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LEADING ARTICLE

Treat-to-Target in Pediatric Inflammatory Bowel Disease: What Does the Evidence Say?

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Abstract
The traditional management of inflammatory bowel disease, based on treatment intensification guided by clinical activity alone, has been revised in the last 10 years and a treat-to-target approach has been proposed and is currently under evaluation as a disease-modifying strategy. Treat-to-target focuses on objective and scheduled measures to monitor intestinal damage, with consequent therapeutic adjustments in case of failure to achieve pre-defined targets. Identification of targets has been set out by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee in 2015. Mucosal healing is universally accepted as the main target both in Crohn's disease and ulcerative colitis, given its proven association with better long-term outcomes than clinical remission alone. Equally important is to ensure patients' clinical remission and improve patient-reported outcomes. Transmural healing (for Crohn's disease) and histological remission (for ulcerative colitis), listed as adjunctive targets, are likely to become primary targets in the near future. The ultimate goal of this approach is to modify the natural history of inflammatory bowel diseases by trying to block bowel damage progression, with interventions in the pre-clinical stage. In this review, we will discuss the current recommended therapeutic targets, as well as those that are considered adjunctive targets, with a focus on the limited pediatric literature available. Prospective long-term trials are warranted in order to identify the most appropriate target for the pediatric population and its specific issues. Identification of reliable predictors of disease course, outcome, and response to treatment will help to individually adapt each step of this monitoring algorithm and consequent therapeutic decision.

1 Introduction

In the last decade, we witnessed a paradigm shift in the management of inflammatory bowel disease (IBD), from the mere control of symptoms to the healing of mucosal inflammation (mucosal healing, MH), with the ultimate goal of modifying the natural history of these diseases. The so-called treat-to-target (T2T) approach, adapted from rheumatoid arthritis and other chronic diseases [1, 2], focuses on an objective measure and monitoring of the intestinal damage at predefined timepoints, with consequent therapeutic adjustments in case of failure [3].

Inflammatory bowel diseases are chronic disorders whose evolution is marked by the occurrence of complications, progressive bowel damage, increased risk of cancer, and disability. Traditional management focused on treating clinical symptoms and has been demonstrated ineffective in modifying this disease's natural history [4–7]. Meanwhile, some evidence showed better long-term outcomes for patients achieving MH [8, 9], and the T2T strategy started to be applied for IBD.

The definition of which targets must be pursued in the context of IBD was proposed in 2015, following an Organization for the Study of Inflammatory Bowel Diseases (IOIBD) initiative, by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee [10]. These recommendations were also applied to the pediatric population, with necessary adaptations to the specifics of the pediatric context. From 2015, new evidence has emerged together with the need for a revision of those therapeutic goals.

While discussing the actual treat-to-target algorithm, this review will focus on the newest data that has emerged in recent years supporting the evolution of this approach with particular attention to the pediatric population.

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Key Points

The treat-to-target approach for inflammatory bowel disease (IBD) focuses on an objective measure and monitoring of the intestinal damage at predefined time-points, with consequent therapeutic adjustments in case of failure

Targets for IBD were defined in 2015 by the STRIDE committee: they include clinical remission (assessed through clinical scores and patient-reported outcomes evaluation) and mucosal healing

Transmural healing, assessed through cross-sectional imaging in patients with Crohn's disease, represents, to date, an adjunctive target, but is likely to be promoted to a primary one, given its beneficial effects on long-term outcomes

Histologic healing and biochemical (serological and fecal) inflammatory markers are listed as adjunctive targets. Magnetic resonance enterography, fecal calprotectin, and C-reactive protein are extremely useful monitoring tools

Structured longitudinal trials to confirm the importance and the efficacy of the treat-to-target strategy are lacking, especially in the pediatric setting, which would actually benefit the most from strategies conceived to alter the natural history of these diseases

2 Recommended Targets

The ideal T2T process is based, firstly, on cooperation between the physician and the patient in identifying appropriate targets and, accordingly, therapies; this will be based on the patient's characteristics, the risk of disease progression, and will be followed by a tight monitoring program with eventual therapy optimization to reach the predefined goals. For both Crohn's disease (CD) and ulcerative colitis (UC), the STRIDE committee recommended a composite endpoint of both clinical/patient-reported outcome (PRO) and endoscopic remission as primary therapeutic targets.

2.1 Clinical Targets

Although symptom control alone is no longer a sufficient target, since it does not alter the disease course, clinical remission remains the primary treatment goal and assessment should be conducted every 3 months during active disease for both UC and CD and every 6–12 months when symptoms are controlled. There is a well documented overlap between functional abdominal symptoms and IBD in both adults and children, thus making clinical remission alone a target requiring careful interpretation [11].

The poor correlation between clinical scoring systems and objective markers of inflammation (i.e., endoscopic assessment) is widely proven, particularly for CD, therefore limiting their use for deciding major therapeutic adjustments [12–14]. As shown in the SONIC (Study of Biologic and Immunomodulator Naive Patients In Crohn's Disease) trial, half of the patients in clinical remission, as measured by the CDAI score, had endoscopic and/or biologic (C-reactive protein, CRP) evidence of persistently active CD, whilst persistent symptomatic activity was found in a substantial proportion of patients who had achieved MH [15]. Similarly, in children, several data have shown the poor correlation between clinical indexes and endoscopic activity in CD [16]. The original Pediatric Crohn's Disease Activity Index (PCDAI) and the mathematically weighted PCDAI (wPCDAI), are those with the best performance (with fair correlation with endoscopic inflammation) and the latter is to be preferred due to its higher feasibility [16]. For both scores, Physician Global Assessment (PGA) was used as a reference for their validation, underlying the importance of the physician's impression on disease activity in guiding treatment adjustment. Regardless of the poor reliability of clinical scoring systems in pediatric CD, treating patients' symptoms and restoring their quality of life is mandatory. Therefore, PROs, or observer-reported outcomes (ObsROs) for young children who are unable to self-report [17], are recommended as co-primary targets to be monitored every 3 months both in clinical practice and in trials [10, 18]. Among them, resolution of abdominal pain and normalization of bowel movements are recommended as clinical/PRO targets in CD, and are increasingly being used as endpoints in clinical trials [19]. Other PROs tools are currently under evaluation, with the objective of screening patients and identifying those who need further assessment of disease activity [20]. Pediatric PROs instruments for CD are warranted for accurately measuring treatment benefit in the pediatric clinical trial setting and daily clinical practice.

Patient-reported outcome targets for UC include cessation of rectal bleeding and normalization of stool frequency. In pediatric UC, the TUMMY-UC index has been developed to address the need for evaluating a composite outcome as stated by the STRIDE committee. Relevant items for children with UC and their caregivers were abdominal pain, rectal bleeding, stool frequency, stool consistency, general wellbeing/fatigue, urgency, nocturnal stools, loss of appetite, and weight loss [21]. Another pediatric instrument for capturing PROs is the daily ulcerative colitis signs and symptoms scale (DUCS) [22]. They both need further validation before entering routine clinical practice.

Compared with CD, clinical UC scores are better correlated with endoscopic activity. The Mayo score, which includes the rectal bleeding and stool frequency subscores, strongly correlates with MH, as shown in two systematic reviews [23, 24]. The rectal bleeding subscore more reliably discriminates between patients with persistent endoscopic activity and those with endoscopic remission, suggesting that this could be confidently used to identify those patients needing treatment adjustments. Interestingly, a time lag between MH and resolution of symptoms (measured with PROs) has been demonstrated in a post-hoc analysis of ULTRA 1 and 2 by Jharap et al., with only 20% of patients with MH at week 52 showing resolution of both rectal bleeding and stool frequency [25]. A possible explanation for this discrepancy might relate to the concomitant presence of functional gastrointestinal disorders or impaired intestinal permeability due to persistent histological activity, whose role as a target will be discussed later in this review. In children, the Pediatric Ulcerative Colitis Activity Index (PUCAI) is not less accurate than endoscopic evaluation in predicting long-term outcomes, such as 1-year sustained steroid-free remission and colectomy by 2 years, being superior to both CRP and erythrocyte sedimentation rate (ESR) [26, 27]. Several studies demonstrated an excellent correlation between PUCAI and Mayo score [28, 29].

2.2 Endoscopic Targets

Along with PROs, MH is the main therapeutic target both in UC and CD. Objective measurement of MH is essential in clinical practice and trials when determining the efficacy of treatment (possibly limiting, in clinical trials, the placebo effect) [30]. According to STRIDE, MH should be assessed in 3–6 months and in 6–9 months after starting therapy in UC and CD, respectively. Cross-sectional imaging is considered a valid alternative to endoscopy in CD, when the latter cannot be performed or cannot adequately assess the degree of inflammation [10]. Several pediatric specificities are worth mentioning in this context. In fact, although the paramount importance of MH is equally acknowledged in children, and its objective measure remains mandatory in CD (where fecal calprotectin (FC) might only help guiding the timing of endoscopy, which is recommended after 6–12 months based on CD severity [31]), this is not the case for UC, where a more conservative approach is suggested. Given the excellent performance of PUCAI and FC (discussed later in this paper) in estimating mucosal inflammation, the invasiveness of repeated colonoscopy (hardly accepted by the patients and the parents, especially when the disease is under control), and the risk of repeated general anesthesia, the 2018 ECCO-ESPGHAN (European Crohn's and Colitis Organisation/European Society for Paediatric Gastroenterology Hepatology and Nutrition) guidelines restrict the use of endoscopy to specific situations—before any major therapeutic change and in case of discrepancies between symptoms and FC results, or unclear origins of symptoms [32]. This less-invasive approach is possibly because of the lower risk of malignancies in pediatric disease; therefore, it is not applicable in the presence of an associated primary sclerosing cholangitis (a major risk for colorectal cancer in itself) or after 10 years of disease.

Several endoscopic indexes have been developed to score and grade mucosal inflammation in both CD and UC. The Simplified Endoscopic Index of Severity (SES-CD) [33] and the Crohn's Disease Endoscopic Index of Severity (CDEIS) [34, 35] are the most widely used for CD. Both scores lack agreement on the optimal cut-off for MH, which has been variously defined [36], but thanks to its ease of execution and the excellent inter-observer agreement, SES-CD (which, moreover, has an excellent correlation with CDEIS) might be considered the best option for clinical practice and research trials to grade and assess endoscopic healing and response. In line with the IOIBD, the Porto IBD Group of ESPGHAN defined endoscopic remission as a SES-CD ≤ 2, while still considering complete MH (absence of mucosal ulceration in all the explored segments) the ideal target. The authors highlight the importance of detailing endoscopic appearance and comparing it with the previous evaluations (i.e., decreased, increased, equal) to correctly assess the efficacy of treatment [31], and enable longitudinal evaluation of disease activity [37].

For UC, the Mayo score, although not fully validated, is the one recommended by STRIDE for its feasibility, with a score of ≤ 1 considered an equivalent of MH10. The UC endoscopic index of severity (UCEIS) is an alternative scoring system that proved its better correlation with disease severity and treatment responsiveness compared with the Mayo, showing better sensitivity in detecting mucosal improvement that the Mayo score tends to overlook [38]. A UCEIS score of 1 is the target selected by STRIDE. A recent modification of the Mayo has been proposed (i.e., incorporating the extent of inflammation along the colon) with the aim of exceeding the original limits of this score, while preserving its ease of use [39, 40]. For both scores, there is debate around whether a more stringent endoscopic goal (i.e., Mayo or UCEIS score of 0) should be proposed as a minimum target, considering the more recent evidence suggesting better outcomes when these targets are achieved [41–43]. On the other hand, a recent retrospective work of de Jong et al., demonstrated that in clinical practice, an UCEIS ≤ 3 was rarely associated with the perceived need for treatment escalation, suggesting the need for a comprehensive decision-making strategy (including symptoms and the available therapeutic options) rather than a blind chase of a score [44].

Mucosal healing has largely proven its association with long-term clinical outcomes (reduced risk of surgery, hospitalizations, treatment escalation, complicated behavior, etc.), particularly in the adult setting [45, 46]. Fewer studies have evaluated MH long-term outcomes in pediatric trials, mostly investigating the efficacy of exclusive enteral nutrition and anti-TNF therapy. In a pediatric cohort of 54 patients, persistent active disease after induction treatment with exclusive enteral nutrition was associated with lower rates of sustained remission compared with patients with MH [47]. Cohen et al., in a small prospective cohort of 10 children with CD, proved the efficacy of a dietary intervention in obtaining and maintaining small bowel MH, as demonstrated by capsule endoscopy at weeks 12 and 52 after inclusion [48]. A better disease course (persistent clinical remission) over a 2-year follow up was demonstrated in a prospective trial on 37 biologic-naive pediatric CD patients treated with anti-TNF [49].

In UC, a positive association between a Mayo 0 or 1 and a reduced risk of colectomy and relapse has been proven as well [50, 51].

Despite this evidence, the natural history of IBD seems not to be altered. A step forward will possibly be provided by proof that changing therapy on the basis of close endoscopic monitoring (T2T) will impact on the disease's long-term evolution. A single-center retrospective study on 67 CD patients with endoscopic active disease at baseline demonstrated a significant correlation between the rate of MH (from 19.4% at week 24 to 50.7% at the end of follow-up) and repeated endoscopies within 26 weeks, and treatment adjustments made in the absence of clinical symptoms [52]. In a prospective study on 48 children with CD, Oliva et al. proved that T2T strategy based on panenteric capsule endoscopy was associated with a significant increase of MH and a deep remission rate (from 21% at baseline to 54% at week 24, to 58% at week 52) [53]. In a cohort of 60 UC patients receiving at least two endoscopies over the study period, MH progressively increased from 31.1% at week 26, 46.6% at week 52, and 53.3% at week 76. In the case of persistent inflammation, therapy adjustments were performed in the absence of clinical symptoms in 15.6% of patients [54]. The ongoing Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy (REACT2) trial (ClinicalTrials.gov identifier, NCT01698307) is a comparison between the early use of combined antimetabolite/adalimumab therapy and treatment intensification based on ileocolonoscopic findings versus a conventional step-up management approach solely based on symptoms. Its results will certainly add valuable information about the efficacy of a T2T algorithm, which was not the case in the REACT1 trial focused on targeting resolution of symptoms [55].

Economic outcomes are positively influenced by a T2T management strategy and tight control. Both in CD and UC, an inflammation-driven decision was more cost effective than a symptom-based one and economic analysis of the CALM trial (Efficacy and Safety of Two Treatment Models in Subjects with Moderate to Severe Crohn's Disease) proved cost effectiveness of a tight control strategy over conventional management [56].

3 Adjunctive Targets

3.1 Histologic Targets

Lack of supporting evidence and validated scores prevented the STRIDE committee from including histological remission among the recommended targets [57]. Particularly for CD, where a uniform histologic evaluation, given the characteristic patchy and transmural inflammation of the disease, is not feasible, only one retrospective study found a lower risk of clinical relapse, treatment escalation, or corticosteroid use in patients with CD achieving complete histologic healing along with MH [58]. Achieving histological remission is more likely to impact on disease course and outcomes in UC, where more evidence is available including a meta-analysis of 15 studies that concluded there was a lower relapse risk in patients with histological healing compared with those with MH and clinical remission but persistent histologic activity [59]. In 2017, there was a step forward in this direction, when two histologic scores (the Nancy Index and the Robarts' Histopathology Index) were validated [60, 61] and subsequently proved to strongly correlate with the UCEIS score [62]. Interestingly, an UCEIS of 0 correlates with the absence of microscopic disease activity, possibly suggesting the need for a more stringent MH definition. Histologic indexes validated in pediatric cohorts are still lacking and are warranted, since including histological remission among primary targets is undoubtedly worth consideration [38].

3.2 Imaging Targets

Cross-sectional imaging methods, although according to the STRIDE program not a therapy target per se, are increasingly used for disease monitoring with high accuracy. Magnetic resonance enterography (MRE) is the imaging modality of choice for the diagnosis of pediatric CD. Other imaging tools, like small bowel ultrasonography (US) and computed tomography enterography (CTE), have similar performance in assessing disease activity and severity. Computed tomography, due to the exposure to ionizing radiation, should not be performed outside the emergency setting [63].

Their use is of particular value in the context of CD, where the transmural inflammation and the frequent small bowel involvement (especially in the pediatric setting [64]) may result in an incomplete assessment by colonoscopy,

especially in the presence of complication (strictures, fistulas, abscesses).

Despite the numerous advantages shown by US (low cost, non-invasiveness, excellent tolerability, and good correlation with MRE [65]), its use is limited by local expertise and lack of validated scores for grading inflammation [66].

Magnetic resonance enterography is a non-ionizing imaging technique with an available and validated index of activity (the Magnetic Resonance Index of Activity (MaRIA) score), which is strongly correlated with endoscopy findings [67–69]. A pediatric score is under validation [70]. A recent systematic review and meta-analysis assessed the diagnostic performance of MRE for the detection of active inflammation in children and adolescents with known or suspected IBD [71]; 18 original articles involving 687 patients were included in the analysis demonstrating a pooled sensitivity and specificity of 83% and 93%, respectively, of this technique, confirming its excellent performance.

Several data support the assessment of the small bowel through imaging to predict clinical outcomes. In a retrospective study, a reduced risk of hospitalization (hazard ratio (HR) 0.28, 95% CI 0.15–0.50) and surgery (HR 0.34, 95% CI 0.18–0.63) was demonstrated for patients with CTE or MRE resolution of small bowel CD inflammation [72]. Fernandes et al., in a prospective study on 214 CD patients, proved that transmural healing (assessed through MRE) is associated with improved long-term outcomes (lower rates of therapy escalation, hospitalization, and surgery at 1 year) [73].

In children, achieving transmural healing was correlated with lower rates of therapy modification (8.3% vs 44.6% in patients with persistent active inflammation) and CD-related surgery (2.8% vs 18.5%) [74]. Nevertheless, so far, the percentage of TH with different therapies seems to be low, with < 30% of children achieving complete bowel healing [75, 76]. Thus, it is reasonable to possibly consider transmural healing a more effective target than simple MH in CD. Prospective, multicenter trials should be constructed to clarify whether this should be elected as a primary or remain an adjunctive target. Considering the declared objective of the treat-to-target strategy of ultimately altering the natural history of the disease, it is conceivable that the more ambitious the target, the better the long-term outcomes would be. Particularly in the pediatric setting, where a long disease history is expected, it is mandatory to heal deeper and look further then in adults.

Fewer considerations can be made in this context about UC, a disease limited to the mucosal layer. In a small cohort of 29 UC patients, the diffusion-weighted magnetic resonance colonography, using the Nancy score, demonstrated good accuracy and responsiveness to change in comparison to sigmoidoscopy used as the gold standard [77].

Ordás et al. prospectively evaluated the accuracy of magnetic resonance colonography for the evaluation of disease activity and severity in 50 UC patients: relative contrast enhancement, presence of edema, enlarged lymph nodes, and the comb sign independently predicted endoscopic activity [78].

As far as the role of US in UC is concerned, development and validation of new indexes are warranted given the suboptimal methodology used in this setting to date [66].

3.3 Biochemical Targets

Due to their limited cost and noninvasiveness, inflammatory biomarkers can be considered, under specific circumstances and taking due precautions, useful surrogate markers of endoscopic activity, particularly in the pediatric setting, where repeated endoscopies are rarely performed or accepted by patients and parents.

FC and CRP are the most widely used and investigated and, although still not recommended as primary targets or guidance to determine therapeutic adjustments, they are leading the way in the context of a non-invasive tight monitoring strategy. Indeed, regardless of symptoms, persistent elevation of CRP or FC warrants further workup [10].

C-reactive protein shows only limited correlation with UC activity [79, 80], while FC can detect colonic inflammation, correlates with histological activity, and predicts relapse in asymptomatic patients as well as in patients with MH with excellent sensitivity, showing a progressive increase in the 3 months before symptomatic recurrence [81–84]. The excellent performance of FC has been acknowledged by the authors of the 2018 pediatric guidelines for the ambulatory management of UC, which recommends its use in conjunction with PUCAI to monitor disease activity and guide the timing of endoscopies and treatment modifications [32]. Various FC thresholds have been proposed and used in different studies [84] in a meta-analysis, reported 50 µg/g as the optimal cut-off, but FC values < 100 µg/g preserve a good sensitivity for discriminating patients with endoscopic remission [84, 26]. A value of 250 µg/g appears to be the most sensitive cut-off to detect mucosal inflammation as largely proven in different settings, both in CD85, 86, and in UC. The 2018 pediatric guidelines for UC entrust to this cut-off the selection of patients who need endoscopy for eventual therapeutic adjustments [32]. Closer monitoring and repeated measurement of FC are needed in the presence of intermediate values (100–250 µg/g). Given its promising role, well designed disease modification pediatric trials need to be led to determine whether FC-guided treatment adjustment can be effective. Two randomized, controlled trials proved that increasing the dose of 5-aminosalicylate drugs in patients in clinical remission but with elevated FC levels resulted in a long-term lower relapse rate [87, 88].

More concerns have been raised about the performance of FC in patients with isolated ileal or small bowel CD who seem to show lower values of FC compared with patients with ileocolonic or colonic disease, highlighting the importance of adapting the cut-offs to this context for FC interpretation [89–91]. Consecutive FC measurements in patients in clinical remission, using a cut-off level of 250 µg/g, have proven to help predict relapse within 3 months [92], therefore guiding the timing of endoscopic assessment or treatment intensification. On the other hand, CRP, as a reflection of transmural inflammation, has an important role in CD monitoring, despite up to one-third of patients having normal values. Nevertheless, CRP has proven its utility in monitoring response to treatment; for example, infliximab-treated patients who showed early normalization of CRP levels were more likely to maintain response to treatment, while persistently high CRP levels correlated with higher relapse risk [93, 94].

The efficacy of a treat-to-target strategy based on symptoms with or without biomarkers has been investigated by the pivotal CALM trial. Therapeutic management based on tight control (FC, CRP, and clinical markers) was associated with higher endoscopic and endoscopic plus clinical remission (45.9 vs 30.3%; $p=0.01$ and 36.9% vs 23%; $p=0.01$, respectively) at 1 year compared with clinically-based treatment modification [86].

A post-induction normalization of wPCDAI and CRP was found to be predictive of long-term response to biologic therapy in a cohort of children with CD (HR 5.51; $p=0.03$), suggesting a possible combination of non-invasive monitoring tools in the pediatric setting [95]. In response to the need for non-invasive monitoring in CD, particularly valuable for children, the Mucosal Inflammation Noninvasive Index (MINI) was recently developed and validated by an international group of experts; it includes evaluation of stool appearance, FC and CRP, and ESR values, and returns a score that is able to identify with up to 80% of sensitivity and specificity patients with MH. The use of MINI should therefore be encouraged in daily clinical practice to judge treatment efficacy and help determining the timing of endoscopic evaluations [96].

Incorporation of FC as a treatment target for both CD and UC, given the available evidence, seems plausible and will possibly determine a revision of STRIDE [97].

4 Conclusions

Since 2015, evidence supporting the importance of applying a T2T strategy in IBD has accumulated, adding valuable information concerning the possible role of new therapeutic goals. Nevertheless, structured, well designed longitudinal trials to confirm this trend are lacking, especially in the pediatric setting, which would actually benefit the most from strategies conceived to alter the natural history of these diseases and maximize therapy efficacy, given the expected long duration of disease, the intrinsic more aggressive disease course, and the limited therapeutic armamentarium. On the other hand, efforts must be focused on implementing non-invasive monitoring tools available for tight control for preserving children's quality of life. This less-invasive approach is already a reality for pediatric UC patients, while we still cannot avoid a comprehensive mucosal and transmural direct evaluation of CD patients. Each of the instruments (clinical and endoscopic indexes, imaging tools, inflammatory fecal and serological markers of disease

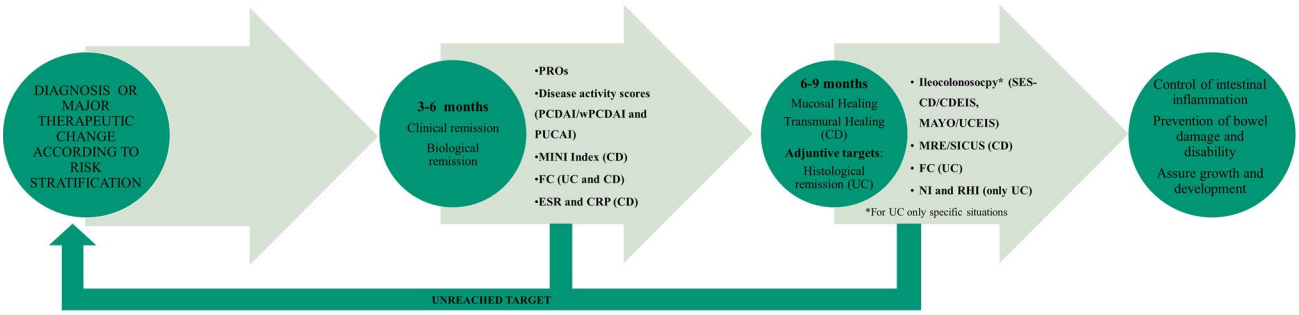

Fig. 1 A proposed treat-to-target algorithm for pediatric inflammatory bowel disease (IBD). Following diagnosis or a major therapeutic change, clinical evaluation and indirect measure (through non-invasive monitoring tools) of mucosal healing (MH) should be performed after 3–6 months. Achievement of MH (and possibly transmural healing in CD) should be documented after 6–9 months. Failure to meet the predefined target must lead to therapeutic adjustment and further reevaluation. *CD* Crohn's disease, *CDEIS* Crohn's Disease Endoscopic Index of Severity, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FC* fecal calprotectin, *MINI* Mucosal Inflammation Noninvasive Index, *MRE* magnetic resonance enterography, *NI* Nancy Index, *PCDAI* pediatric Crohn's disease activity index, *PROs* patient-reported outcomes, *PUCAI* pediatric ulcerative colitis activity index, *RHI* Robarts' Histopathology Index, *SES-CD* Simplified Endoscopic Index of Severity, *SICUS* small intestine contrast ultrasonography, *UC* ulcerative colitis, *UCEIS* Ulcerative Colitis Endoscopic Index of Severity, *wPCDAI* weighted pediatric Crohn's disease activity index

activity) discussed in this review represent a single piece of the puzzle that has to be composed to comprehensively and precisely assess the level of bowel inflammation and consequently guide therapeutic decision making (Fig. 1). We currently still lean on the "one size fit all paradigm", since we lack reliable predictors of disease course, outcome, and response to treatment that would help to individually adapt each step of this monitoring algorithm and consequent treatment decision.

Compliance with Ethical Standards

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