm Bowel Dis*. 2023;29:1380-1389.
125. Xu Y, Guo Z, Cao L, et al. Isolated colonic Crohn's disease is associated with a reduced response to exclusive enteral nutrition compared to ileal or ileocolonic disease. *Clin Nutr*. 2019;38:1629-1635.
126. Levine A, Sigall Boneh R, Wine E. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gut*. 2018;67:1726-1738.
127. Zhu Z, Lei Y, Lin Z. Effects of Crohn's disease exclusion diet on remission: a systematic review. *Ther Adv Gastroenterol*. 2023;16:17562848231184056.
128. Correia I, Oliveira PA, Antunes ML, Raimundo MDG, Moreira AC. Is there evidence of Crohn's disease exclusion diet (CDED) in remission of active disease in children and adults? a systematic review. *Nutrients*. 2024;16:987.
129. Sigall Boneh R, Navas-López VM, Hussey S, et al. Modified Crohn's disease exclusion diet maintains remission in pediatric Crohn's disease; randomized controlled trial. *Clin Gastroenterol Hepatol*. 2025;23:2001-2011.
130. Landorf E, Hammond P, Abu-Assi R, et al. Formula modifications to the Crohn's disease exclusion diet do not impact therapy success in paediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2024;78:1279-1286.
131. Matuszczyk M, Meglicka M, Wiernicka A, et al. Effect of the Crohn's disease exclusion diet (CDED) on the fecal calprotectin level in children with active Crohn's disease. *J Clin Med*. 2022;11:4146.

132. Niseteo T, Sila S, Trivić I, Mišak Z, Kolaček S, Hojsak I. Modified Crohn's disease exclusion diet is equally effective as exclusive enteral nutrition: real-world data. *Nutr Clin Pract*. 2022;37:435-441.
133. Urlep D, Orel R, Kunstek P, Benedik E. Treatment of active Crohn's disease in children using partial enteral nutrition combined with a modified Crohn's disease exclusion diet: a pilot prospective cohort trial on clinical and endoscopic outcomes. *Nutrients*. 2023;15:4676.
134. Zhou S, Huang Z, Hou W, Lin Y, Yu J. Prospective study of an adalimumab combined with partial enteral nutrition in the induction period of Crohn's disease. *Inflamm Res*. 2024;73:199-209.
135. Scarallo L, Banci E, De Blasi A, et al. A real-life pediatric experience of Crohn's disease exclusion diet at disease onset and in refractory patients. *J Pediatr Gastroenterol Nutr*. 2024;79:592-601.
136. Aharoni-Frutkoff Y, Plotkin L, Pollak D, et al. Whole food diet induces remission in children and young adults with mild to moderate Crohn's disease and is more tolerable than exclusive enteral nutrition: a randomized controlled trial. *Gastroenterology*. 2025;169:1462-1474.e2.
137. Plotkin L, Aharoni Frutkoff Y, Shavit Z, et al. Fecal calprotectin response to Tasty&Healthy dietary intervention in asymptomatic children and young adults with biologically active Crohn's disease: results of the "TASTI-E" randomized controlled trial. *J Crohn Colitis*. 2025;19:i1952.
138. Plotkin L, Aharoni Y, Fenster D, et al. Tasty&Healthy is a dietary approach for inducing and maintaining remission in Crohn's disease: a prospective case series. *United European Gastroenterol J*. 2021;9:521. PO431).
139. Plott N, Steiner S, Firestine A, Galanko J, Kappelman M. Improvement in growth and nutrition status after anti-TNF therapy initiation among patients with pediatric Crohn's disease: results from the Combine trial. *Inflamm Bowel Dis*. 2024;30:S71.
140. Wong K, Isaac DM, Wine E. Growth delay in inflammatory bowel diseases: significance, causes, and management. *Dig Dis Sci*. 2021;66:954-964.
141. Cameron FLGK, Papangelou A, Missiou D, et al. Clinical progress in the two years following a course of exclusive enteral nutrition in 109 paediatric patients with Crohn's disease. *Aliment Pharmacol Ther*. 2013;37:622-629.
142. Luo Y, Yu J, Lou J, Fang Y, Chen J. Exclusive enteral nutrition versus infliximab in inducing therapy of paediatric Crohn's disease. *Gastroenterol Res Pract*. 2017;2017:6595048.
143. Lv YLY, Yang G, Luo Y, et al. Outcomes of pediatric patients with Crohn's disease received infliximab or exclusive enteral nutrition during induction remission. *Gastroenterol Res Pract*. 2022;2022:3813915.
144. Walters TD, Kim M-O, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. *Gastroenterology*. 2014;146:383-391.
145. Coward S, Kuenzig ME, Hazlewood G, et al. Comparative Effectiveness of Mesalamine, Sulfasalazine, Corticosteroids, and Budesonide for the Induction of Remission in Crohn's Disease: A Bayesian Network Meta-analysis. *Inflamm Bowel Dis*. 2017;23:461-472.
146. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology*. 2000;119:895-902.
147. Levine A, Weizman Z, Broide E, et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2003;36:248-252.
148. Levine A, Kori M, Dinari G, et al. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: a randomized placebo-controlled trial. *Inflamm Bowel Dis*. 2009;15:1055-1061.
149. Feuerstein JD, Rubin DT, Aberra FN, Yarur AJ, Malter L. Appropriate use and complications of corticosteroids in inflammatory bowel disease: a comprehensive review. *Clin Gastroenterol Hepatol*. 2025;23:2068-2082.
150. Pigneur B, Lepage P, Mondot S, et al. Mucosal healing and bacterial composition in response to enteral nutrition vs steroid-based induction therapy-a randomised prospective clinical trial in children with Crohn's disease. *J Crohns Colitis*. 2019;13:846-855.
151. Jongsma MME, Vuijk SA, Cozijnsen MA, et al. Evaluation of exclusive enteral nutrition and corticosteroid induction treatment in new-onset moderate-to-severe luminal paediatric Crohn's disease. *Eur J Pediatr*. 2022;181:3055-3065.
152. Plotkin L, Buchuk R, Lujan R, et al. Enteral nutrition compared with corticosteroids in children with Crohn's disease: A long-term nationwide study from the epi-IIRN. *Aliment Pharmacol Ther*. 2024;60:224-232.
153. Svolos V, Hansen R, Nichols B, et al. Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition. *Gastroenterology*. 2019;156:1354-1367.e6.
154. Svolos V, Hansen R, Russell R, et al. DOP68 CD CD-TREAT diet induces remission and improves quality of life in an open label trial in children and adults with active Crohn's Disease. *J Crohns Colitis*. 2022;16:i112.
155. Ledder O, Turner D. Antibiotics in IBD: still a role in the biological era? *Inflamm Bowel Dis*. 2018;24:1676-1688.
156. Levine A, Kori M, Kierkus J, et al. Azithromycin and metronidazole versus metronidazole-based therapy for the induction of remission in mild to moderate paediatric Crohn's disease: a randomised controlled trial. *Gut*. 2019;68:239-247.
157. Fioretti MT, Gianolio L, Armstrong K, et al. A decade of real-world clinical experience with 8-week azithromycin-metronidazole combined therapy in paediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2025;80:300-307.
158. Nielsen OH, Steenholdt C, Juhl CB, Rogler G. Efficacy and safety of methotrexate in the management of inflammatory bowel disease: A systematic review and meta-analysis of randomized, controlled trials. *EClinicalMedicine*. 2020;20:100271.
159. Li S, Reynaert C, Su AL, Sawh S. Efficacy and safety of infliximab in pediatric Crohn disease: a systematic review and meta-analysis. *Can J Hosp Pharm*. 2019;72:227-238.
160. Chen B, Zou Z, Zhang X, Xiao D, Li X. Efficacy and safety of adalimumab in pediatric patients with Crohn's disease: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2024;80:395-407.
161. Martín-García P, Alonso-Arroyo A, Catalá-López F. Tumour necrosis factor (TNF) antagonist therapy for paediatric inflammatory bowel disease: a systematic review. *Med Clin (Barc)*. 2023;160:501-516.
162. Meredith J, Henderson P, Wilson DC, Van Limbergen J, Wine E, Russell RK. Withdrawal of combination immunotherapy in paediatric inflammatory bowel disease: an international survey of practice. *J Pediatr Gastroenterol Nutr*. 2021;73:54-60.
163. Dohos D, Hanák L, Szakács Z, et al. Systematic review with meta-analysis: the effects of immunomodulator or biological withdrawal from mono- or combination therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2021;53:220-233.
164. El-Matary W, Carroll MW, Debruyn JC, et al. Discontinuation of immunosuppressive medications in children with inflammatory bowel disease on combination therapy. *J Pediatr Gastroenterol Nutr*. 2020;71:740-743.

165. Iovino NA, McClinchie MG, Abdel-Rasoul M, et al. Clinical impacts of immunomodulator withdrawal from anti-tumor necrosis factor combination therapy in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2024;79:885-894.
166. Kang B, Choi SY, Choi YO, et al. Subtherapeutic infliximab trough levels and complete mucosal healing are associated with sustained clinical remission after infliximab cessation in paediatric-onset Crohn's disease patients treated with combined immunosuppressive therapy. *J Crohns Colitis*. 2018;12:644-652.
167. Scarallo L, Bolasco G, Barp J, et al. Anti-tumor necrosis factor-alpha withdrawal in children with inflammatory bowel disease in endoscopic and histologic remission. *Inflamm Bowel Dis*. 2022;28:183-191.
168. Stein R, Daniel SG, Baldassano RN, et al. Outcomes and predictors of sustained remission after drug withdrawal in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2022;75:608-615.
169. Reenaers C, Mary J-Y, Nachury M, et al. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. *Clin Gastroenterol Hepatol*. 2018;16:234-243.e2.
170. Katibian DJ, Solitano V, Polk DB, et al. Withdrawal of immunomodulators or TNF antagonists in patients with inflammatory bowel diseases in remission on combination therapy: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2024;22:22-33.e6.
171. Louis E, Resche-Rigon M, Laharie D, et al. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2023;8:215-227.
172. Jeong TJ, Kim ES, Kwon Y, et al. Discontinuation of azathioprine could be considered in pediatric patients with Crohn's disease who have sustained clinical and deep remission. *Sci Rep*. 2022;12:507.
173. Pauwels RWM, van der Woude CJ, Nieboer D, et al. Prediction of relapse after anti-tumor necrosis factor cessation in Crohn's disease: individual participant data meta-analysis of 1317 patients from 14 studies. *Clin Gastroenterol Hepatol*. 2022;20:1671-1686.e16.
174. Gisbert JP, Donday MG, Riestra S, et al. Withdrawal of antitumour necrosis factor in inflammatory bowel disease patients in remission: a randomised placebo-controlled clinical trial of GETECCU. *Gut*. 2025;74:387-396.
175. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;2015:CD000067.
176. Singh A, Mahajan R, Kedia S, et al. Use of thiopurines in inflammatory bowel disease: an update. *Intest Res*. 2022;20:11-30.
177. Dassopoulos T, Dubinsky MC, Bentsen JL, et al. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. *Aliment Pharmacol Ther*. 2014;39:163-175.
178. Reinshagen M, Schütz E, Armstrong VW, et al. 6-thioguanine nucleotide-adapted azathioprine therapy does not lead to higher remission rates than standard therapy in chronic active Crohn's disease: results from a randomized, controlled, open trial. *Clin Chem*. 2007;53:1306-1314.
179. Kennedy AM, Griffiths AM, Muise AM, et al. Landscape of TPMT and NUDT15 pharmacogenetic variation in a cohort of Canadian Pediatric Inflammatory Bowel Disease Patients. *Inflamm Bowel Dis*. 2024;Dec 530:2418-2427.
180. Gerich ME, Quiros JA, Marcin JP, Tennyson L, Henthorn M, Prindiville TP. A prospective evaluation of the impact of allopurinol in pediatric and adult IBD patients with preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. *J Crohns Colitis*. 2010;4:546-552.
181. Mao R, Guo J, Luber R, et al. 6-thioguanine nucleotide levels are associated with mucosal healing in patients with Crohn's disease. *Inflamm Bowel Dis*. 2018;24:2621-2627.
182. Moreau AC, Paul S, Del Tedesco E, et al. Association between 6-thioguanine nucleotides levels and clinical remission in inflammatory disease: a meta-analysis. *Inflamm Bowel Dis*. 2014;20:464-471.
183. Osterman MT, Kundu R, Lichtenstein GR, Lewis JD. Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology*. 2006;130:1047-1053.
184. Chanchlani N, Lin S, Bewshea C, et al. PANTS Consortium. Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study. *Lancet Gastroenterol Hepatol*. 2024;9:521-538.
185. Baldwin K, Goldfarb A, Brimacombe M, Hopkins D, Hyams JS. Methotrexate for primary maintenance therapy in mild-to-moderate Crohn disease in children. *J Pediatr Gastroenterol Nutr*. 2022;75:320-324.
186. Ananthakrishnan AN, Whelan K, Allegretti JR, Sokol H. Diet and microbiome-directed therapy 2.0 for IBD. *Clin Gastroenterol Hepatol*. 2025;23:406-418.
187. Gkikas K, Gerasimidis K, Milling S, Ijaz UZ, Hansen R, Russell RK. Dietary strategies for maintenance of clinical remission in inflammatory bowel diseases: are we there yet? *Nutrients*. 2020;12:
188. Lawley M, Wu JW, Navas-López VM, et al. Global variation in use of enteral nutrition for pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2018;67:e22-e9.
189. Gavin J, Ashton JJ, Heather N, Marino LV, Beattie RM. Nutritional support in paediatric Crohn's disease: outcome at 12 months. *Acta Paediatr*. 2018;107:156-162.
190. Jatkowska A, White B, Gkikas K, Seenan JP, MacDonald J, Gerasimidis K. Partial enteral nutrition in the management of Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2025;19:jjae177.
191. Yang H, Feng R, Li T, et al. Systematic review with meta-analysis of partial enteral nutrition for the maintenance of remission in Crohn's disease. *Nutr Res*. 2020;81:7-18.
192. Davidson N, Rutsky J, Bricker JB, et al. 6- and 12-month outcomes after 90:10 enteral nutrition induction therapy in pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2022;75:70-75.
193. Yanai H, Levine A, Hirsch A, et al. The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial. *Lancet Gastroenterol Hepatol*. 2022;7:49-59.
194. Fliss-Isakov N, Aviv Cohen N, Bromberg A, et al. Crohn's disease exclusion diet for the treatment of Crohn's disease: real-world experience from a tertiary center. *J Clin Med*. 2023;12:5428.
195. Pasta A, Formisano E, Calabrese F, et al. The use of the Crohn's disease exclusion diet (CDED) in adults with Crohn's disease: a randomized controlled trial. *Eur J Clin Invest*. 2025;55:e14389.
196. Chicco F, Magrì S, Cingolani A, et al. Multidimensional impact of mediterranean diet on IBD patients. *Inflamm Bowel Dis*. 2021;27:1-9.
197. Zhang JL, Vootukuru N, Niewiadomski O. The effect of solid food diet therapies on the induction and maintenance of remission in Crohn's disease: a systematic review. *BMC Gastroenterol*. 2024;24:250.

198. Svolos V, Gordon H, Lomer MCE, et al. European Crohn's and colitis organisation consensus on dietary management of inflammatory bowel disease. *J Crohns Colitis*. 2025;19:jjaf122.
199. Limketkai BN, Godoy-Brewer G, Parian AM, et al. Dietary interventions for the treatment of inflammatory bowel diseases: an updated systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2023;21:2508-2525.e10.
200. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2016;9:CD003715.
201. Noureldin M, Cohen-Mekelburg S, Mahmood A, et al. Trends of 5-aminosalicylate medication use in patients with Crohn's disease. *Inflamm Bowel Dis*. 2021;27:516-521.
202. Atia O, Goren I, Fischler TS, et al. 5-aminosalicylate maintenance is not superior to no maintenance in patients with newly diagnosed Crohn's disease-a nationwide cohort study. *Aliment Pharmacol Ther*. 2023;57:1004-1013.
203. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev*. 2016;7:CD008870.
204. Gjuladin-Hellon T, Gordon M, Iheozor-Ejiofor Z, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2019;6:CD008414.
205. Herfarth H, Vavricka SR. 5-aminosalicylic acid chemoprevention in inflammatory bowel diseases: is it necessary in the age of biologics and small molecules? *Inflamm Intest Dis*. 2022;7:28-35.
206. Atia O, Benchimol EI, Ledderman N, et al. Incidence, management, and outcomes of very early onset inflammatory bowel diseases and infantile-onset disease: an Epi-IIRN study. *Clin Gastroenterol Hepatol*. 2023;21:2639-2648.e6.
207. Sieber A, Aberra FN, Bonhomme B, McKeever L, Lewis JD. Influence of corticosteroid use on short- and long-term outcomes of biologic therapy for inflammatory bowel diseases. *Dig Dis Sci*. 2022;67:5168-5176.
208. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014;20:2247-2259.
209. Lie MR, Peppelenbosch MP, West RL, Zelinkova Z, van der Woude CJ. Adalimumab in Crohn's disease patients: pharmacokinetics in the first 6 months of treatment. *Aliment Pharmacol Ther*. 2014;40:1202-1208.
210. Sila S, Aloi M, Cucinotta U, et al. Effect of overweight and obesity on the response to anti-TNF therapy and disease course in children with IBD. *Inflamm Bowel Dis*. 2025;31:1263-1271.
211. Chung A, Carroll M, Almeida P, et al. early infliximab clearance predicts remission in children with Crohn's disease. *Dig Dis Sci*. 2023;68:1995-2005.
212. Stallard L, Frost K, Frost N, et al. Body surface area-based dosing of infliximab is superior to standard weight-based dosing in children with very early onset inflammatory bowel disease. *Gastro Hep Adv*. 2024;3:215-220.
213. Ward MG, Thwaites PA, Beswick L, et al. Intra-patient variability in adalimumab drug levels within and between cycles in Crohn's disease. *Aliment Pharmacol Ther*. 2017;45:1135-1145.
214. Gibson DJ, Ward MG, Rentsch C, et al. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020;51:612-628.
215. Dreesen E, Baert F, Laharie D, et al. Monitoring a combination of calprotectin and infliximab identifies patients with mucosal healing of Crohn's disease. *Clin Gastroenterol Hepatol*. 2020;18:637-646.e11.
216. Bevers N, Aliu A, Wong DR, Wjnkens B, Vreugdenhil A, et al. Early infliximab trough levels in paediatric IBD patients predict sustained remission. *Ther Adv Gastroenterol*. 2023;30:17: 17562848231222337.
217. Burgess CJ, Reilly C, Steward-Harrison L, Balouch F, Lewindon PJ. Utility of proactive infliximab levels in paediatric Crohn's disease. *Arch Dis Child*. 2019;104:251-255.
218. Reinisch W, Colombel J-F, Sandborn WJ, et al. Factors associated with short- and long-term outcomes of therapy for Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13:539-547.e2.
219. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2016;14:550-557.e2.
220. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. *Inflamm Bowel Dis*. 2018;24:2266-2271.
221. Kang B, Choi SY, Choi YO, et al. Infliximab trough levels are associated with mucosal healing during maintenance treatment with infliximab in paediatric Crohn's disease. *J Crohns Colitis*. 2019;13:189-197.
222. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2017;45:933-940.
223. Davidov Y, Ungar B, Bar-Yoseph H, et al. Association of induction infliximab levels with clinical response in perianal Crohn's disease. *J Crohns Colitis*. 2017;11:549-555.
224. El-Matary W, Walters TD, Huynh HQ, et al. Higher postinduction infliximab serum trough levels are associated with healing of fistulizing perianal Crohn's disease in children. *Inflamm Bowel Dis*. 2019;25:150-155.
225. Iborra M, Caballol B, Garrido A, et al. Subcutaneous infliximab cutoff points in patients with inflammatory bowel disease: data from the ENEIDA registry. *J Crohns Colitis*. 2025;19:jjae127.
226. Hong SN, Song JH, Kim SJ, et al. Subcutaneous infliximab concentration thresholds for mucosal and transmural healing in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2025;61:313-322.
227. Levy R, Matar M, Zvuloni M, Shamir R, Assa A. Trough concentration response in infliximab and adalimumab treated children with inflammatory bowel disease following treatment adjustment: a pharmacokinetic model. *J Pediatr Gastroenterol Nutr*. 2023;76:576-581.
228. Lucafo M, Curci D, Bramuzzo M, et al. Serum adalimumab levels after induction are associated with long-term remission in children with inflammatory bowel disease. *Front Pediatr*. 2021;9:646671.
229. Ancona S, Armstrong K, Longo C, et al. Adalimumab biosimilars demonstrate long-term durability and cost-effectiveness in paediatric inflammatory bowel disease: a real-world two-centre european cohort study. *Biologics*. 2025;19:265-279.
230. Rinawi F, Popalis C, Tersigni C, et al. Long-term outcomes with adalimumab therapy in pediatric Crohn disease: associations with adalimumab exposure. *J Pediatr Gastroenterol Nutr*. 2022;74:389-395.
231. Yarur AJ, Jain A, Hauenstein SI, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients

with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2016;22:409-415.
232. Zittan E, Kabakchiev B, Milgrom R, et al. Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease. *J Crohns Colitis*. 2016;10:510-515.
233. Watanabe K, Matsumoto T, Hisamatsu T, et al. Clinical and pharmacokinetic factors associated with adalimumab-induced mucosal healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2018;16:542-549.e1.
234. Juncadella A, Papamichael K, Vaughn BP, Cheifetz AS. Maintenance adalimumab concentrations are associated with biochemical, endoscopic, and histologic remission in inflammatory bowel disease. *Dig Dis Sci*. 2018;63:3067-3073.
235. Kim MJ, Kim E, Kang B, Choe YH. Therapeutic drug monitoring of adalimumab during long-term follow-up in paediatric patients with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2021;72:870-876.
236. Gu B, Venkatesh K, Williams A-J, et al. Higher infliximab and adalimumab trough levels are associated with fistula healing in patients with fistulising perianal Crohn's disease. *World J Gastroenterol*. 2022;28:2597-2608.
237. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: a systematic review with meta-analysis. *J Crohns Colitis*. 2018;12:1302-1315.
238. Serrano-Diaz L, Iniesta-Navalon C, Gomez-Espin R, Nicolas-de Prado I, Bernal-Morell E, Rentero-Redondo L. Impact of proactive therapeutic drug monitoring of infliximab during the induction phase in IBD patients. A Bayesian approach. *Rev Esp Enferm Dig*. 2023;115:435-443.
239. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23:1202-1209.
240. Gofin Y, Matar M, Shamir R, Assa A. Therapeutic drug monitoring increases drug retention of anti-tumor necrosis factor alpha agents in pediatric patients with Crohn's disease. *Inflamm Bowel Dis*. 2020;26:1276-1282.
241. Velayos FS, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost-effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. *Clin Gastroenterol Hepatol*. 2013;11:654-666.
242. Steenholdt C, Brynskov J, Thomsen OØ, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut*. 2014;63:919-927.
243. Guidi L, Pugliese D, Panici Tonucci T, et al. Therapeutic drug monitoring is more cost-effective than a clinically based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multicentre study. *J Crohns Colitis*. 2018;12:1079-1088.
244. Mancenido Marcos N, Novella Arribas B, Mora Navarro G, Rodriguez Salvanes F, Loeches Belinchon P, Gisbert JP. Efficacy and safety of proactive drug monitoring in inflammatory bowel disease treated with anti-TNF agents: a systematic review and meta-analysis. *Dig Liver Dis*. 2024;56:421-428.
245. Papamichael K, Juncadella A, Wong D, et al. Proactive therapeutic drug monitoring of adalimumab is associated with better long-term outcomes compared with standard of care in patients with inflammatory bowel disease. *J Crohns Colitis*. 2019;13:976-981.
246. Fernandes SR, Bernardo S, Simões C, et al. Proactive infliximab drug monitoring is superior to conventional management in inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:263-270.
247. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol*. 2017;15:1580-1588.e3.
248. Lega S, Phan BL, Rosenthal CJ, et al. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. *Inflamm Bowel Dis*. 2019;25:134-141.
249. Ali S, Pasternak B, Moses J, et al. Characterization of biologic discontinuation among pediatric patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2024;22:2075-2083.e1.
250. Holland K, Bennett WE, Slaven JE, Collier J, Waltz G, Pfefferkorn M. Proactive measurement of infliximab drug levels in children with Crohn's disease. *Ann Gastroenterol*. 2022;35:56-62.
251. Lyles JL, Mulgund AA, Bauman LE, et al. Effect of a practice-wide anti-TNF proactive therapeutic drug monitoring program on outcomes in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27:482-492.
252. Kang B, Kim ES, Choi S, et al. Proactive drug monitoring versus clinically based dosing for endoscopic healing in pediatric Crohn's disease receiving infliximab. *Clin Gastroenterol Hepatol*. 2026;24:201-209.e6.
253. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13:514-521.e4.
254. Lucidarme C, Petitcollin A, Brochard C, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: the value of a strategy based on therapeutic drug monitoring. *Aliment Pharmacol Ther*. 2019;49:147-154.
255. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946-1960.
256. Rosh JR, Turner D, Griffiths A, et al. Ustekinumab in paediatric patients with moderately to severely active Crohn's disease: pharmacokinetics, safety, and efficacy results from UniStar, a phase 1 study. *J Crohns Colitis*. 2021;15:1931-1942.
257. de Greef E, Strauss R, Van Limbergh E, et al. Ustekinumab open-label induction and randomized blinded maintenance therapy in pediatric participants with moderately to severely active Crohn's Disease: the phase 3 Unity Jr Study. *Gastroenterology*. 2025;169:S-16.
258. Turner D, Rosh JR, Cohen SA, et al. UniStar Study Group. Ustekinumab in paediatric patients with moderately to severely active Crohn's disease: UniStar study long-term extension results. *J Pediatr Gastroenterol Nutr*. 2024;79:315-324.
259. Turner E, De Greef J, Kierkuś B, et al. The UNITI Jr Study: safety and efficacy results of ustekinumab in paediatric patients with Crohn's disease. *J Crohn's Colitis*. 2026;20:jjaf231.
260. Kim FS, Patel PV, Stekol E, et al. Experience using ustekinumab in pediatric patients with medically refractory Crohn disease. *J Pediatr Gastroenterol Nutr*. 2021;73:610-614.
261. Li P, Wang L, Tang Z, et al. Ustekinumab in pediatric patients with Crohn's disease: safety, and efficacy results from a multicenter retrospective study in China. *Front Pediatr*. 2024;12:1371322.
262. Dayan JR, Dolinger M, Benkov K, et al. Real world experience with ustekinumab in children and young adults at a tertiary care

pediatric inflammatory bowel disease center. *J Pediatr Gastroenterol Nutr*. 2019;69:61-67.
263. Koudsi M, Martinez-Vinson C, Pigneur B, et al. Ustekinumab use in pediatric inflammatory bowel disease: a french multicenter study from the pediatric GETAID. *J Pediatr Gastroenterol Nutr*. 2023;76:763-770.
264. Yerushalmy-Feler A, Pujol-Muncunill G, Martin-de-Carpi J, et al. Safety and potential efficacy of escalating dose of ustekinumab in pediatric Crohn disease (the speed-up study): a multicenter study from the pediatric IBD porto group of ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2022;75:717-723.
265. Dolinger MT, Rolfes P, Spencer E, Stoffels G, Dunkin D, Dubinsky MC. Outcomes of children with inflammatory bowel disease who develop anti-tumour necrosis factor-induced skin reactions. *J Crohns Colitis*. 2022;16:1420-1427.
266. Walters TH, De Bruyn J, McKay J. One-year outcomes with Ustekinumab therapy in bionaive paediatric Crohn's Disease: a prospective multi-centre cohort study from the Canadian children IBD network (CIDSCANN). In: Reports J, editor. ESPGHAN 57th Annual Meeting 13 May, 2025. S1-S1656.
267. Pujol-Muncunill G, Navas-López VM, Ledder O, et al. STEP-CD study: ustekinumab use in paediatric Crohn's disease-a multicentre retrospective study from paediatric IBD Porto group of ESPGHAN. *Eur J Pediatr*. 2024;183:3253-3262.
268. Bouhuys M, Mian P, van Rheenen PF. Ustekinumab trough levels in children with Crohn's disease refractory to anti-tumor necrosis factor agents: a prospective case series of off-label use. *Front Pharmacol*. 2023;14:1180750.
269. Fang S, Zhang S, Zhang C, Wang L. Effectiveness and Safety of Ustekinumab for Pediatric Inflammatory Bowel Disease: A Systematic Review. *Paediatr Drugs*. 2023;25:499-513.
270. Marques BO, Gusmão ABF, Gusmão ALF, et. Long-term effects of ustekinumab in children with inflammatory bowel disease: a systematic review. *J Pediatr Gastroenterol Nutr*. 2025;81:1045-1059.
271. Mitchel EB, Dolinger MT, Constant B, et al. Ustekinumab is safe and effective in pediatric patients with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2025;80:653-663.
272. Panaccione R, Feagan BG, Afzali A, et al. Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3): 48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials. *Lancet*. 2025;406:358-375.
273. Ferrante M, D'Haens G, Jairath V, et al. Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study. *Lancet*. 2024;404:2423-2436.
274. Peyrin-Biroulet L, Chapman JC, Colombel J-F, et al. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. *N Engl J Med*. 2024;391:213-223.
275. Dziegielewski C, Yuan Y, Ma C, et al. IL-23p19 Antagonists vs ustekinumab for treatment of Crohn's disease: a meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2025;120:2260-2267.
276. Pugliano CL, Liang RF, Ruffa A, Iacucci M, Ghosh S. Practical considerations for the use of IL-23p19 inhibitors in inflammatory bowel disease: how to choose between them and why it matters? *J Crohns Colitis*. 2025;19:jjaf144.
277. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet*. 2022;399:2015-2030.
278. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet*. 2022;399:2031-2046.
279. Spencer EA, Buck Q, Collen R, Stein R, Shouval D, et al. Real-world effectiveness of Risankizumab induction and maintenance therapy in pediatric patients with Crohn's Disease: a multicenter retrospective analysis. Reports: Volume 6, Issue S3 7th International Symposium Bowel Disease On Paediatric Inflammatory, S10. 2025
280. 13. U.S. National Library of Medicine: ClinicalTrials.gov. Study of vedolizumab (MLN0002) in patients with moderate to severe Crohn's disease (GEMINI II) [Internet]. c2014 [cited 2018 Mar 30]. https://clinicaltrials.gov/ct2/show/NCT00783692.
281. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369:711-721.
282. Garcia-Romero R, Martinez de Zabarte Fernandez JM, Pujol-Muncunill G, et al. Safety and effectiveness of vedolizumab in paediatric patients with inflammatory bowel disease: an observational multicentre Spanish study. *Eur J Pediatr*. 2021;180:3029-3038.
283. Hajjat TM, Mosha M, Whaley KG, et al. Vedolizumab experience in children and adolescents with inflammatory bowel disease: a multicenter observational study. *Crohns Colitis 360*. 2021;3:otab039.
284. Hyams JS, Turner D, Cohen SA, et al. Pharmacokinetics, safety and efficacy of intravenous vedolizumab in paediatric patients with ulcerative colitis or Crohn's disease: results from the phase 2 HUBBLE study. *J Crohns Colitis*. 2022;16:1243-1254.
285. Atia O, Shavit-Brunschwig Z, Mould DR, et al. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet Gastroenterol Hepatol*. 2023;8:31-42.
286. Atia O, Shavit-Brunschwig Z, Lev-Tzion R, et al. Maintenance treatment with vedolizumab in paediatric inflammatory bowel disease (VEDOKIDS): 54-week outcomes of a multicentre, prospective, cohort study. *Lancet Gastroenterol Hepatol*. 2025;10:234-247.
287. Singh N, Rabizadeh S, Jossen J, et al. Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22:2121-2126.
288. Schneider A-M, Weghuber D, Hetzer B, et al. Vedolizumab use after failure of TNF-α antagonists in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol*. 2018;18:140.
289. Hemming-Harlo M, Merras-Salmio L, Nikkonen A, Kolho KL. Drug levels of VEDOLIZUMAB in patients with pediatric-onset inflammatory bowel disease in a real-life setting. *Eur J Pediatr*. 2024;183:313-322.
290. Aardoom MA, Jongsma MME, de Vries A, Wolthoorn J, de Ridder L, Escher JC. Vedolizumab trough levels in children with anti-tumor necrosis factor refractory inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;71:501-507.
291. Jossen J, Kiernan BD, Pittman N, Dubinsky MC. Anti-tumor necrosis factor-alpha exposure impacts vedolizumab mucosal healing rates in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;70:304-309.
292. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381:1201-1214.
293. Verstockt B, Dreesen E, Noman M, et al. Ustekinumab exposure-outcome analysis in Crohn's disease only in part explains

limited endoscopic remission rates. *J Crohns Colitis*. 2019;13:864-872.
294. Porth R, Deyhim T, Geeganage G, et al. Proactive therapeutic drug monitoring of ustekinumab is associated with increased drug persistence in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2025;31:1806-1810.
295. Afif W, Sattin B, Dajnowiec D, et al. Ustekinumab therapeutic drug monitoring-impact on clinical practice: a multicenter cross-sectional observational trial. *Dig Dis Sci*. 2022;67:3148-3157.
296. Ricciuto A, McKay HE, deBruyn J, et al. A257 early proactive therapeutic drug monitoring with ustekinumab therapy in paediatric Crohn's disease. *Journal of the Canadian Association of Gastroenterology*. 2024;7:206-207.
297. Roblin X, Moschetti E, Barrau M, Cheifetz AS, Papamichael K, Paul S. Risankizumab concentration but not IL-22 levels are associated with clinical and biochemical remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2024;22: 2340-2343.e2.
298. Zeissig S, Rosati E, Dowds CM, et al. Vedolizumab is associated with changes in innate rather than adaptive immunity in patients with inflammatory bowel disease. *Gut*. 2019;68:25-39.
299. Ungar B, Kopylov U, Yavzori M, et al. Association of vedolizumab level, anti-drug antibodies, and α4β7 occupancy with response in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2018;16:697-705.e7.
300. Rosario M, French JL, Dirks NL, et al. Exposure-efficacy relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn's disease. *J Crohns Colitis*. 2018;12:510-519.
301. Yacoub W, Williet N, Pouillon L, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. *Aliment Pharmacol Ther*. 2018;47:906-912.
302. Löwenberg M, Vermeire S, Mostafavi N, et al. Vedolizumab induces endoscopic and histologic remission in patients with Crohn's disease. *Gastroenterology*. 2019;157:997-1006.e6.
303. Porth R, Deyhim T, Zullow S, et al. Proactive therapeutic drug monitoring is associated with increased drug persistence in patients with inflammatory bowel disease treated with intravenous vedolizumab. *Inflamm Bowel Dis*. 2025;31:485-491.
304. Ungar B, Malickova K, Hanžel J, et al. Dose optimisation for loss of response to vedolizumab- pharmacokinetics and immune mechanisms. *J Crohns Colitis*. 2021;15:1707-1719.
305. Loftus EV, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2023;388:1966-1980.
306. Peyrin-Biroulet L, Panaccione R, Louis E, et al. Upadacitinib achieves clinical and endoscopic outcomes in Crohn's disease regardless of prior biologic exposure. *Clin Gastroenterol Hepatol*. 2024;22:2096-2106.
307. Colombel J-F, Hisamatsu T, Atreya R, et al. Upadacitinib reduces Crohn's disease symptoms within the first week of induction therapy. *Clin Gastroenterol Hepatol*. 2024;22:1668-1677.
308. Cohen S, Spencer EA, Dolinger MT, et al. Upadacitinib for induction of remission in paediatric Crohn's disease: an international multicentre retrospective study. *Aliment Pharmacol Ther*. 2025;61:1372-1380.
309. Attauabi M, Steenholdt C, Poulsen A, et al. Network meta-analysis: comparative onset of early effect of biologics and small molecules in moderately to severely active luminal Crohn's disease. *Aliment Pharmacol Ther*. 2024;60:124-143.
310. Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. *Gut*. 2023;72:264-274.
311. Singh S, Murad MH, Fumery M, et al. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6:1002-1014.
312. Kapizioni C, Desoki R, Lam D, et al. Biologic therapy for inflammatory bowel disease: real-world comparative effectiveness and impact of drug sequencing in 13 222 patients within the UK IBD BioResource. *J Crohns Colitis*. 2024;18:790-800.
313. Chetwood JD, Ko Y, Pudipeddi A, Kariyawasam V, Paramsothy S, Leong RW. Biological agents in the treatment of Crohn's disease: a propensity score-matched analysis from the prospective persistence australian national IBD cohort (PANIC3) study. *Am J Gastroenterol*. 2024;119:1536-1544.
314. Ibing S, Cho JH, Böttinger EP, Ungaro RC. Second-line biologic therapy following tumor necrosis factor antagonist failure: a real-world propensity score-weighted analysis. *Clin Gastroenterol Hepatol*. 2023;21:2629-2638.
315. Yang H, Huang Z, Li M, et al. Comparative effectiveness of ustekinumab vs. vedolizumab for anti-TNF-naïve or anti-TNF-exposed Crohn's disease: a multicenter cohort study. *EClinicalMedicine*. 2023;66:102337.
316. Yerushalmy-Feler A, Brauner C, Cohen S. Dual-targeted therapy in pediatric inflammatory bowel disease: a comprehensive review. *Paediatr Drugs*. 2023;25:489-498.
317. Yerushalmy-Feler A, Olbjorn C, Kolho K-L, et al. Dual biologic or small molecule therapy in refractory pediatric inflammatory bowel disease (DOUBLE-PIBD): a multicenter study from the pediatric IBD porto group of ESPGHAN. *Inflamm Bowel Dis*. 2024;30:159-166.
318. Wlazlo M, Meglicka M, Wiernicka A, Osiecki M, Matuszczyk M, Kierkus J. Combination biologic therapy in pediatric inflammatory bowel disease: safety and efficacy over a minimum 12-month follow-up period. *J Pediatr Gastroenterol Nutr*. 2024;79:54-61.
319. Kellar A, Dolinger MT, Spencer EA, Dubinsky MC. Real-world outcomes of dual advanced therapy in children and young adults with inflammatory bowel disease. *Dig Dis Sci*. 2024;69:1826-1833.
320. Dolinger MT, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual biologic and small molecule therapy for the treatment of refractory pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27:1210-1214.
321. Wlazło M, Meglicka M, Wiernicka A, Osiecki M, Kierkuś J. Dual biologic therapy in moderate to severe pediatric inflammatory bowel disease: a retrospective study. *Children (Basel)*. 2022;10:
322. Olbjørn C, Rove JB, Jahnsen J. Combination of biological agents in moderate to severe pediatric inflammatory bowel disease: a case series and review of the literature. *Paediatr Drugs*. 2020;22:409-416.
323. Alayo QA, Fenster M, Altayar O, et al. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel disease. *Crohns Colitis 360*. 2022;4:otac002.
324. Ahmed W, Galati J, Kumar A, et al. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20:e361-e79.
325. Kaur M, Dalal RL, Shaffer S, Schwartz DA, Rubin DT. Inpatient management of inflammatory bowel disease-related complications. *Clin Gastroenterol Hepatol*. 2020;18:1346-1355.
326. Adegbola SO, Dibley L, Sahnan K, et al. Burden of disease and adaptation to life in patients with Crohn's perianal fistula: a qualitative exploration. *Health Qual Life Outcomes*. 2020;18:370.

327. Atia O, Focht G, Lujan R, et al. Perianal Crohn disease is more common in children and is associated with complicated disease course despite higher utilization of biologics: a population-based study from the epidemiology group of the Israeli IBD Research Nucleus (epiIIRN). *J Pediatr Gastroenterol Nutr*. 2022;74:788-793.
328. Tsai L, McCurdy JD, Ma C, Jairath V, Singh S. Epidemiology and natural history of perianal Crohn's disease: a systematic review and meta-analysis of population-based cohorts. *Inflamm Bowel Dis*. 2022;28:1477-1484.
329. Fung M, Farbod Y, Kankouni H, Singh S, McCurdy JD. Does combined medical and surgical treatment improve perianal fistula outcomes in patients with Crohn's disease? A systematic review and meta-analysis. *J Crohns Colitis*. 2024;18:1261-1269.
330. Geldof J, Iqbal N, LeBlanc J-F, et al. Classifying perianal fistulising Crohn's disease: an expert consensus to guide decision-making in daily practice and clinical trials. *Lancet Gastroenterol Hepatol*. 2022;7:576-584.
331. Carnovale C, Maffioli A, Zaffaroni G, et al. Efficacy of tumour necrosis factor-alpha therapy in paediatric Crohn's disease patients with perianal lesions: a systematic review. *Expert Opin Biol Ther*. 2020;20:239-251.
332. Forsdick VK, Tan Tanny SP, King SK. Medical and surgical management of pediatric perianal Crohn's disease: a systematic review. *J Pediatr Surg*. 2019;54:2554-2558.
333. Ruemmele FM, Rosh J, Faubion WA, et al. Efficacy of adalimumab for treatment of perianal fistula in children with moderately to severely active Crohn's disease: results from IMAgINE 1 and IMAgINE 2. *J Crohns Colitis*. 2018;12:1249-1254.
334. De Gregorio M, Lee T, Krishnaprasad K, et al. Higher anti-tumor necrosis factor-alpha levels correlate with improved radiologic outcomes in Crohn's perianal fistulas. *Clin Gastroenterol Hepatol*. 2022;20:1306-1314.
335. Strik AS, Löwenberg M, Buskens CJ, et al. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. *Scand J Gastroenterol*. 2019;54:453-458.
336. Colombel J-F, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut*. 2009;58:940-948.
337. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol*. 2013;11:975-981 e1-4.
338. Attauabi M, Burisch J, Seidelin JB. Efficacy of ustekinumab for active perianal fistulizing Crohn's disease: a systematic review and meta-analysis of the current literature. *Scand J Gastroenterol*. 2021;56:53-58.
339. Vuyyuru SK, Solitano V, Narula N, et al. Pharmacological therapies for the management of fistulizing Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2024;18:589-603.
340. Colombel J-F, Lacerda AP, Irving PM, et al. Efficacy and safety of upadacitinib for perianal fistulizing Crohn's disease: a post hoc analysis of 3 phase 3 trials. *Clin Gastroenterol Hepatol*. 2025;23:1019-1029.
341. Ayoub F, Odenwald M, Micic D, et al. Vedolizumab for perianal fistulizing Crohn's disease: systematic review and meta-analysis. *Intest Res*. 2022;20:240-250.
342. Rosen MJ, Moulton DE, Koyama T, et al. Endoscopic ultrasound to guide the combined medical and surgical management of pediatric perianal Crohn's disease. *Inflamm Bowel Dis*. 2010;16:461-468.
343. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis*. 2003;9:98-103.
344. Vu JV, Kurowski JA, Achkar J-P, et al. Long-term outcomes of perianal fistulas in pediatric Crohn's disease. *Dis Colon Rectum*. 2023;66:816-822.
345. Herissay A, Siproudhis L, Le Balc'h E, et al. Combined strategies following surgical drainage for perianal fistulizing Crohn's disease: failure rates and prognostic factors. *Colorectal Dis*. 2021;23:159-168.
346. Papaconstantinou I, Kontis E, Koutoulidis V, Mantzaris G, Vassiliou I. Surgical management of fistula-in-ano among patients with Crohn's disease: analysis of outcomes after fistulotomy or seton placement-single-center experience. *Scand J Surg*. 2017;106:211-215.
347. Park MY, Yoon YS, Kim HE, et al. Surgical options for perianal fistula in patients with Crohn's disease: a comparison of seton placement, fistulotomy, and stem cell therapy. *Asian J Surg*. 2021;44:1383-1388.
348. Williams JG, Rothenberger DA, Nemer FD, Goldberg SM. Fistula-in-ano in Crohn's disease. Results of aggressive surgical treatment. *Dis Colon Rectum*. 1991;34:378-384.
349. Bessi G, Siproudhis L, Merlini l'Héritier A, et al. Advancement flap procedure in Crohn and non-Crohn perineal fistulas: a simple surgical approach. *Colorectal Dis*. 2019;21:66-72.
350. Roper MT, Trinidad SM, Ramamoorthy SL, et al. Endorectal advancement flaps for perianal fistulae in Crohn's disease: careful patient selection leads to optimal outcomes. *J Gastrointest Surg*. 2019;23:2277-2284.
351. Rozalén V, Parés D, Sanchez E, et al. Advancement flap technique for anal fistula in patients with Crohn's disease: a systematic review of the literature. *Cir Esp*. 2017;95:558-565.
352. Seifarth C, Lehmann KS, Holmer C, Pozios I. Healing of rectal advancement flaps for anal fistulas in patients with and without Crohn's disease: a retrospective cohort analysis. *BMC Surg*. 2021;21:283.
353. van Praag EM, Stellingwerf ME, van der Bilt JDW, Bemelman WA, Gecse KB, Buskens CJ. Ligation of the intersphincteric fistula tract and endorectal advancement flap for high perianal fistulas in Crohn's disease: a retrospective cohort study. *J Crohns Colitis*. 2020;14:757-763.
354. Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas. *BJS Open*. 2019;3:231-241.
355. Emile SH, Khan SM, Adejumo A, Koroye O. Ligation of intersphincteric fistula tract (LIFT) in treatment of anal fistula: an updated systematic review, meta-analysis, and meta-regression of the predictors of failure. *Surgery*. 2020;167:484-492.
356. Wood T, Truong A, Mujukian A, Zaghiyan K, Fleshner P. Increasing experience with the LIFT procedure in Crohn's disease patients with complex anal fistula. *Tech Coloproctol*. 2022;26:205-212.
357. Mujukian A, Truong A, Fleshner P, Zaghiyan K. Long-term healing after complex anal fistula repair in patients with Crohn's disease. *Tech Coloproctol*. 2020;24:833-841.
358. Vidon M, Munoz-Bongrand N, Lambert J, et al. Long-term efficacy of fibrin glue injection for perianal fistulas in patients with Crohn's disease. *Colorectal Dis*. 2021;23:894-900.
359. Esposito C, Autorino G, Cerulo M, et al. Video-assisted anal fistula treatment (VAAFT) combined with ozonide oil dressing: standardization of technique in pediatric patients. *Surg Endosc*. 2024;38:2273-2279.
360. Adegbola SO, Sahnan K, Tozer PJ, et al. Symptom amelioration in Crohn's perianal fistulas using video-assisted anal fistula treatment (VAAFT). *J Crohns Colitis*. 2018;12:1067-1072.

361. Cao D, Li W, Ji Y, Wang X, Cui Z. Efficacy and safety of FiLaC for perianal fistulizing Crohn's disease: a systematic review and meta-analysis. *Tech Coloproctol*. 2022;26:775-781.
362. Alam A, Lin F, Fathallah N, et al. FiLaC((R)) and Crohn's disease perianal fistulas: a pilot study of 20 consecutive patients. *Tech Coloproctol*. 2020;24:75-78.
363. Senéjoux A, Siproudhis L, Abramowitz L, et al. Fistula plug in fistulising ano-perineal Crohn's disease: a randomised controlled trial. *J Crohns Colitis*.. 2016;10:141-148.
364. Nasseri Y, Cassella L, Berns M, Zaghiyan K, Cohen J. The anal fistula plug in Crohn's disease patients with fistula-in-ano: a systematic review. *Colorectal Dis*. 2016;18:351-356.
365. Garg P, Song J, Bhatia A, Kalia H, Menon GR. The efficacy of anal fistula plug in fistula-in-ano: a systematic review. *Colorectal Dis*. 2010;12:965-970.
366. Thia KT, Mahadevan U, Feagan BG, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2009;15:17-24.
367. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:661-673.
368. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut*. 2014;63:292-299.
369. Dharmaraj R, Nugent M, Simpson P, Arca M, Gurram B, Werlin S. Outcomes after fecal diversion for colonic and perianal Crohn disease in children. *J Pediatr Surg*. 2018;53:472-476.
370. Johnston WR, Hwang R, Mattei P. Ostomy management for pediatric perianal Crohn's disease. *J Pediatr Surg*. 2024;59:1108-1112.
371. Jew M, Meserve J, Eisenstein S, Jairath V, McCurdy J, Singh S. Temporary faecal diversion for refractory perianal and/or distal colonic Crohn's disease in the biologic era: an updated systematic review with meta-analysis. *J Crohns Colitis*. 2024;18:375-391.
372. Nordenvall C, Rosvall O, Bottai M, et al. Surgical treatment in childhood-onset inflammatory bowel disease-a nationwide register-based study of 4695 incident patients in Sweden 2002-2014. *J Crohns Colitis*. 2018;12:157-166.
373. Mattioli G, Rossi V, Palo F, et al. Minimal invasive approach to paediatric colorectal surgery. *J Ped Endosc Surg*. 2021;3:129-139.
374. Bettenworth D, Baker ME, Fletcher JG, et al. A global consensus on the definitions, diagnosis and management of fibrostenosing small bowel Crohn's disease in clinical practice. *Nat Rev Gastroenterol Hepatol*. 2024;21:572-584.
375. de Carvalho MF, Carlos AdS, Kum AST, et al. Invasive therapeutic strategies for stricturing Crohn's disease in childhood: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2025;1031:1032-1040.
376. Neville JJ, Macdonald A, Fell J, Choudhry M, Haddad M. Therapeutic strategies for stricturing Crohn's disease in childhood: a systematic review. *Pediatr Surg Int*. 2021;37:569-577.
377. Ledder O, Viala J, Serban DE, et al. Endoscopic balloon dilatation in pediatric Crohn disease: an IBD Porto group study. *J Pediatr Gastroenterol Nutr*. 2023;77:62-69.
378. Schulberg JD, Wright EK, Holt BA, et al. Efficacy of drug and endoscopic treatment of Crohn's disease strictures: a systematic review. *J Gastroenterol Hepatol*. 2021;36:344-361.
379. Bronsky J, Zarubova K, Kubat M, Dotlacil V. Preventing recurrence of Crohn's disease post-ileocaecal surgery in paediatric patients: a therapy guide based on systematic review of the evidence. *Paediatr Drugs*. 2024;26:659-672.
380. Beelen EMJ, Nieboer D, Arkenbosch JHC, et al. Risk prediction and comparative efficacy of anti-TNF vs thiopurines, for preventing postoperative recurrence in Crohn's disease: a pooled analysis of 6 trials. *Clin Gastroenterol Hepatol*. 2022;20:2741-2752.e6.
381. D'Haens G, Taxonera C, Lopez-Sanroman A, et al. Vedolizumab to prevent postoperative recurrence of Crohn's disease (REPREVIO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Gastroenterol Hepatol*. 2025;10:26-33.
382. Yerushalmy-Feler A, Assa A. Pharmacological prevention and management of postoperative relapse in pediatric Crohn's disease. *Paediatr Drugs*. 2019;21:451-460.
383. Chavoshi M, Zamani S, Kolahdoozan S, Radmard AR. Diagnostic value of MR and CT enterography in post-operative recurrence of Crohn's disease: a systematic review and meta-analysis. *Abdom Radiol (NY)*. 2024;49:3975-3986.
384. Sauer CG, Kugathasan S, Martin DR, Applegate KE. Medical radiation exposure in children with inflammatory bowel disease estimates high cumulative doses. *Inflamm Bowel Dis*. 2011;17:2326-2332.
385. Constant BD, de Zoeten EF, Weinman JP, Albenberg L, Scott FI. Early anti-tumor-necrosis-factor therapy for Crohn's disease-related abdominal abscesses and phlegmon in children. *Dig Dis Sci*. 2023;68:877-888.
386. Lee KE, Sizemore JA, Kim G, Shen B, Sands BE. Impact of biologics and small-molecule agents on postoperative complications in IBD: a systematic review. *Dis Colon Rectum*. 2024;67:S11-S25.
387. Byrne LW, McKay D. Does perioperative biological therapy increase 30-day post-operative complication rates in inflammatory bowel disease patients undergoing intra-abdominal surgery? A systematic review. *Surgeon*. 2021;19:e153-e67.
388. Amil-Dias J, Kolacek S, Turner D, et al. Surgical management of Crohn disease in children: guidelines from the paediatric IBD Porto Group of ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2017;64:818-835.
389. Li G, Ren J, Wang G, et al. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. *Eur J Clin Nutr*. 2014;68:441-446.
390. Ge X, Tang S, Yang X, et al. The role of exclusive enteral nutrition in the preoperative optimization of laparoscopic surgery for patients with Crohn's disease: a cohort study. *Int J Surg*. 2019;65:39-44.
391. Rocha A, Bessa I, Lago P, Santos MD, Leite J, Castro-Poças F. Preoperative enteral nutrition and surgical outcomes in adults with Crohn's disease: a systematic review. *GE Port J Gastroenterol*. 2019;26:184-195.
392. Ahn MB, Yoo IH. Risk factors of low bone mineral density in newly diagnosed pediatric inflammatory bowel disease. *Nutrients*. 2023;15:5048.
393. Ronel NTR, Orlanski-Meyer E, Shteyer E, et al. Clinical criteria can identify children with osteopenia in newly diagnosed Crohn disease. *J Pediatr Gastroenterol Nutr*. 2021;72:270-275.
394. Morrow R, de Zoeten EF, Ma N, Chun C, Scott FI. Bone health screening practices with dual-energy X-ray absorptiometry and prediction of abnormal results in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2024;78:252-260.
395. Fritz J, Walia C, Elkadri A, et al. Systematic review of micronutrient deficiencies in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25:445-459.
396. Martin NG, Rigterink T, Adamji M, Wall CL, Day AS. Single high-dose oral vitamin D3 treatment in New Zealand children with inflammatory bowel disease. *Transl Pediatr*. 2019;8:35-41.

397. Lamberg-Allardt CJ, Viljakainen HT. 25-hydroxyvitamin D and functional outcomes in adolescents. *Am J Clin Nutr*. 2008;88:534S-536S.
398. Matias JNLV, Nutels GS, Laurindo LF, et al. The use of vitamin D for patients with inflammatory bowel diseases. *Int J Vitam Nutr Res*. 2024;94:54-70.
399. Ham NSHS, Oh EH, Kim J, et al. Influence of severe vitamin D deficiency on the clinical course of inflammatory bowel disease. *Dig Dis Sci*. 2021;66:587-596.
400. Janssen CE, Globig AM, Busse Grawitz A, Bettinger D, Hasselblatt P. Seasonal variability of vitamin D status in patients with inflammatory bowel disease - a retrospective cohort study. *PLoS One*. 2019;14:e0217238.
401. Kim S, Kang Y, Park S, Koh H, Kim S. Association of vitamin D with inflammatory bowel disease activity in pediatric patients. *J Korean Med Sci*. 2019;34:e204.
402. Strisciuglio CSE, Cenni S, Serra MR, et al. Improvement of body composition and bone mineral density after enteral nutrition in pediatric Crohn disease. *Dig Liver Dis*. 2020;52:630-636.
403. Goulart RdA, Barbalho SM. Can vitamin D induce remission in patients with inflammatory bowel disease? *Ann Gastroenterol*. 2022;35:140-149.
404. Guzman-Prado Y, Samson O, Segal JP, Limdi JK, Hayee B. Vitamin D therapy in adults with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2020;26:1819-1830.
405. El Amrousy D, El Ashry H, Hodeib H, Hassan S. Vitamin D in children with inflammatory bowel disease: a randomized controlled clinical trial. *J Clin Gastroenterol*. 2021;55:815-820.
406. Lee R, Maltz RM, Crandall WV, et al. Single high-dose vitamin D3 supplementation in pediatric patients with inflammatory bowel disease and hypovitaminosis D. *J Pediatr Gastroenterol Nutr*. 2020;70:e77-e80.
407. Shepherd D, Day AS, Leach ST, et al. Single high-dose oral vitamin D3 therapy (stoss): a solution to vitamin D deficiency in children with inflammatory bowel disease? *J Pediatr Gastroenterol Nutr*. 2015;61:411-414.
408. Pappa H, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C. Skeletal health of children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2011;53:11-25.
409. Gordon M, Sinopoulou V, Iheozor-Ejiofor Z, et al. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2021;1:CD013529.
410. Aljomah G, Baker SS, Schmidt K, et al. Anemia in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2018;67:351-355.
411. D'Arcangelo G, Distante M, Veraldi S, Tarani F, Musto F, Aloi M. Natural history of anemia and efficacy and safety of oral iron therapy in children newly diagnosed with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2023;76:771-775.
412. El Amrousy D, El-Afify D, Elsawy A, Elsheikh M, Donia A, Nassar M. Lactoferrin for iron-deficiency anemia in children with inflammatory bowel disease: a clinical trial. *Pediatr Res*. 2022;92:762-766.
413. Jacobson-Kelly AE, Stanek JR, Powers JM, Dotson JL, O'Brien SH. Trends in anemia, iron, therapy, and transfusion in hospitalized pediatric patients with inflammatory bowel disease. *J Pediatr*. 2020;222:141-145.e1.
414. Papadopoulos M, Patel D, Korologou-Linden R, et al. Safety and efficacy of parenteral iron in children with inflammatory bowel disease. *Br J Clin Pharmacol*. 2018;84:694-699.
415. Loveikyte R, Boer M, van der Meulen CN, et al. Anemia and iron deficiency in outpatients with inflammatory bowel disease: ubiquitous yet suboptimally managed. *J Clin Med*. 2022;11:6843.
416. Breton J, Witmer CM, Zhang Y, et al. Utilization of an electronic medical record-integrated dashboard improves identification and treatment of anemia and iron deficiency in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27:1409-1417.
417. Carman N, Muir R, Lewindon P. Ferric carboxymaltose in the treatment of iron deficiency in pediatric inflammatory bowel disease. *Transl Pediatr*. 2019;8:28-34.
418. Smith J, Jacobson-Kelly A, Donegan A, et al. Diagnosis and treatment of iron deficiency and anemia in youth with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2023;76:313-318.
419. Rempel J, Grover K, El-Matary W. Micronutrient deficiencies and anemia in children with inflammatory bowel disease. *Nutrients*. 2021;13:236.
420. Akhuemonkhan E, Parian A, Carson KA, Hutfless S. Adverse reactions after intravenous iron infusion among inflammatory bowel disease patients in the United States, 2010-2014. *Inflamm Bowel Dis*. 2018;24:1801-1807.
421. Bevers ND, Aliu A, Ardabili AR, et al. Ferric carboxymaltose versus ferrous fumarate in anemic children with inflammatory bowel disease: the POPEYE randomized controlled clinical trial. *J Pediatr*. 2023;256:113-119.e4.
422. Cococcioni L, Pensabene L, El-Khouly S, et al. Ferric carboxymaltose treatment for iron deficiency anemia in children with inflammatory bowel disease: efficacy and risk of hypophosphatemia. *Dig Liver Dis*. 2021;53:830-834.
423. Alhalabi M, Nasri D, Aji W. Portal vein thrombosis as extraintestinal complications of Crohn's disease: a case report and review of literature. *J Med Case Rep*. 2024;18:246.
424. Bickston SJ, Patrone MV. Current venous thromboembolism chemoprophylaxis practices after surgery for inflammatory bowel diseases. *Inflamm Bowel Dis*. 2022;28:1296-1297.
425. Gandhi J, Mages K, Kucine N, Chien K. Venous thromboembolism in pediatric inflammatory bowel disease: a scoping review. *J Pediatr Gastroenterol Nutr*. 2023;77:491-498.
426. Gue YX, Lip GYH. Increased risk of venous thromboembolism in patients with gastrointestinal disorders. *Am J Hematol*. 2023;98:1824-1825.
427. Murthy SK, Robertson McCurdy AB, Carrier M, McCurdy JD. Venous thromboembolic events in inflammatory bowel diseases: a review of current evidence and guidance on risk in the post-hospitalization setting. *Thromb Res*. 2020;194:26-32.
428. Rohani P, Taraghikhah N, Nasehi MM, Alimadadi H, Assadzadeh Aghdaei H. Cerebrovascular events in pediatric inflammatory bowel disease: a review of published cases. *Pediatr Gastroenterol Hepatol Nutr*. 2022;25:180-193.
429. De Laffolie J, Ballauff A, Wirth S, et al. Occurrence of thromboembolism in paediatric patients with inflammatory bowel disease: data from the CEDATA-GPGE registry. *Front Pediatr*. 2022;10:883183.
430. DeFilippis EM, Barfield E, Leifer D, et al. Cerebral venous thrombosis in inflammatory bowel disease. *J Dig Dis*. 2015;16:104-108.
431. Klomberg RCW, Vlug LE, de Koning BAE, de Ridder L. Venous thromboembolic complications in pediatric gastrointestinal diseases: inflammatory bowel disease and intestinal failure. *Front Pediatr*. 2022;2810:885876.
432. Aardoom MA, Klomberg RCW, Kemos P, et al. The incidence and characteristics of venous thromboembolisms in paediatric-onset inflammatory bowel disease: a prospective international cohort study based on the PIBD-SETQuality safety registry. *J Crohns Colitis*. 2022;16:695-707.
433. Assa A, Aloi M, Van Biervliet S, et al. Management of paediatric ulcerative colitis, part 2: acute severe colitis-an updated evidence-based consensus guideline from the European Society of

Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization. *J Pediatr Gastroenterol Nutr*. 2025;81:816-851.
434. Faye AS, Hung KW, Cheng K, et al. Minor hematochezia decreases use of venous thromboembolism prophylaxis in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:1394-1400.
435. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. *Value Health*. 2004;7:79-92.
436. Megari K. Quality of life in chronic disease patients. *Health Psychol Res*. 2013;1:e27.
437. Virta LJ, Kolho KL. Antidepressant use among paediatric patients with recent-onset inflammatory bowel disease: a nationwide case control study in Finland. *J Paediatr Child Health*. 2014;50:562-565.
438. Baudino MN, Gamwell KL, Roberts CM, et al. Disease severity and depressive symptoms in adolescents with inflammatory bowel disease: the mediating role of parent and youth illness uncertainty. *J Pediatr Psychol*. 2019;44:490-498.
439. Stapersma L, van den Brink G, van der Ende J, et al. Illness perceptions and depression are associated with health-related quality of life in youth with inflammatory bowel disease. *IntJ Behav Med*. 2019;26:415-426.
440. Hinnant L, Rios Villacorta N, Chen E, et al. Consensus statement on managing anxiety and depression in individuals with inflammatory bowel disease. *Inflamm Bowel Dis*. 2024;izae151.
441. Mackner LM, Greenley RN, Szigethy E, Herzer M, Deer K, Hommel KA. Psychosocial issues in pediatric inflammatory bowel disease: report of the north american society for pediatric gastroenterology, hepatology, and nutrition. *J Pediatr Gastroenterol Nutr*. 2013;56:449-458.
442. Gourdonneau A, Bruneau L, Ruemmele FM, et al. Clinical remission and psychological management are major issues for the quality of life in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2021;72:74-79.
443. Reed-Knight B, Lee JL, Greenley RN, Lewis JD, Blount RL. Disease activity does not explain it all: how internalizing symptoms and caregiver depressive symptoms relate to health-related quality of life among youth with inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22:963-967.
444. Bisgaard TH, Allin KH, Elmahdi R, Jess T. The bidirectional risk of inflammatory bowel disease and anxiety or depression: a systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2023;83:109-116.
445. Massironi S, Pigoni A, Vegni EAM, et al. The burden of psychiatric manifestations in inflammatory bowel diseases: a systematic review with meta-analysis. *Inflamm Bowel Dis*. 2025;31:izae206-1459.
446. Dubinsky MC, Dotan I, Rubin DT, et al. Burden of comorbid anxiety and depression in patients with inflammatory bowel disease: a systematic literature review. *Expert Rev Gastroenterol Hepatol*. 2021;15:985-997.
447. Stapersma L, van den Brink G, Szigethy EM, Escher JC, Utens E. Systematic review with meta-analysis: anxiety and depression in children and adolescents with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48:496-506.
448. Loftus EV, Guérin A, Yu AP, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. *Am J Gastroenterol*. 2011;106:1670-1677.
449. Butwicka A, Olén O, Larsson H, et al. Association of childhood-onset inflammatory bowel disease with risk of psychiatric disorders and suicide attempt. *JAMA Pediatr*. 2019;173:969-978.
450. Cooney R, Tang D, Barrett K, Russell RK. Children and young adults with inflammatory bowel disease have an increased incidence and risk of developing mental health conditions: a uk population-based cohort study. *Inflamm Bowel Dis*. 2024;30:1264-1273.
451. Arp L, Jansson S, Wewer V, Burisch J. psychiatric disorders in adult and paediatric patients with inflammatory bowel diseases – a systematic review and meta-analysis. *J Crohns Colitis*. 2022;16:1933-1945.
452. McDermott E, Mullen G, Moloney J, et al. Body image dissatisfaction: clinical features, and psychosocial disability in inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:353-360.
453. Claytor JD, Kochar B, Kappelman MD, Long MD. Body image dissatisfaction among pediatric patients with inflammatory bowel disease. *J Pediatr*. 2020;223:68-72.e1.
454. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6:359-370.
455. Brooks AJ, Norman P, Peach EJ, et al. Prospective study of psychological morbidity and illness perceptions in young people with inflammatory bowel disease. *J Crohns Colitis*. 2019;13:1003-1011.
456. Fairbrass KM, Lovatt J, Barberio B, Yuan Y, Gracie DJ, Ford AC. Bidirectional brain–gut axis effects influence mood and prognosis in IBD: a systematic review and meta-analysis. *Gut*. 2022;71:1773-1780.
457. Hoogkamer AB, Brooks AJ, Rowse G, Lobo AJ. Predicting the development of psychological morbidity in inflammatory bowel disease: a systematic review. *Frontline Gastroenterol*. 2021;12:137-144.
458. Kristensen MS, Kjærulff TM, Ersbøll AK, Green A, Hallas J, Thygesen LC. the influence of antidepressants on the disease course among patients with Crohn's disease and ulcerative colitis—a Danish nationwide register–based cohort study. *Inflamm Bowel Dis*. 2019;25:886-893.
459. Milo F, Imondi C, D'Amore C, et al. Short-term psychodynamic psychotherapy in addition to standard medical therapy increases clinical remission in adolescents and young adults with inflammatory bowel disease: a randomised controlled trial. *J Crohns Colitis*. 2024;18:256-263.
460. Piovani D, Armuzzi A, Bonovas S. Association of depression with incident inflammatory bowel diseases: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2024;30:573-584.
461. Ji Y, Li H, Dai G, Zhang X, Ju W. Systematic review and meta-analysis: impact of depression on prognosis in inflammatory bowel disease. *J Gastroenterol Hepatol*. 2024;39:1476-1488.
462. van den Brink G, Stapersma L, Vlug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48:358-369.
463. Clark JG, Srinath AI, Youk AO, et al. Predictors of depression in youth with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2014;58:569-573.
464. Mikocka-Walus A, Pittet V, Rossel J-B, et al. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2016;14:829-835.e1.
465. Frolkis AD, Vallerand IA, Shaheen A-A, et al. Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. *Gut*. 2019;68:1606-1612.

466. Guo L, Rohde J, Farraye FA. Stigma and disclosure in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:1010-1016.
467. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2002;35:557-563.
468. Brenner EJ, Long MD, Mann CM, et al. Responsiveness of the patient-reported outcomes measurement information system (PROMIS) pediatric measures to changes in disease status and quality of life among children and adolescents with Crohn's disease. *Inflamm Bowel Dis*. 2021;27:344-351.
469. Arvanitis M, DeWalt DA, Martin CF, et al. Patient-reported outcomes measurement information system in children with Crohn's disease. *J Pediatr*. 2016;174:153-159.e2.
470. Cushman GK, Stolz MG, Shih S, et al. Parent IMPACT-III: development and validation of an inflammatory bowel disease-specific health-related quality-of-life measure. *J Pediatr Gastroenterol Nutr*. 2020;70:205-210.
471. Azevedo S, Oliveira MM, Nogueira P, Lopes AI. Clinical usefulness of patient-reported-outcome-measurement information system in pediatric Crohn's Disease: a cross-sectional study. *Health Qual Life Outcomes*. 2024;22:112.
472. Chen J, Chen X, Sun Y, et al. The physiological and psychological effects of cognitive behavior therapy on patients with inflammatory bowel disease before COVID-19: a systematic review. *BMC Gastroenterol*. 2021;21:469.
473. Naude C, Skvarc D, Knowles S, Russell L, Evans S, Mikocka-Walus A. The effectiveness of mindfulness-based interventions in inflammatory bowel disease: a systematic review & meta-analysis. *J Psychosom Res*. 2023;169:111232.
474. Riggott C, Mikocka-Walus A, Gracie D, Ford A. Efficacy of psychological therapies in people with inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2023;8:919-931.
475. van den Brink G, Stapersma L, Bom AS, et al. Effect of cognitive behavioral therapy on clinical disease course in adolescents and young adults with inflammatory bowel disease and subclinical anxiety and/or depression: results of a randomized trial. *Inflamm Bowel Dis*. 2019;25:1945-1956.
476. Wren AA, Neiman N, Caruso TJ, et al. Mindfulness-based virtual reality intervention for children and young adults with inflammatory bowel disease: a pilot feasibility and acceptability study. *Children*. 2021;8:368.
477. Ahola Kohut S, Stinson J, Jelen A, Ruskin D. Feasibility and acceptability of a mindfulness-based group intervention for adolescents with inflammatory bowel disease. *J Clin Psychol Med Settings*. 2020;27:68-78.
478. Ewais T, Begun J, Kenny M, et al. Mindfulness based cognitive therapy for youth with inflammatory bowel disease and depression - findings from a pilot randomised controlled trial. *J Psychosom Res*. 2021;149:110594.
479. Keerthy D, Youk A, Srinath AI, et al. Effect of psychotherapy on health care utilization in children with inflammatory bowel disease and depression. *J Pediatr Gastroenterol Nutr*. 2016;63:658-664.
480. Stapersma L, van den Brink G, van der Ende J, et al. Psychological outcomes of a cognitive behavioral therapy for youth with inflammatory bowel disease: results of the HAPPY-IBD randomized controlled trial at 6- and 12-month follow-up. *J Clin Psychol Med Settings*. 2020;27:490-506.
481. Stapersma L, van den Brink G, van der Ende J, et al. Effectiveness of disease-specific cognitive behavioral therapy on anxiety, depression, and quality of life in youth with inflammatory bowel disease: a randomized controlled trial. *J Pediatr Psychol*. 2018;43:967-980.
482. Thompson RD, Craig A, Crawford EA, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings*. 2012;19:329-337.
483. Szigethy E, Bujoreanu SI, Youk AO, et al. Randomized efficacy trial of two psychotherapies for depression in youth with inflammatory bowel disease. *J Am Acad Child Adolesc Psychiatry*. 2014;53:726-735.
484. Szigethy E, Youk AO, Gonzalez-Heydrich J, et al. Effect of 2 psychotherapies on depression and disease activity in pediatric Crohn's disease. *Inflamm Bowel Dis*. 2015;21:1321-1328.
485. Thorkelson G, Bielefeldt K, Szigethy E. Empirically supported use of psychiatric medications in adolescents and adults with IBD. *Inflamm Bowel Dis*. 2016;22:1509-1522.
486. Levy RL, van Tilburg MAL, Langer SL, et al. Effects of a cognitive behavioral therapy intervention trial to improve disease outcomes in children with inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22:2134-2148.
487. Farrell D, McCarthy G, Savage E. Self-reported symptom burden in individuals with inflammatory bowel disease. *J Crohns Colitis*. 2016;10:315-322.
488. Jagt JZ, van Rheenen PF, Thoma SMA, Gower J, Reimering-Hartgerink PB. The top 10 research priorities for inflammatory bowel disease in children and young adults: results of a James Lind Alliance Priority Setting Partnership. 2023;8:690-691.
489. Hart AL, Lomer M, Verjee A, et al. What are the top 10 research questions in the treatment of inflammatory bowel disease? A priority setting partnership with the James Lind Alliance. *J Crohns Colitis*. 2017;11:204-211.
490. D'Silva A, Fox DE, Nasser Y, et al. Prevalence and risk factors for fatigue in adults with inflammatory bowel disease: a systematic review with meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20:995-1009.e7.
491. Turner ST, Focht G, Orlanski-Meyer E, et al. Fatigue in pediatric inflammatory bowel diseases: a systematic review and a single center experience. *J Pediatr Gastroenterol Nutr*. 2024;78:241-251.
492. Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *J Crohns Colitis*. 2014;8:1398-1406.
493. Farrell D, Artom M, Czuber-Dochan W, Jelsness-Jørgensen LP, Norton C, Savage E. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2020;4:CD012005.
494. Bager P, Hvas CL, Rud CL, Dahlerup JF. Randomised clinical trial: high-dose oral thiamine versus placebo for chronic fatigue in patients with quiescent inflammatory bowel disease. *Aliment Pharmacol Ther*. 2021;53:79-86.
495. Moulton CD, Young AH, Hart AL. Modafinil for severe fatigue in inflammatory bowel disease: a prospective case series. *Clin Gastroenterol Hepatol*. 2024;22:1737-1740.
496. Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut*. 2012;61:241-247.
497. Ghosh S, Louis E, Beaugerie L, et al. Development of the IBD disk: a visual self-administered tool for assessing disability in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2017;23:333-340.

498. Al Khoury A, Balram B, Bessissow T, et al. Patient perspectives and expectations in inflammatory bowel disease: a systematic review. *Dig Dis Sci*. 2022;67:1956-1974.
499. Bramuzzo M, De Carlo C, Arrigo S, et al. Parental psychological factors and quality of life of children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;70:211-217.
500. Cooney R, Barrett K, Russell RK. Impact of mental health comorbidity in children and young adults with inflammatory bowel disease: a UK population-based cohort study. *BMJ Open*. 2024;14:e080408.
501. Guilfoyle SM, Gray WN, Herzer-Maddux M, Hommel KA. Parenting stress predicts depressive symptoms in adolescents with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2014;26:964-971.
502. Turner D, Assa A, Malham M, et al. Reshaping study design for faster extrapolation-based drug approval in pediatric inflammatory bowel diseases: an ESPGHAN-NASPGHAN position paper. *J Pediatr Gastroenterol Nutr*. 2026;82:867-894.

Journal of Crohn's and Colitis 2026 20(8) 1–38
https://doi.org/10.1093/ecco-jcc/jjag084
ECCO Guideline