Pediatric Drugs (2026) 28:331–342
https://doi.org/10.1007/s40272-026-00751-8

CURRENT OPINION

Risks of Undertreatment and Overtreatment in Pediatric Inflammatory Bowel Disease: Navigating the Balance

Giulia D'Arcangelo[2] · Silvana Ancona[1] · Giulia Naspi Catassi[2] · Francesca Musto[2] · Rosaria Celano[2] · Marina Aloi[1,2]

Received: 5 February 2026 / Accepted: 6 May 2026 / Published online: 11 June 2026

Abstract

Despite major therapeutic advances in recent years, and early signs that the overall standard of care we can deliver to children with inflammatory bowel disease (IBD) is improving, the promise of precision medicine remains largely unfulfilled in daily practice. The goal is to match the right therapy to the right patient, in the right time window, so that treatment intensity reflects true disease biology and future risk rather than broad population averages. However, this approach is still an unmet need. Even when management is framed within a risk-based paradigm, clinical decisions are often guided by generalized recommendations and imperfect predictors, with limited capacity to individualize strategies at diagnosis and during follow-up. As a result, two opposite but equally relevant pitfalls remain very real. On one hand, overtreatment can lead to unnecessary exposure to immunosuppressive regimens in children and adolescents with mild, slowly progressive, or self-limited disease, increasing the burden of adverse events, monitoring, and psychosocial impact. On the other hand, undertreatment in truly high-risk patients can delay effective control of inflammation, allowing ongoing tissue damage, disease extension, growth impairment, and avoidable complications, ultimately worsening long-term outcomes. This critical review summarizes and critically appraises current recommendations and available evidence, focusing on the pitfalls of overtreatment and undertreatment in pediatric IBD.

Key Points

Pediatric inflammatory bowel disease management requires balancing effective disease control with the risk of both overtreatment and undertreatment.

Current risk stratification approaches may be incomplete and may not fully capture individual disease behavior in clinical practice.

Precision medicine and predictive biomarkers are needed to enable truly individualized treatment strategies.

1 Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and IBD–unclassified (IBD-U), are chronic, immune-mediated disorders of the gastrointestinal tract, resulting from a complex interplay between genetic susceptibility, environmental exposures, and microbiome-driven immune dysregulation. Approximately 10% of IBD cases present during childhood [1–3], with peak incidence in adolescents and young adults aged 15–29 years [4]. While incidence appears to stabilize in Western adult populations [5], pediatric IBD (PIBD) continues to rise globally, including in low- and middle-income countries [3, 6, 7]. This trend translates into a substantial and sustained burden on healthcare systems, as children and adolescents require longer-term care and often more intensive inpatient and outpatient management than adults [8–12].

PIBD is also characterized by distinct characteristics, including more extensive colonic involvement, higher disease activity at diagnosis, and an increased need for immunosuppressive and biologic therapies [13–16].

Therapeutic goals therefore extend beyond symptom control to include sustained mucosal healing, preservation of growth and pubertal development, and optimization of psychosocial wellbeing [17]. The STRIDE-II (Selecting Therapeutic Targets

✉ Marina Aloi
marina.aloi@unimi.it

1 Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

2 Gastroenterology, Hepatology and Cystic Fibrosis Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy

in Inflammatory Bowel Disease) principles provide an evidence-based, treat-to-target framework for both adult and pediatric IBD, defining therapeutic goals within specific timelines and prioritizing objective measures of disease control over symptom-based management [17]. Although STRIDE-II does not provide therapy-specific algorithms, international pediatric guidelines integrate risk stratification based on predictors of poor outcome [18], a concept central to the discussion of overtreatment and undertreatment.

The introduction of biologics has highlighted this issue. The growing availability of multiple effective agents, facilitated by the favorable cost profiles of biosimilars, has enabled earlier and broader biologic exposure in pediatric populations. For instance, in Canada, anti-tumor necrosis factor (anti-TNF) use increased from 13% to 60% in CD and from 4.9% to 25.5% in UC between 2010 and 2016 [19]. Similar trends have been observed in Scotland and Israel, with marked reductions in time to biologic initiation [20, 21]. These changes have been associated with improved outcomes, including reduced relapse rates, surgery, and colectomy risk [21–23].

Nevertheless, the key challenge remains striking a balance between preventing overtreatment (unnecessary exposure to immunosuppressive regimens) in children and adolescents with mild or indolent disease and avoiding harm from undertreatment in high-risk patients [24]. This balance lies at the core of precision medicine in PIBD: delivering the right therapy to the right patient at the right time through reliable risk stratification and tailored treatment strategies.

This narrative review addresses this challenge by providing an updated overview of current treatment paradigms for pediatric CD and UC, synthesizing contemporary evidence on risk stratification and prognostic assessment and a critical discussion of the risks of overtreatment and undertreatment in children and adolescents with IBD. We conclude by outlining a forward-looking perspective on the 'ideal' patient journey over the next decade, integrating treat-to-target principles, evolving biomarkers, and increasingly personalized models of care.

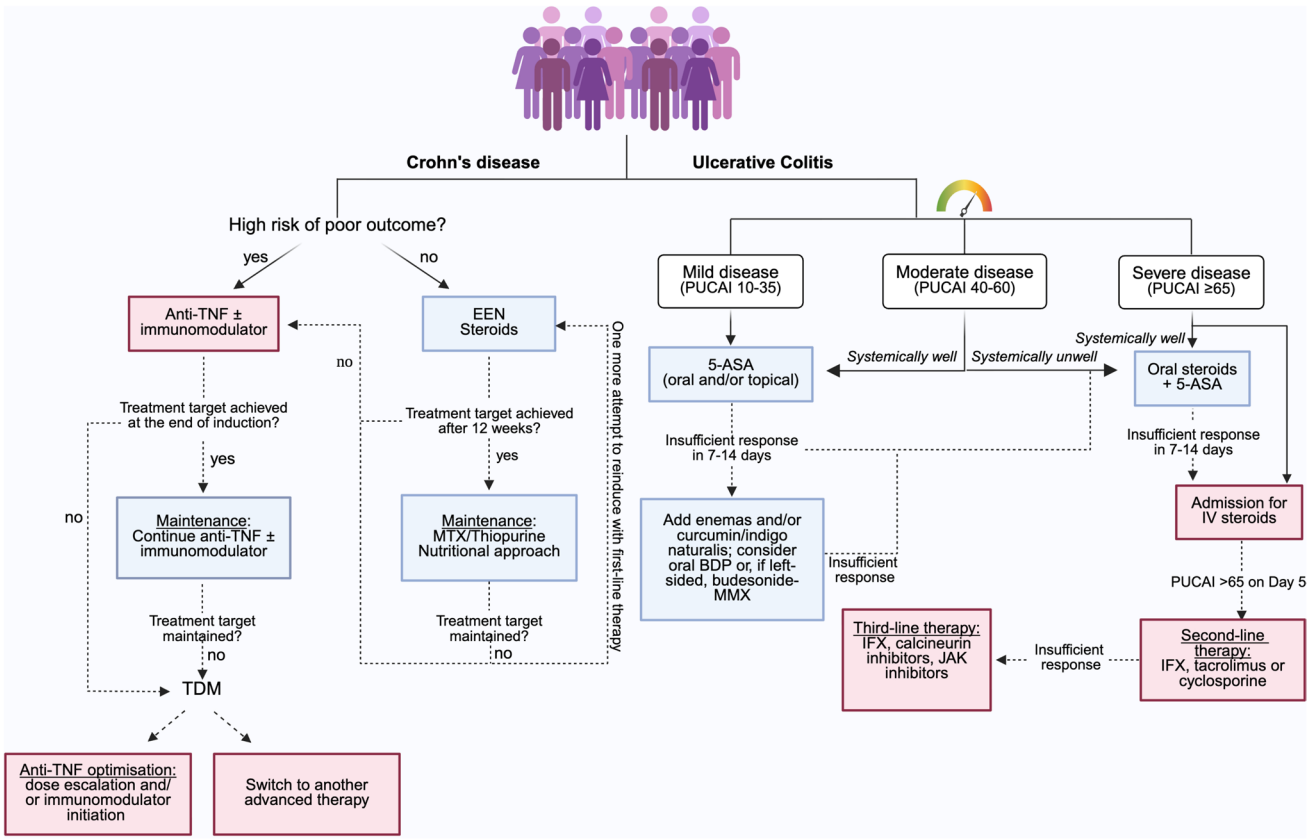

Fig. 1 Current treatment algorithms in pediatric inflammatory bowel disease. Therapeutic escalation is guided by clinical disease severity in ulcerative colitis and by predictors of poor outcome in Crohn's disease. Adapted from current pediatric guidelines for Crohn's disease [18] and ulcerative colitis [29, 98]. *BDP* beclomethasone dipropionate, *EEN* exclusive enteral nutrition, *IFX* infliximab, *IV* intravenous, *JAK* Janus kinase, *MTX* methotrexate, *PUCAI* Pediatric Ulcerative Colitis Activity Index, *TDM* therapeutic drug monitoring, *TNF* tumor necrosis factor, *5-ASA* 5-aminosalicylic acid

2 From Options to Strategy: Treatment Selection in Pediatric Crohn's Disease and Ulcerative Colitis to Avoid Undertreatment and Overtreatment

2.1 Induction of Remission in Pediatric Inflammatory Bowel Diseases (PIBD)

Figure 1 depicts the therapeutic algorithm for newly diagnosed PIBD.

Since 2020, pediatric CD management has been firmly grounded in risk stratification at diagnosis. Treatment intensity is guided by predictors of poor outcome, including panenteric disease, deep colonic ulcerations, perianal fistulizing disease, stricturing or penetrating behavior (B2/B3), severe growth impairment, and persistent disease activity despite initial therapy (Table 1) [18]. Children with these features have increased risk of complications, failure to achieve sustained remission, and surgery, justifying upfront biologic therapy, typically an anti-TNF agent [18]. Evidence from multiple cohorts supports the concept that early effective intervention may favorably modify disease trajectory and prevent progression to more aggressive phenotypes [25].

Conversely, children without predictors of poor outcome are most vulnerable to overtreatment. In low-to-moderate luminal CD with an inflammatory (B1) phenotype, a 6- to 8-week course of exclusive enteral nutrition (EEN) remains the recommended first-line induction therapy [18]. Where nutritional therapy is not feasible, an 8-week course of combined azithromycin and metronidazole (CD-AZCRO) represent an effective alternative induction in mild-to-moderate CD [26, 27].

Pediatric UC management, outside steroid-refractory acute severe colitis where strict adherence to day-by-day guideline recommendations is mandatory, generally follows a step-up approach. Baseline disease severity assessed using the Pediatric Ulcerative Colitis Activity Index (PUCAI) [28], fecal calprotectin (FC), and systemic inflammatory markers (fever, elevated C-reactive protein [CRP] and/or erythrocyte sedimentation rate [ESR], hypoalbuminemia), drives treatment decisions (Table 1). Topical and oral mesalamine remains first-line therapy in mild to-moderate UC, while oral corticosteroids are required in more aggressive disease [29].

2.1.1 Where Does the Risk of Under- and Overtreatment Lie?

Pediatric guidelines provide clear recommendations: in CD, risk-stratification dictates upfront anti-TNF therapy in high-risk patients, while in UC, PUCAI-guided step-up strategies predominate (Fig. 2). Adherence to these algorithms would theoretically minimizes both overtreatment and undertreatment in early disease.

However, several scenarios complicate real-world practice. Risk of overtreatment should be considered when prescribing combination therapy (biologic plus immunomodulator), which, in fact, remains debated: while the SONIC trial suggested benefits in adults [30], subsequent analyses indicate that proactive therapeutic drug monitoring (TDM)

Table 1 Predictors of poor outcome in pediatric inflammatory disease currently used in clinical practice

Crohn's disease
Panenteric disease
Deep colonic ulcerations
Perianal fistulizing disease
Stricturing or penetrating behavior (B2/B3)
Marked growth retardation
Persistent severe disease activity despite adequate induction therapy
Ulcerative colitis
High PUCAI score
Elevated fecal calprotectin levels
Low serum albumin and/or hemoglobin levels
Abnormal inflammatory markers (elevated CRP and/or ESR, thrombocytosis)

Based on ECCO-ESPGHAN guidelines [18, 29, 94]

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *PUCAI* Pediatric Ulcerative Colitis Activity Index

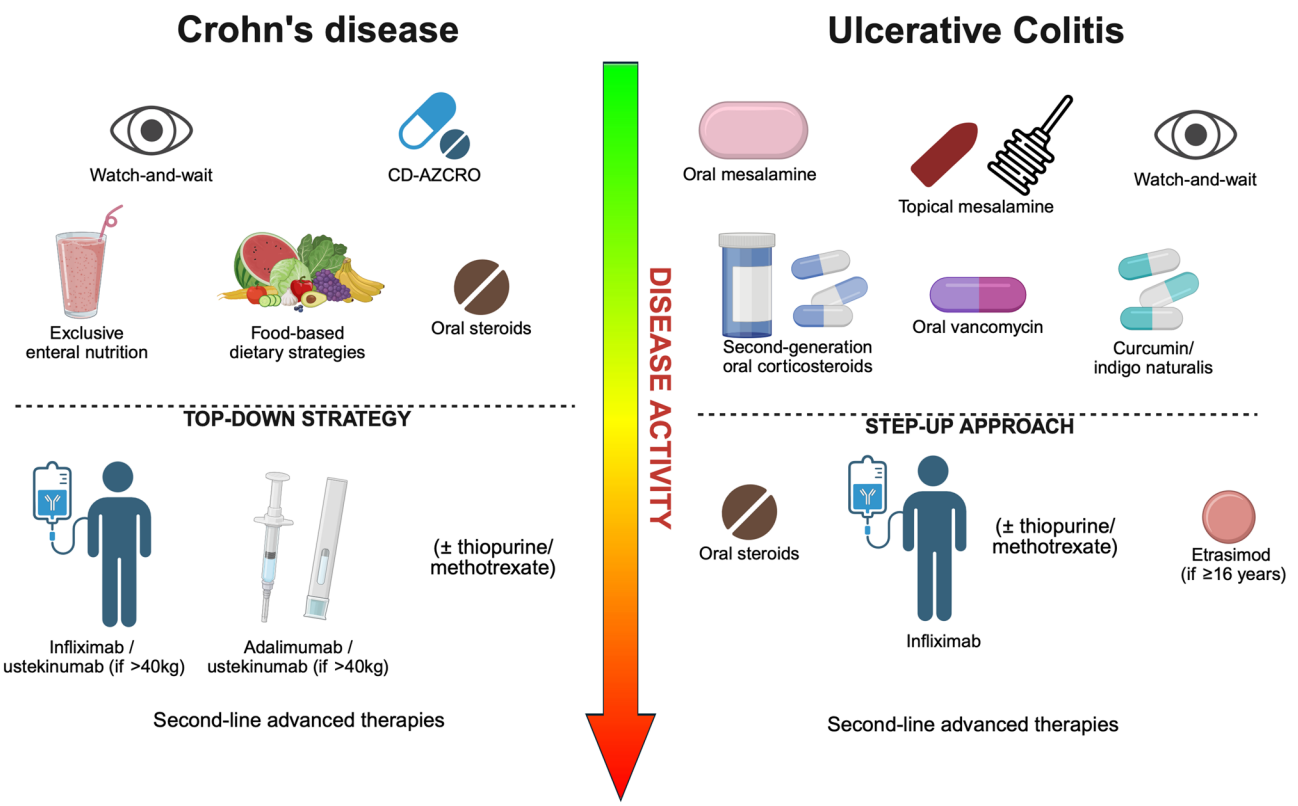

Fig. 2 Currently available therapeutic options for pediatric Crohn's disease and ulcerative colitis according to disease activity. *CD-AZCRO* azithromycin and metronidazole

may achieve similar outcomes with infliximab monotherapy [31]. Current pediatric guidelines recommend a concomitant immunomodulator with infliximab [18, 29], but this approach is controversial due to potential toxicities, including an increased risk of highly aggressive cancers associated with thiopurines, particularly in young males [32–38]. Importantly, guidelines also suggest considering withdrawal of the immunomodulator after at least 6 months of combination therapy in patients achieving endoscopic healing or normalization of FC [29], aiming to reduce long-term toxicity while maintaining protection against immunogenicity during the early phase of treatment. As a consequence, the decision to use combination versus monotherapy at the start of infliximab treatment varies widely among pediatric gastroenterologists [39].

In parallel, the risk of undertreatment should not be underestimated, particularly in younger children. In this population, standard dosing strategies may lead to subtherapeutic drug exposure, as younger patients often require higher mg/kg dosing compared with older children and adults [40, 41]. A similar issue arises in patients with a high inflammatory burden and/or hypoalbuminemia, in whom increased drug clearance may further reduce adequate exposure. In these settings, initiating anti-TNF therapy with intensified induction regimens may increase the likelihood of achieving early clinical and endoscopic remission [29], thereby limiting persistent inflammation and preserving the therapeutic window of opportunity.

Access to advanced therapies in children has historically lagged behind adult IBD, with infliximab and adalimumab long representing the only approved biologics in PIBD, compared with a rapidly expanding therapeutic landscape in adults. This gap in regulatory approval timelines may contribute to undertreatment or suboptimal disease control in pediatric populations [46, 47], where the use of non-anti-TNF biologics or small molecules often relies on complex off-label prescribing, when available.

Encouragingly, recent approvals of newer agents, such as ustekinumab for children with CD weighing >40 kg and etrasimod for adolescents with UC aged ≥16 years, mark an important step forward. However, the introduction of these advanced therapies also raises questions regarding potential overtreatment, particularly in patients with milder disease. In adult populations, ustekinumab has demonstrated efficacy comparable to anti-TNF agents when used as a first-line therapy, while being associated with a more favorable

safety profile [42–45]. From an overtreatment perspective, if similar outcomes are confirmed in pediatric cohorts, and especially with the increasing availability of biosimilars within this drug class, it is conceivable that, when prioritizing safety, anti-TNF agents may no longer represent the default first-line biologic options in adolescents with CD.

Finally, the role of upfront ileal resection warrants consideration. In the absence of pediatric data comparable to those generated by the LIR!C trial in adults [48], the conclusion at present remains straightforward: upfront surgical resection cannot be considered a preferred therapeutic option at the time of diagnosis in pediatric CD.

In UC, established clinical and biochemical parameters, including PUCAI, FC, albumin, hemoglobin, and inflammatory markers (Table 1), may support therapeutic decision making, including top-down strategies. However, a premature application of this therapeutic scheme might expose children to an unnecessary escalation and, as a consequence, an overtreatment of those who could achieved remission with mesalamine alone. Conversely, delayed escalation within a step-up strategy may compromise timely disease control in patients with more aggressive disease, thereby increasing the risk of undertreatment.

2.2 Maintenance Therapy in PIBD

While induction therapy is often straightforward, selecting and adjusting maintenance strategies presents a greater challenge, carrying significant risk of overtreatment and undertreatment (Fig. 3). According to the STRIDE-II recommendations [17], in both CD and UC, symptomatic relief represents an immediate goal, whereas clinical remission and normalization of inflammatory markers (CRP, FC) are medium-term targets, alongside normal growth in children. Long-term goals include endoscopic healing, restoration of quality of life, and prevention of disability. The expected timing for achieving these targets varies according to the therapeutic strategy employed [17], and serial reassessment should guide maintenance decisions. While such reassessment is essential to guide therapy, the need for repeated endoscopic evaluation, particularly in patients with clinical and biochemical remission or an indolent disease course, should be carefully weighed, as it may contribute to overtreatment. Failure to reach predefined targets within the expected timeframe should prompt treatment escalation to avoid undertreatment. Conversely, sustained deep remission may support cautious treatment de-escalation to minimize the risk of overtreatment.

Children with mild-to-moderate luminal CD responding to EEN may continue nutritional strategies or initiate

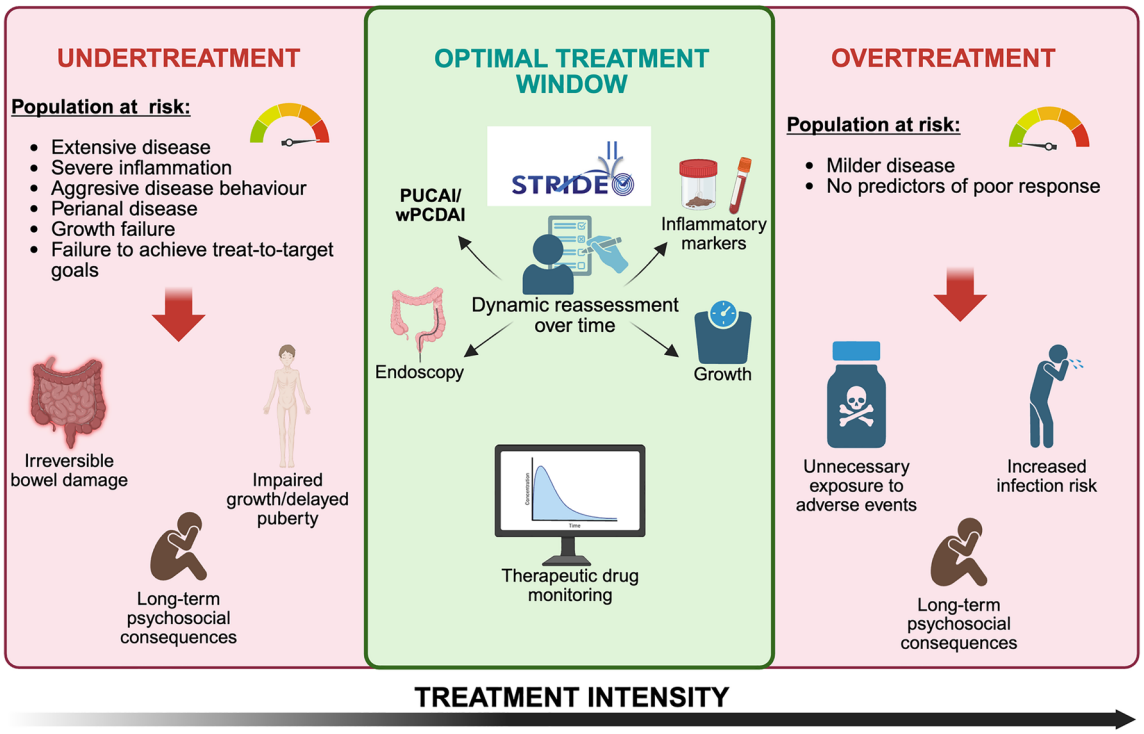

Fig. 3 Spectrum of undertreatment and overtreatment, associated risk population, and potential adverse effects. The balance lies within the optimal treatment window, which can be achieved in accordance with STRIDE-II principles and, when feasible, through therapeutic drug monitoring. *PUCAI* Pediatric Ulcerative Colitis Activity Index, *wPCDAI* weighted Pediatric Crohn's Disease Activity Index

immunomodulatory therapy, such as methotrexate or thiopurines. In fact, it is well recognized that completion of EEN followed by reintroduction of an unrestricted diet results in a rapid increase in FC levels [49], reflecting a rebound shift toward pre-treatment dysbiosis [50].

Immunomodulators are effective but carry long-term safety concerns, whereas continuing nutritional approaches avoid immunosuppression but require high levels of patient adherence and family motivation. Partial enteral nutrition (PEN) has been included as a maintenance option in the recent ECCO consensus on dietary management of IBD [51], particularly when providing ≥35% of daily energy requirements [52].

Children with mild-to-moderate CD achieving remission with corticosteroids or CD-AZCRO also require maintenance therapy with immunomodulators or nutritional strategies, as outlined above. In selected patients with very mild disease, a watch-and-wait approach may be considered; however, this strategy requires strict clinical and biochemical monitoring to detect disease recurrence at a very early stage. To date, no specific evidence supports this approach in PIBD.

Conversely, patients with mild-to-moderate CD who fail to respond to induction therapy require prompt escalation to biologic treatment. Similarly, children with high-risk predictors of poor outcome who are induced with biologics require close and timely reassessment according to STRIDE-II principles. In this context, TDM has significantly improved anti-TNF management by enabling dose optimization and timely escalation [53]. Proactive TDM, performed during remission to maintain adequate drug exposure, has been associated with higher rates of sustained clinical remission and greater biologic durability compared with reactive TDM [54]. This strategy is particularly relevant in patients at increased risk of drug underexposure, including those with low body weight, hypoalbuminemia, high inflammatory burden, or increased drug clearance [55], especially during the early post-induction phase.

Patients who fail to respond to anti-TNF therapy despite adequate trough levels should switch to alternative advanced therapy. However, data guiding second-line treatment positioning in PIBD remain limited, and therapeutic choices are often based on clinician experience, patient preference, and an individualized risk–benefit assessment.

In UC, topical and oral mesalamine remain first-line therapy for maintenance of remission in mild-to-moderate disease. Additional maintenance options include curcumin and indigo naturalis, which may be used as adjuvant therapies to mesalamine [29].

In selected children with mild UC, particularly those with concomitant primary sclerosing cholangitis (PSC), oral vancomycin has shown favorable effects on both biliary and intestinal disease [56]. Evidence supporting its use in patients without PSC remains limited to preliminary studies [57, 58].

The challenge in maintaining remission in UC lies in the capacity to escalate therapies in a timely manner, avoiding excessive use of steroids, and selecting therapies based on their rapidity of action (steroids) [26]. Recently, an S1P inhibitor (etrasimod) has been approved in adolescents, providing pediatric gastroenterologists with an additional advanced therapy option beyond TNF inhibitors.

2.2.1 Avoiding Overtreatment and Undertreatment During Maintenance: The Real Challenge

Earlier and more intensive treatment has improved outcomes in aggressive PIBD but raises concerns in milder disease lacking predictors of poor outcome. Overtreatment exposes patients to unnecessary risks without proportional clinical benefit. Pharmacological treatments carry a non-negligible burden of adverse events (AEs). Corticosteroids, particularly when used at high doses or for prolonged periods, carry the highest risk of short- and long-term toxicity [59], including infections, growth impairment, metabolic complications, and psychiatric disturbances [60]. Thiopurines, which rank immediately after corticosteroids in terms of safety concerns [59], are associated with relevant toxicities such as pancreatitis, myelotoxicity, and an increased risk of malignancies, particularly lymphoma [34, 61, 62]. Advanced therapies, including biologics and small molecules, also carry potential risks, albeit generally to a lesser extent [59]. Anti-TNF agents are associated with immunogenicity, infections, psoriasiform skin reactions [53], and a potential risk of skin cancer, while their association with lymphoma remains controversial [32–38]. Although experience with Janus kinase (JAK) inhibitors in PIBD is still limited [63–65], concerns regarding herpes zoster reactivation, venous thromboembolism, and cardiovascular events warrant careful patient selection. Even therapies generally considered to have a more favorable safety profile, such as vedolizumab and agents targeting the interleukin (IL)−12/23 or IL-23 pathways, have been associated with mild AEs [59].

In this context, treat-to-target strategies allow clinicians to tailor treatment intensity, optimizing disease control while minimizing unnecessary exposure to therapy-related harm.

In CD, children with mild disease activity and no predictors of poor outcomes should generally be managed with less intensive approaches and avoid overtreatment. Given the limited acceptability of prolonged EEN, several personalized food-based dietary strategies have been proposed, including the Crohn's Disease Exclusion Diet (CDED) [50], CD-TREAT [66], and the more recent Tasty&Healthy diet [67]. These approaches are generally more palatable, easier to follow, and better tolerated than prolonged EEN, and may

represent potential long-term maintenance options either alone or as adjunctive therapy [68]. However, evidence supporting their efficacy as standalone maintenance strategies remains limited, and inappropriate reliance on dietary therapy alone may expose patients to the risk of undertreatment. Recent data from Sigall Boneh et al. support the potential of CDED as a long-term management strategy in selected early responders [69] and important results are starting to elucidate the potential of such a regimen to induce important changes in the microbiome profile and to correct dysbiosis [70]. Notably, results from the French CD-HOPE trial demonstrated that cyclic EEN was superior to PEN in maintaining clinical remission over 1 year in pediatric patients who responded to EEN induction. This study introduced the concept of cyclic EEN (2-week EEN every 8 weeks for at least six cycles), offering a potentially more feasible nutritional maintenance strategy [71].

In the setting of sustained deep remission, treatment de-escalation has emerged as a potential strategy to reduce long-term treatment burden and minimize the risk of overtreatment in PIBD. De-escalation may include dose reduction, interval extension, or withdrawal of immunomodulators or biologic therapies, and should be considered only in carefully selected patients. A key challenge lies in identifying the subgroup of patients most suitable for de-escalation, particularly those achieving sustained clinical, biochemical, and radiological remission, supported by objective measures of disease control. Endoscopic reassessment and magnetic resonance imaging are currently used to guide these decisions, enabling evaluation of mucosal and transmural healing. Intestinal ultrasound may represent a promising, non-invasive, and more accessible tool for disease monitoring in this context; however further evidence is needed to define its role in guiding de-escalation strategies. Close monitoring and prompt re-escalation in case of disease recurrence remain essential [72]. In pediatric patients, concerns regarding relapse, growth impairment, and long-term disease control warrant a particularly cautious approach. De-escalation should therefore be viewed not as treatment withdrawal per se, but as a controlled, stepwise reduction in treatment intensity, balancing reduced drug exposure against the risks of disease reactivation.

In CD, this concept has recently been supported by data on extended adalimumab dosing intervals in children with CD [73]. Nevertheless, available evidence suggests that complete biologic withdrawal in pediatric CD remains inadvisable.

In UC, patients achieving concurrent clinical, mucosal, and histological remission may be candidates for de-escalating therapy and withdrawing biologics [61]. This is made possible by the option to use 5-ASA as maintenance therapy once deep remission or disease clearance has been achieved. This is not the case for CD, where mesalamine has no role in either induction or maintenance.

More robust evidence supports de-escalation from combination therapy to anti-TNF monotherapy, particularly after at least 6 months of sustained remission in patients without predictors of poor outcome [74–77].

Pursuing deeper endpoints, such as histological healing in UC and transmural healing in CD, may improve long-term prognosis but is not currently part of STRIDE-II formal goals [17]. In clinical practice, aiming for these outcomes may inadvertently drive overtreatment if additional therapy is initiated for clinical, biochemical, and endoscopic remission.

While overtreatment has gained increasing attention, undertreatment remains an equally relevant and potentially harmful issue in PIBD.

Delayed inflammation control may result in irreversible bowel damage, loss of the therapeutic window of opportunity, impaired growth [78], delayed puberty, and long-term psychosocial consequences [79].

In clinical practice, undertreatment often manifests as delayed escalation, prolonged steroid dependence, or persistence with suboptimal therapies driven by concerns about AEs. Optimizing drug dosing and ensuring timely access to effective therapies are therefore essential [53]. System-level barriers, including insurance-related delays [80, 81] and limited access to biologics in low- and middle-income countries [82, 83], further contribute to this risk.

3 Conclusions: Takeaways, Gaps, and Next Steps

Despite major therapeutic advances in IBD management, the optimal balance between overtreatment and undertreatment remains un unmet challenge in PIBD. While outcomes such as colectomy rates and disease-related complications have improved [21, 23, 84–87], the field is increasingly moving toward precision medicine and truly individualized care [88]. Stratifying patients according to molecular endotypes or microbial profile and predicting disease course at diagnosis and response to treatment remain critical research priorities [89–91].

Large cohort studies and multi-omics approaches have identified distinct disease trajectories and molecular profiles associated with disease severity and treatment response [92–95]. Emerging single-cell omics technologies and microbiome-integrated analyses further enhance our ability to define disease mechanisms and predict outcomes [96]. However, translation into routine clinical practice remains limited, highlighting the need for prospective validation in multicenter pediatric cohorts [97].

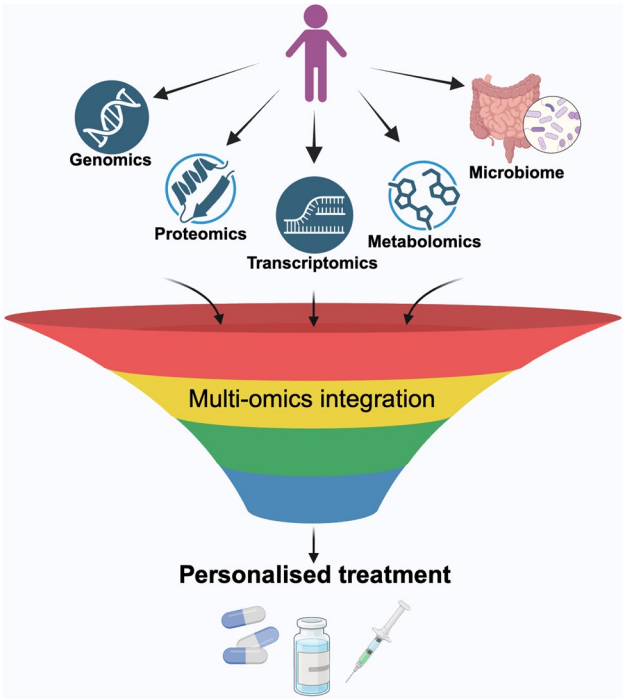

Fig. 4 Future precision medicine approaches in pediatric inflammatory bowel disease. Integration of multi-omics data is expected to enable personalized treatment selection

Ultimately, avoiding both overtreatment and undertreatment in PIBD requires a shift from current population-based algorithms (Fig. 1) toward future precision-based strategies (Fig. 4). The goal is a future in which each child receives the right treatment, at the right time, and at the right intensity, targeting the specific drivers of inflammation rather than applying uniform therapeutic escalation (Fig. 4). In this context, de-escalation strategies represent an essential yet understudied component of precision medicine in PIBD, aiming to reduce unnecessary long-term treatment exposure without compromising disease control. In parallel, the identification of predictive biomarkers capable of anticipating disease relapse remains a key unmet need, particularly in patients undergoing treatment de-escalation. Such tools could enable earlier therapeutic intervention, preventing progression to overt inflammation and symptomatic disease.

Funding Open access funding provided by Università degli Studi di Milano within the CRUI-CARE Agreement.

Declarations

Data availability Not applicable.

Funding No honorarium, grant, or other form of payment was given to anyone to write and produce the manuscript.

Conflict of Interest Marina Aloi is an Editorial Board member of Pediatric Drugs. Dr Aloi was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. All other authors have no financial disclosures or conflicts of interest related to the article to declare.

Ethical approval Not applicable

Consent to participate/Consent to publish Not applicable

Availability of data and material Not applicable

Code availability Not applicable.

Author contributions Giulia D'Arcangelo, as first author, contributed substantially to the conception and development of the manuscript. She performed the literature search and review, analyzed and interpreted the relevant literature, drafted the manuscript, and critically revised its content throughout the writing process. Silvana Ancona contributed to the literature search and review, conducted the figure production, and contributed to the writing of the manuscript. Giulia Naspi Catassi contributed to the literature search, figure editing, revision of the manuscript draft, and approval of the final version for publication. Francesca Musto contributed to the literature search, figure editing, revision of the manuscript draft, and approval of the final version for publication. Rosaria Celano contributed to the literature search, figure editing, revision of the manuscript draft, and approval of the final version for publication. Marina Aloi, as corresponding author, contributed to the conception of the manuscript, supervised the overall process, critically reviewed the content, edited and revised the final version, and approved the final version for publication.

References

1. Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr. 2003;143:525–31. https://doi.org/10.1067/s0022-3476(03)00444-x.
2. Burgess CJ, Henderson P, Jones G, Lees CW, Wilson DC. Pediatric patients (less than age of 17 years) account for less than 1.5% of all prevalent inflammatory bowel disease cases. J Pediatr Gastroenterol Nutr. 2020;71:521–3. https://doi.org/10.1097/MPG.0000000000002842.
3. Ghione S, Sarter H, Fumery M, Armengol-Debeir L, Savoye G, Ley D, et al. Dramatic increase in incidence of ulcerative colitis and Crohn's disease (1988–2011): a population-based study

of French adolescents. Am J Gastroenterol. 2018;113:265–72. https://doi.org/10.1038/ajg.2017.228.
4. Kuenzig ME, Fung SG, Marderfeld L, Mak JWY, Kaplan GG, Ng SC, et al. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. Gastroenterology. 2022;162:1147-1159.e4. https://doi.org/10.1053/j.gastro.2021.12.282.
5. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–78. https://doi.org/10.1016/S0140-6736(17)32448-0.
6. Khan R, Kuenzig ME, Benchimol EI. Epidemiology of pediatric inflammatory bowel disease. Gastroenterol Clin North Am. 2023;52:483–96. https://doi.org/10.1016/j.gtc.2023.05.001.
7. Alvisi P, Labriola F, Scarallo L, Gandullia P, Knafelz D, Bramuzzo M, 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;54:469–76. https://doi.org/10.1016/j.dld.2021.12.018.
8. El-Matary W, Carroll MW, Deslandres C, Griffiths AM, Kuenzig ME, Mack DR, et al. The 2023 impact of inflammatory bowel disease in Canada: special populations—children and adolescents with IBD. J Can Assoc Gastroenterol. 2023;6:S35-44. https://doi.org/10.1093/jcag/gwad016.
9. Kappelman MD, Rifas–Shiman SL, Porter CQ, Ollendorf DA, Sandler RS, Galanko JA, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology. 2008;135:1907–13. https://doi.org/10.1053/j.gastro.2008.09.012.
10. Park KT, Ehrlich OG, Allen JI, Meadows P, Szigethy EM, Henrichsen K, et al. The cost of inflammatory bowel disease: an initiative from the Crohn's & Colitis Foundation. Inflamm Bowel Dis. 2020;26:1–10. https://doi.org/10.1093/ibd/izz104.
11. El-Matary W, Kuenzig ME, Singh H, Okoli G, Moghareh M, Kumar H, et al. Disease-associated costs in children with inflammatory bowel disease: a systematic review. Inflamm Bowel Dis. 2020;26:206–15. https://doi.org/10.1093/ibd/izz120.
12. Turner D. Making the invisible visible: the hidden cost of pediatric inflammatory bowel disease. EMJ Gastroenterol. 2019. https://doi.org/10.33590/emjgastroenterol/10312720.
13. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr. 2015;169:1053. https://doi.org/10.1001/jamapediatrics.2015.1982.
14. Fumery M, Savoye G, Sarter H, Dupont-Lucas C, Bertrand V, Wils P, et al. Long-term outcome of colonic and ileal Crohn's disease: a two-decade population-based study in pediatric-onset disease. Inflamm Bowel Dis. 2025;31:3093–102. https://doi.org/10.1093/ibd/izaf133.
15. Gasparetto M, Guariso G, Pozza LVD, Ross A, Heuschkel R, Zilbauer M. Clinical course and outcomes of diagnosing Inflammatory Bowel Disease in children 10 years and under: retrospective cohort study from two tertiary centres in the United Kingdom and in Italy. BMC Gastroenterol. 2016;16:35. https://doi.org/10.1186/s12876-016-0455-y.
16. Akkelle BS, Ertem D, Volkan B, Tutar E. Phenotypic pattern of early versus later-onset pediatric inflammatory bowel disease in a Eurasian country. J Pediatr Gastroenterol Nutr. 2022. https://doi.org/10.1097/MPG.0000000000003557.
17. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, 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;160:1570–83. https://doi.org/10.1053/j.gastro.2020.12.031.
18. Van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical management of pediatric Crohn's disease: an ECCO-ESPGHAN guideline update. J Crohns Colitis. 2021;15:171–94. https://doi.org/10.1093/ecco-jcc/jjaa161.
19. El-Matary W, Leung S, Tennakoon A, Benchimol EI, Bernstein CN, Targownik LE. Trends of utilization of tumor necrosis factor antagonists in children with inflammatory bowel disease: a Canadian population-based study. Inflamm Bowel Dis. 2019;26:134–8. https://doi.org/10.1093/ibd/izz157.
20. Burgess CJ, Jackson R, Chalmers I, Russell RK, Hansen R, Scott G, et al. The inexorable increase of biologic exposure in pediatric inflammatory bowel disease: a Scottish, population-based, longitudinal study. Aliment Pharmacol Ther. 2022;56:1453–9. https://doi.org/10.1111/apt.17217.
21. Atia O, Orlanski-Meyer E, Lujan R, Ledderman N, Greenfeld S, Kariv R, et al. Improved outcomes of pediatric and adult Crohn's disease and association with emerging use of biologics—a nationwide study from the Epi-IIRN. J Crohns Colitis. 2022;16:778–85. https://doi.org/10.1093/ecco-jcc/jjab204.
22. D'Arcangelo G, Abi Nader E, Charbit-Henrion F, Talbotec C, Goulet O, Ruemmele FM, et al. Increased use of anti-tumor necrosis factor following the implementation of the ECCO–ESPGHAN guidelines and its impact on the outcome of pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2022;74:79–84. https://doi.org/10.1097/MPG.0000000000003301.
23. Ley D, Leroyer A, Dupont C, Sarter H, Bertrand V, Spyckerelle C, et al. New therapeutic strategies are associated with a significant decrease in colectomy rate in pediatric ulcerative colitis. Am J Gastroenterol. 2023;118:1997–2004. https://doi.org/10.14309/ajg.0000000000002316.
24. Temido MJ, Honap S, Jairath V, Vermeire S, Danese S, Portela F, et al. Overcoming the challenges of overtreating and undertreating inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2025;10:462–74. https://doi.org/10.1016/S2468-1253(24)00355-8.
25. Noor NM, Lee JC, Bond S, Dowling F, Brezina B, Patel KV, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol. 2024;9:415–27. https://doi.org/10.1016/S2468-1253(24)00034-7.
26. Levine A, Kori M, Kierkus J, Sigall Boneh R, Sladek M, Escher JC, et al. Azithromycin and metronidazole versus metronidazole-based therapy for the induction of remission in mild to moderate pediatric Crohn's disease : a randomised controlled trial. Gut. 2019;68:239–47. https://doi.org/10.1136/gutjnl-2017-315199.
27. Fioretti MT, Gianolio L, Armstrong K, Rabone RM, Henderson P, Wilson DC, et al. A decade of real-world clinical experience with 8-week azithromycin-metronidazole combined therapy in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2025;80:300–7. https://doi.org/10.1002/jpn3.12430.
28. Turner D, Hyams J, Markowitz J, Lerer T, Mack DR, Evans J, et al. Appraisal of the pediatric Ulcerative Colitis activity index (PUCAI). Inflamm Bowel Dis. 2009;15:1218–23. https://doi.org/10.1002/ibd.20867.
29. Wine E, Aloi M, Van Biervliet S, Bronsky J, di Carpi JM, Gasparetto M, et al. Management of pediatric ulcerative colitis, part 1: ambulatory care—an updated evidence-based consensus guideline from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation. J Pediatr Gastroenterol Nutr. 2025;81:765–815. https://doi.org/10.1002/jpn3.70097.
30. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–95. https://doi.org/10.1056/NEJMoa0904492.

31. Colombel J-F, Adedokun OJ, Gasink C, Gao L-L, Cornillie FJ, D'Haens GR, et al. Combination therapy with Infliximab and azathioprine improves Infliximab pharmacokinetic features and efficacy: a post hoc analysis. Clin Gastroenterol Hepatol. 2019;17:1525-1532.e1. https://doi.org/10.1016/j.cgh.2018.09.033.
32. Atia O, Harel S, Ledderman N, Greenfeld S, Kariv R, Dotan I, et al. Risk of cancer in pediatric onset Inflammatory Bowel diseases: a nation-wide study from the epi-IIRN. J Crohns Colitis. 2022;16:786–95. https://doi.org/10.1093/ecco-jcc/jjab205.
33. Kjærgaard VS, Jensen CB, Elmahdi R, Burisch J, Allin KH, Jess T. Cancer risk in pediatric-onset Inflammatory bowel disease: a population-based Danish cohort study. Gastroenterology. 2020;159:1609–11. https://doi.org/10.1053/j.gastro.2020.06.030.
34. Ehrström A, Jansson S, Jørgensen MH, Wewer V, Malham M. The risk of cancer in pediatric-onset immune-mediated inflammatory diseases – a nationwide study. J Autoimmun. 2024;149:103321. https://doi.org/10.1016/j.jaut.2024.103321.
35. Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;318:1679. https://doi.org/10.1001/jama.2017.16071.
36. Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol. 2014;12(9):1443–51. https://doi.org/10.1016/j.cgh.2014.01.021.
37. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda APM. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013;72:517–24. https://doi.org/10.1136/annrheumdis-2011-201244.
38. Zamani M, Alizadeh-Tabari S, Murad MH, Singh S, Ananthakrishnan AN, Malekzadeh R, et al. Meta-analysis: risk of lymphoma in patients with inflammatory bowel disease in population-based cohort studies. Aliment Pharmacol Ther. 2024. https://doi.org/10.1111/apt.18277.
39. Church PC, Hyams J, Ruemmele F, de Ridder L, Turner D, Griffiths AM. The continental divide: anti-TNF use in pediatric IBD is different in North America compared to other parts of the world. Can J Gastroenterol Hepatol. 2018;2018:1–8. https://doi.org/10.1155/2018/3190548.
40. Jongsma MME, Winter DA, Huynh HQ, Norsa L, Hussey S, Kolho K-L, et al. Infliximab in young pediatric IBD patients: it is all about the dosing. Eur J Pediatr. 2020;179:1935–44. https://doi.org/10.1007/s00431-020-03750-0.
41. Church PC, Ho S, Sharma A, Tomalty D, Frost K, Muise A, et al. Intensified infliximab induction is associated with improved response and decreased colectomy in steroid-refractory pediatric ulcerative colitis. J Crohns Colitis. 2019;13:982–9. https://doi.org/10.1093/ecco-jcc/jjz019.
42. Šubic Ž, Drobne D, Novak G. High persistence and efficacy of ustekinumab as a first-line biological therapy in inflammatory bowel disease: a real-world cohort study. Scand J Gastroenterol. 2026;61:95–103. https://doi.org/10.1080/00365521.2025.2597263.
43. Bessissow T, Narula N, Ma C, In TSH, Eberg M, Karra K, et al. Real-world effectiveness and safety of ustekinumab in bio-naive patients with moderate-to-severe Crohn's disease: a Canadian multi-center study. Dig Liver Dis. 2024;56:61–9. https://doi.org/10.1016/j.dld.2023.08.042.
44. Supovec E, Hanžel J, Novak G, Manevski D, Štabuc B, Drobne D. First-line anti-TNF agents, ustekinumab and vedolizumab perform similarly in Crohn' disease, but not in ulcerative colitis. Eur J Gastroenterol Hepatol. 2025;37:557–64. https://doi.org/10.1097/MEG.0000000000002940.
45. Shani U, Yaakobi H, Leibovitzh H, Maharshak N, Abitbol CM, Ungar B, et al. P1067 comparative effectiveness of first-line ustekinumab, vedolizumab and anti-TNF for Crohn's disease—a real-world study at two tertiary centers. J Crohns Colitis. 2026. https://doi.org/10.1093/ecco-jcc/jjaf231.1248.
46. Turner D, Assa A, Malham M, Bar-Asher SY, Rayan C, Hyams JS, 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;82:867–94. https://doi.org/10.1002/jpn3.70275.
47. Turner D, Griffiths AM, Wilson D, Mould DR, Baldassano RN, Russell RK, et al. Designing clinical trials in pediatric inflammatory bowel diseases: a PIBDnet commentary. Gut. 2020;69:32–41. https://doi.org/10.1136/gutjnl-2018-317987.
48. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol. 2017;2:785–92. https://doi.org/10.1016/S2468-1253(17)30248-0.
49. Logan M, Clark CM, Ijaz UZ, Gervais L, Duncan H, Garrick V, et al. The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction. Aliment Pharmacol Ther. 2019;50:664–74. https://doi.org/10.1111/apt.15425.
50. Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. Gastroenterology. 2019;157:440-450.e8. https://doi.org/10.1053/j.gastro.2019.04.021.
51. Svolos V, Gordon H, Lomer MCE, Aloi M, Bancil A, Day AS, et al. European Crohn's and Colitis Organisation consensus on dietary management of inflammatory bowel disease. J Crohns Colitis. 2025. https://doi.org/10.1093/ecco-jcc/jjaf122.
52. 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. https://doi.org/10.1093/ecco-jcc/jjae177.
53. Conrad MA, Kelsen JR. The treatment of pediatric inflammatory bowel disease with biologic therapies. Curr Gastroenterol Rep. 2020. https://doi.org/10.1007/s11894-020-00773-3.
54. Assa A, Matar M, Turner D, Broide E, Weiss B, Ledder O, 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. https://doi.org/10.1053/j.gastro.2019.06.003.
55. Clarkston K, Tsai Y, Jackson K, Rosen MJ, Denson LA, Minar P. Development of infliximab target concentrations during induction in pediatric Crohn disease patients. J Pediatr Gastroenterol Nutr. 2019;69:68–74. https://doi.org/10.1097/MPG.0000000000002304.
56. Ricciuto A, Liu K, El-Matary W, Amin M, Amir AZ, Aumar M, et al. Oral vancomycin is associated with improved inflammatory bowel disease clinical outcomes in primary sclerosing cholangitis-associated inflammatory bowel disease (PSC-IBD): a matched analysis from the Pediatric PSC Consortium. Aliment Pharmacol Ther. 2024;59:1236–47. https://doi.org/10.1111/apt.17936.
57. Ancona S, Gianolio L, Armstrong K, Rabone R, Merrick V, Henderson P, et al. Effectiveness and safety of oral vancomycin in non-primary sclerosing cholangitis pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2025. https://doi.org/10.1002/jpn3.70180.

58. Räisänen L, Balouch F, McLaren-Kennedy A, Clark JE, Lewindon P. Outcomes of oral vancomycin therapy in children with atypical ulcerative colitis with or without confirmed primary sclerosing cholangitis: a real-world observational study. BMJ Open Gastroenterol. 2025. https://doi.org/10.1136/bmjgast-2024-001605.
59. Bhat S, Click B, Regueiro M. Safety and monitoring of inflammatory bowel disease advanced therapies. Inflamm Bowel Dis. 2024;30:829–43. https://doi.org/10.1093/ibd/izad120.
60. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30. https://doi.org/10.1186/1710-1492-9-30.
61. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13:847-858.e4. https://doi.org/10.1016/j.cgh.2014.05.015.
62. Malham M, Jansson S, Malmborg P, Olén O, Paerregaard A, Virta LJ, et al. Risk factors of cancer in pediatric-onset Inflammatory Bowel Disease in Denmark and Finland. J Pediatr Gastroenterol Nutr. 2023;77:55–61. https://doi.org/10.1097/MPG.0000000000003781.
63. Yerushalmy-Feler A, Spencer EA, Dolinger MT, Suskind DL, Mitrova K, Hradsky O, et al. Upadacitinib for induction of remission in pediatric ulcerative colitis: an international multicenter study. J Crohns Colitis. 2025;19:jjae182. https://doi.org/10.1093/ecco-jcc/jjae182.
64. Cohen S, Spencer EA, Dolinger MT, Suskind DL, Mitrova K, Hradsky O, et al. Upadacitinib for induction of remission in pediatric Crohn's Disease: an international multicentre retrospective study. Aliment Pharmacol Ther. 2025;61:1372–80. https://doi.org/10.1111/apt.70016.
65. Yerushalmy-Feler A, Spencer EA, Bergstein S, Mitrova K, Hradsky O, Bramuzzo M, et al. Real-world experience with Upadacitinib for pediatric acute severe Ulcerative Colitis: an international multicenter retrospective study from the Pediatric IBD Porto Group of ESPGHAN. Inflamm Bowel Dis. 2025;31:3320–6. https://doi.org/10.1093/ibd/izaf166.
66. Svolos V, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, 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. https://doi.org/10.1053/j.gastro.2018.12.002.
67. Aharoni-Frutkoff Y, Plotkin L, Pollak D, Livovsky J, Focht G, Lev-Tzion R, 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. https://doi.org/10.1053/j.gastro.2025.06.011.
68. Sigall Boneh R, Westoby C, Oseran I, Sarbagili-Shabat C, Albenberg LG, Lionetti P, et al. The Crohn's disease exclusion diet: a comprehensive review of evidence, implementation strategies, practical guidance, and future directions. Inflamm Bowel Dis. 2024;30:1888–902. https://doi.org/10.1093/ibd/izad255.
69. Sigall Boneh R, Navas-López VM, Hussey S, Pujol-Muncunill G, Lawrence S, Rolandsdotter H, et al. Modified Crohn's disease exclusion diet maintains remission in pediatric Crohn's disease: randomized controlled trial. Clin Gastroenterol Hepatol. 2025;23:2001–11. https://doi.org/10.1016/j.cgh.2024.12.006.
70. Verburgt CM, Dunn KA, Ghiboub M, Lewis JD, Wine E, Sigall Boneh R, et al. Successful dietary therapy in pediatric Crohn's disease is associated with shifts in bacterial dysbiosis and inflammatory metabotype towards healthy controls. J Crohns Colitis. 2023;17:61–72. https://doi.org/10.1093/ecco-jcc/jjac105.
71. Pigneur B, Martinez-Vinson C, Bourmaud A, Dabadie A, Duclaux-Loras R, Hugot J-P, et al. Cyclic Exclusive Enteral Nutrition versus Partial Enteral Nutrition to maintain long-term drug-free remission in pediatric Crohn's Disease (CD-HOPE): an open-label, endpoint-blinded, randomised controlled trial. Lancet Gastroenterol Hepatol. 2026;11:204–17. https://doi.org/10.1016/S2468-1253(25)00262-6.
72. Doherty G, Katsanos KH, Burisch J, Allez M, Papamichael K, Stallmach A, et al. European Crohn's and colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. J Crohns Colitis. 2018;12:17–31. https://doi.org/10.1093/ecco-jcc/jjx101.
73. Elimeleh Y, Feler AY, Badarni RT, Lahad A, Rinawi F. Safety and efficacy of adalimumab 40 mg every 3 weeks in pediatric-onset Crohn's disease. J Pediatr Gastroenterol Nutr. 2025;80:998–1001. https://doi.org/10.1002/jpn3.70036.
74. Meredith J, Henderson P, Wilson DC, Russell RK. Combination immunotherapy use and withdrawal in pediatric inflammatory bowel disease—a review of the evidence. Front Pediatr. 2021. https://doi.org/10.3389/fped.2021.708310.
75. Iovino NA, McClinchie MG, Abdel-Rasoul M, Boyle B, Dotson JL, Michel HK, et al. Clinical impacts of immunomodulator withdrawal from anti-tumor necrosis factor combination therapy in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2024;79:885–94. https://doi.org/10.1002/jpn3.12299.
76. Cekin S, Huenseler C, Cantez S, Broekaert I, de Laffolie J. Therapy de-escalation in pediatric patients with inflammatory bowel disease in remission: data analysis from the CEDATA registry. J Pediatr Gastroenterol Nutr. 2026;82:690–8. https://doi.org/10.1002/jpn3.70297.
77. El-Matary W, Carroll MW, Debruyn JC, Huynh H, Wine E, Lawrence S, et al. Discontinuation of immunosuppressive medications in children with inflammatory bowel disease on combination therapy. J Pediatr Gastroenterol Nutr. 2020;71:740–3. https://doi.org/10.1097/MPG.0000000000002857.
78. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. Nat Rev Gastroenterol Hepatol. 2009;6:513–23. https://doi.org/10.1038/nrgastro.2009.124.
79. Gourdonneau A, Bruneau L, Ruemmele FM, Norsa L, Takeda A, Le Gall C, et al. Clinical remission and psychological management are major issues for the quality of life in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2021;72:74–9. https://doi.org/10.1097/MPG.0000000000002865.
80. Lepus CA, Hyams JS. Barriers from third-party payers to biologic use in pediatric inflammatory bowel disease. JPGN Rep. 2022. https://doi.org/10.1097/pg9.0000000000000215.
81. Constant BD, Adler J, Gold BD, Dotson J, Lightdale JR, Scott F, et al. National perspectives of barriers by insurance and pharmacy benefit managers in pediatric inflammatory bowel disease. JPGN Rep. 2025;6:80–90. https://doi.org/10.1002/jpr3.70004.
82. El-Hussuna A, Hauer AC, Karakan T, Pittet V, Yanai H, Devi J, et al. ECCO consensus on management of inflammatory bowel disease in low- and middle-income countries. J Crohns Colitis. 2026. https://doi.org/10.1093/ecco-jcc/jjaf125.
83. Hauer AC, Sultan M, Darma A, Altamimi E, Serban DE, Assa A, et al. Management of pediatric inflammatory bowel diseases in limited-resource settings: a position paper from the Pediatric IBD Porto Group of ESPGHAN. J Pediatr Gastroenterol Nutr. 2025;81:866–98. https://doi.org/10.1002/jpn3.70121.
84. Tsai L, Ma C, Dulai PS, Prokop LJ, Eisenstein S, Ramamoorthy SL, et al. Contemporary risk of surgery in patients with ulcerative colitis and Crohn's disease: a meta-analysis of population-based cohorts. Clin Gastroenterol Hepatol. 2021;19:2031-2045.e11. https://doi.org/10.1016/j.cgh.2020.10.039.

85. Privitera G, Bezzio C, Buono AD, Gabbiadini R, Loy L, Ranucci L, et al. Treat-to-target optimization of biologic therapy is effective on endoscopic and histologic outcomes in a real-life cohort of ulcerative colitis—the TACTIC-UC study. J Crohns Colitis. 2026;20(2):jjaf239. https://doi.org/10.1093/ecco-jcc/jjaf239.
86. Scott G, Wands DIF, Wilson DC, Hansen R, Chalmers I. Selecting high-risk patients with pediatric Crohn's disease for top-down Anti-TNF as per the 2021 ECCO-ESPGHAN guidelines: a 5-year nationwide retrospective analysis from Scotland (2016-2020). Inflamm Bowel Dis. 2025;31:2059–65. https://doi.org/10.1093/ibd/izae298.
87. Atia O, Orlanski-Meyer E, Lujan R, Ledderman N, Greenfeld S, Kariv R, et al. Colectomy rates did not decrease in pediatric- and adult-onset ulcerative colitis during the biologics era: a nationwide study from the epi-IIRN. J Crohns Colitis. 2022;16:796–803. https://doi.org/10.1093/ecco-jcc/jjab210.
88. Atreya R, Neurath MF. Biomarkers for personalizing IBD therapy: the quest continues. Clin Gastroenterol Hepatol. 2024;22:1353–64. https://doi.org/10.1016/j.cgh.2024.01.026.
89. Syed S, Boland BS, Bourke LT, Chen LA, Churchill L, Dobes A, et al. Challenges in IBD research 2024: precision medicine. Inflamm Bowel Dis. 2024;30:S39-54. https://doi.org/10.1093/ibd/izae084.
90. Vermeer E, Jagt JZ, Lap EM, Struys EA, Budding AE, Verhoeven-Duif NM, et al. Fecal gut microbiota and amino acids as non-invasive diagnostic biomarkers of pediatric inflammatory bowel disease. Gut Microbes. 2025. https://doi.org/10.1080/19490976.2025.2517828.
91. Verburgt CM, van der Kruk N, Dunn KA, Van Limbergen JE. Personalized AZithromycin/metronidAZole + dietary therapy in pediatric Crohn disease: results of a pilot study. J Pediatr Gastroenterol Nutr. 2026. https://doi.org/10.1002/jpn3.70357.
92. Distante M, Rotulo S, Ranalli M, Pedace E, Lionetti P, Arrigo S, et al. Clusters of disease activity and early risk factors of clinical course of pediatric Crohn's disease. Inflamm Bowel Dis. 2024;30:1983–91. https://doi.org/10.1093/ibd/izad275.
93. Aloi M, Bramuzzo M, Norsa L, Arrigo S, Distante M, Miele E, et al. Disease activity patterns in the first 5 years after diagnosis in children with ulcerative colitis: a population-based study. J Crohns Colitis. 2021;15:367–74. https://doi.org/10.1093/ecco-jcc/jjaa203.
94. Chen L, Zhang C, Niu R, Xiong S, He J, Wang Y, et al. Multi-omics biomarkers for predicting efficacy of biologic and small-molecule therapies in adults with inflammatory bowel disease: a systematic review. United Eur Gastroenterol J. 2025;13:517–30. https://doi.org/10.1002/ueg2.12720.
95. Preto AJ, Chanana S, Ence D, Healy MD, Domingo-Fernández D, West KA. Multi-omics data integration identifies novel biomarkers and patient subgroups in inflammatory bowel disease. J Crohns Colitis. 2025. https://doi.org/10.1093/ecco-jcc/jjae197.
96. Tao Y, Wang L-F, Li P, Sun R, Li Y-J, Sun M, et al. Decoding IBD progression: a dynamic biomarker atlas for personalized disease stratification. J Transl Med. 2025;23:1076. https://doi.org/10.1186/s12967-025-07024-x.
97. Rotem-Tryfus O, Kang B, Orlanski-Meyer E, Ledder O, Lev Tzion R, Choi S, et al. Validation of prediction models for anti-tumor necrosis factor treatment response in pediatric Crohn's disease: a systematic review and prospective cohort study. J Crohns Colitis. 2025. https://doi.org/10.1093/ecco-jcc/jjaf172.
98. Assa A, Aloi M, Van Biervliet S, Bronsky J, di Carpi JM, Gasparetto M, et al. Management of pediatric ulcerative colitis, part 2: acute severe colitis—an updated evidence-based consensus guideline from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization. J Pediatr Gastroenterol Nutr. 2025;81:816–51. https://doi.org/10.1002/jpn3.70096.