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Original Research Articles - Clinical

A Treat-to-Target Strategy Guided by Pan-Enteric Evaluation in Children With Crohn's Disease Improves Outcomes at 2 Years

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Background and Aims: It is uncertain whether a treat-to-target approach could be an effective strategy for improving outcomes in children with Crohn's disease (CD). Previously, we reported mucosal healing (MH) and deep remission rates throughout the intestinal tract by performing 3 pan-enteric capsule assessments and using a treat-to-target strategy over 52 weeks in children with CD. This report describes the outcomes of this approach at 104 weeks.

Methods: Children with known CD who completed the 52-week protocol repeated pan-enteric capsule endoscopy (PCE) at 104 weeks. Results at weeks 52 and 104 were compared, and long-term outcomes between patients, with and without MH, were calculated using an intention-to-treat analysis of clinical relapse, need for steroids, treatment escalation, hospitalization, and surgery.

Results: Of the previous study cohort of 48 patients, 46 (96%) were available for this extension study (28 [61%] of 46 with MH and 18 [39%] of 46 without MH at 52 weeks). When evaluated at 104 weeks, MH was maintained in 93% of patients with MH at 52 weeks. In the intention-to-treat analysis, complete MH at 52 weeks was associated with reduced risk of steroid use (log-rank $P < .0001$), treatment escalation (log-rank $P < .0001$), hospitalization (log-rank $P < .0001$), and clinical relapse (log-rank $P < .0001$).

Conclusions: When a PCE-based, treat-to-target strategy is employed, MH is sustainable (93%) over a 1-year period and is correlated with improved patient outcomes, including reduced need for steroids, treatment escalation, hospitalization, and clinical relapses at 104 weeks.

ClinicalTrials.gov number: NCT03161886.

Key Words: treat-to-target, Crohn's disease, mucosal healing, pan-enteric capsule endoscopy

Introduction

The importance of mucosal healing (MH) in patients with Crohn's disease (CD) has never been disproven since its introduction as the main treatment target. The 2021 update of the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) consensus confirmed MH highest ranking among long-term treatment goals.[1] Endoscopic healing must also be assessed even in the presence of clinical remission because the latter often does not correspond to the endoscopic mucosal appearance.[2] Achieving these outcomes should be the result of a timely and prompt introduction or adjustment of therapies as part of the so-called treat-to-target approach, which requires frequent and close monitoring.[3,4] Ileocolonoscopy is still the gold standard for assessing mucosal inflammation, but its invasiveness combined with the need for repeated anesthesia or deep sedation justifies the validation of less invasive assessment methods. In addition, its inability to assess the small bowel (SB), which is often involved in pediatric CD, must be considered. Therefore, the use of pan-enteric capsule endoscopy (PCE) for monitoring is particularly attractive.[5,6]

Previously, we reported a substantial increase in MH (SB MH reached 67%, colonic MH reached 75%) and deep remission (DR) rates (58%) achieved by a treat-to-target strategy based primarily on PCE findings in a cohort of 48 CD children, confirming the validity of such an approach over a 1-year period. After treatment adjustments, the rate of MH and DR increased from 21% at baseline to 54% and 58% at weeks 24 and 52, respectively.[7] To date, long-term outcomes of this strategy and effect of MH have been barely assessed. Indeed, the ultimate goal of any strategy and therapeutic intervention in inflammatory bowel disease is to alter

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Key Messages

What is already known?

Few data have evaluated the long-term outcomes of the treat-to-target strategy in pediatric Crohn's disease, focusing on whether the achieved mucosal healing might have long-term implications.

What is new here?

Mucosal healing achieved through a treat-to-target strategy guided by pan-enteric capsule endoscopy improves patient outcomes over a 1-year period in children with Crohn's disease.

How can this study help patients care?

We support pan-enteric capsule endoscopy as a method of applying a treat-to-target strategy in pediatric Crohn's disease, which must be strictly followed in order to increase mucosal healing rate and, hence, clinical outcomes.

the natural disease course and prevent irreversible bowel damage.[8] This extension study aims to evaluate outcomes of this treat-to-target strategy a year after the previous analysis. We aimed to assess the impact of the initial approach comparing the outcome of patients with MH at 52 weeks with those without. In addition, the persistence of MH and DR achieved at 104 weeks was investigated, as well as the performance of the PCE in comparison with the other noninvasive assessment tools.

Methods

As previously reported,[7] children (6-18 years of age) with a diagnosis of SB or colonic CD requiring endoscopy or cross-sectional imaging were prospectively enrolled in the first 52-week study. Detailed information on the protocol and methodology has been previously reported[7] and are available in the Supplementary Appendix. All capsules were analyzed using the Rapid Reader v. 9.0 software (Medtronic). All patients who received the 3 PCE assessments (baseline, 24 weeks, and 52 weeks) participated in this extension phase of the study. At the 104-week follow-up, all assessments were repeated (including Pediatric Crohn's Disease Activity Index [PCDAI], biomarkers [fecal calprotectin (FCP) and C-reactive protein (CRP)], imaging [small intestine contrast ultrasonography and magnetic resonance enterography (MRE)], and PCE) with the aim of obtaining a full assessment of MH and DR 1 year after the end of the treat-to-target strategy. Figure 1 summarizes the study design and algorithm. MH in the SB and colon was defined as a Lewis score <135 and Simple Endoscopic Score for CD (SES-CD) ≤1, respectively.[1,9,10] Partial MH was defined as a decrease of at least 50% from the previous assessment. Clinical remission was defined as PCDAI below 10.[11] Biomarker remission was defined by FCP <100 µg/g and CRP <5 mg/L. A DR consisted of the presence of clinical remission and MH. The impact of the treat-to-target strategy was assessed at the 104-week assessment considering the following clinical outcomes: the need for surgery (defined as any surgical procedure associated with CD), steroids (any use of steroids during disease flare-up), treatment escalation (defined as the need to optimize or escalate drug), and the number of hospitalizations (related to the disease) and clinical relapses (defined as an increase in PCDAI by at least 10 points).

As the primary aim of this analysis, we attempted to compare the clinical outcomes between patients with MH at 52 weeks with those without MH. As secondary aims, the rates of complete remission, biomarker remission, MH (both colonic and SB), and DR at 104 weeks were assessed and compared with the 52-week observed rates. Finally, the diagnostic yields (rate of patients with positive findings) of PCE, MRE, and biomarkers (FCP and CRP) were assessed and compared at 104 weeks. All authors had access to study data and reviewed and approved the final manuscript.

Statistical Considerations

Continuous variables were summarized and displayed as mean ± SD and categorical data were expressed as frequency and percentage. Comparison of groups was performed by Student's *t* test for unpaired data in a 2-group comparison. Chi-square test with Fisher's correction was used to address any differences for categorical variables. A *P* value of .05 or less was considered as significant. The Kaplan-Meier survival method was used to estimate the interval free from surgery,

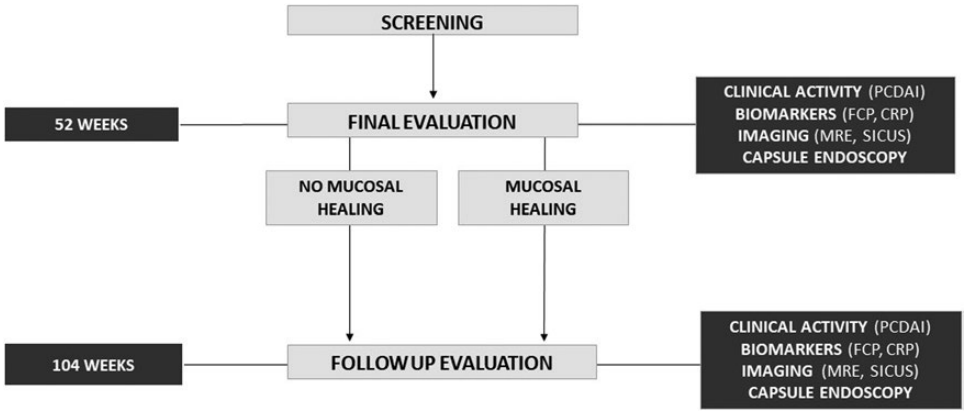

Figure 1. Study design and algorithm. CRP, C-reactive protein; FCP, fecal calprotectin; MH, mucosal healing; MRE, magnetic resonance enterography; PCDAI, Pediatric Crohn's Disease Activity Index; SICUS, small intestine contrast ultrasonography.

hospitalization, steroid courses, treatment escalation, and clinical flare-up. Differences between curves were tested using the log-rank test. All children receiving the 52-week evaluation were included in the analyses, utilizing the intention-to-treat approach. The GraphPad Prism 9.0 statistical package (GraphPad Software) was used to perform all statistical analyses.

Table 1. Demographic and clinical characteristics of the extension study population.

	Total (N = 46)	MH (n = 28)	No MH (n = 18)	*P*
Age at diagnosis, y	14.51 ± 2.6	14.65 ± 2.63	14.48 ± 1.65	.84
Female/male	20/26	13/15	7/11	.7
Disease location				
L1	10 (21)	7 (25)	3 (17)	.9
L2	12 (26)	8 (29)	4 (22)	.7
L3	15 (33)	8 (29)	7 (39)	.52
L4a	4 (9)	2 (7)	2 (11)	.6
L4b	21 (46)	13 (46)	8 (44)	.93
PCDAI	2.44 ± 5.13	0.53 ± 1.2	4.75 ± 6.8	.002
Treatment				
EEN	2 (4)	2 (7)	0	.54
IFX	18 (39)	10 (36)	8 (44)	.12
ADA	15 (33)	8 (29)	7 (39)	.52
AZA/6-MP	19 (41)	11 (39)	8 (44)	.76
MTX	3 (6.5)	2 (7)	1 (5)	1
UST	3 (6.5)	2 (7)	1 (5)	1
VEDO	1 (2)	1 (4)	0	.99

Values are n, mean ± SD, or n (%).
Abbreviations: 6-MP, 6 mercaptopurine; ADA, adalimumab; AZA, azathioprine; EEN, exclusive enteral nutrition; IFX, infliximab; MH, mucosal healing; MTX, methotrexate; PCDAI, Pediatric Crohn's Disease Activity Index; UST, ustekinumab; VEDO, vedolizumab.

Results

Baseline Characteristics

Of the original study cohort of 48 patients, 46 (96%) had completed the 52-week assessment and were available for this extension study (2 had developed a stricture and were not assessed at 1 year). Of these, 28 (61%) of 46 had MH and 14 (30%) of 46 still had mucosal inflammation despite clinical remission at the 52-week evaluation, while the remaining 4 (9%) were clinically active and had persistent mucosal inflammation. Of the latter, 3 required surgery, and 1 developed a perianal fistula and did not receive the final evaluation; therefore, 42 (91%) of 46 patients underwent the 104-week full assessment. All PCE exams were completed, showed satisfactory bowel cleanliness, and were adequately read by the investigator. All baseline demographics and clinical characteristics of children assessed at 52 weeks are reported in Table 1.

Evaluation at 104 Weeks

At 2 years (104-week evaluation), of the 28 patients with MH at 52 weeks, 26 (93%) were still in clinical remission and MH, and 2 (7%) became clinically and endoscopically active. While among the 14 patients in clinical remission but with persistent mucosal inflammation at 52 weeks, none achieved MH (9 [64%] maintained clinical remission and 5 [36%] developed clinically active disease). These results are summarized in Figure 2.

Clinical Outcomes

Children with MH were comparable to those without MH for all baseline characteristics (Table 1). The intention-to-treat analysis and comparison of 104-week outcomes between the 28 (61%) of 46 patients with MH at 52 weeks and those without MH (n = 18 of 46 [39%]) are reported in Table 2. Patients without MH had a significantly higher risk of steroid use compared with patients with MH (11 [61%] of 18 vs 2 [7%] of 28; $P < .0001$), need for treatment escalation (13

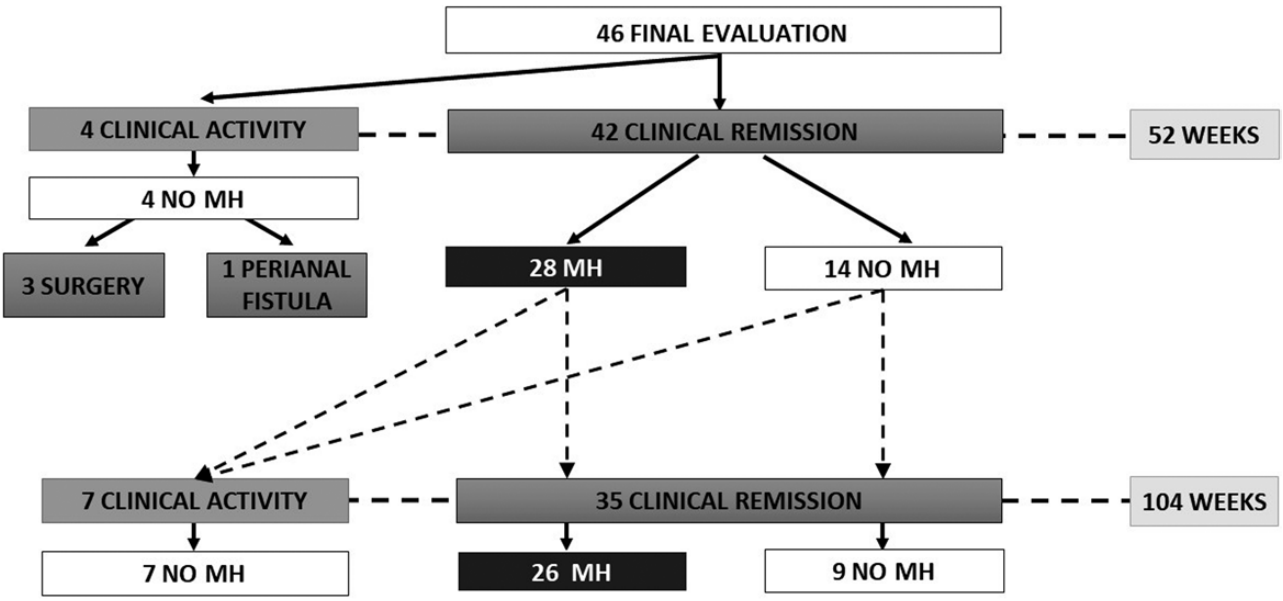

Figure 2. Long-term results (2-year follow up) of the 1-year treat-to-target strategy. MH, mucosal healing.

[72%] of 18 vs 3 [11%] of 28; $P < .0001$), hospitalization (9 [50%] of 18 vs 2 [7%] of 28; $P = .001$), and clinical relapse (9 [50%] of 18 vs 2 [7%] of 28; $P = .001$). Three patients among those without MH (n = 3 of 18 [16%]) required surgery (none in the MH group; $P = .03$). Figure 3 reports the Kaplan-Mayer survival analysis for the clinical outcomes, showing that MH patients had a significantly longer interval free from surgery (log-rank $P = .01$), steroid use (log-rank $P < .0001$), treatment escalation (log-rank $P < .0001$), hospitalization (log-rank $P < .0001$), and clinical relapse (log-rank $P < .0001$) compared with those without MH.

Table 2. 104-week clinical outcomes analysis and comparison in the 2 groups.

	MH (n = 28)	No MH (n = 18)	*P*
Surgery	0	3 (21)	.03
Steroids	2 (7)	11 (61)	<.0001
Treatment escalation	3 (11)	13 (72)	<.0001
Hospitalization	2 (7)	9 (50)	.001
Clinical relapse	2 (7)	9 (50)	.001

Values are n (%).
Abbreviation: MH, mucosal healing.

Remission Rates and Diagnostic Yield

Figure 4 shows the rates of clinical remission, biomarker remission, SB MH, colonic MH, and DR at 52 and 104 weeks in the entire cohort. At 104 weeks, rates of SB MH (65%) and colonic MH (76%) were similar to those at 52 weeks (69% and 78%, respectively); thus, only a 4% decrease in DR rate (from 61% [n = 28 of 46] to 57% [n = 26 of 46]) was observed a year after the treat-to-target strategy. The 104-week diagnostic yield of PCE and MRE was 67% and 42%, respectively, while FCP and CRP had 27% and 13%, respectively (35% if combined).

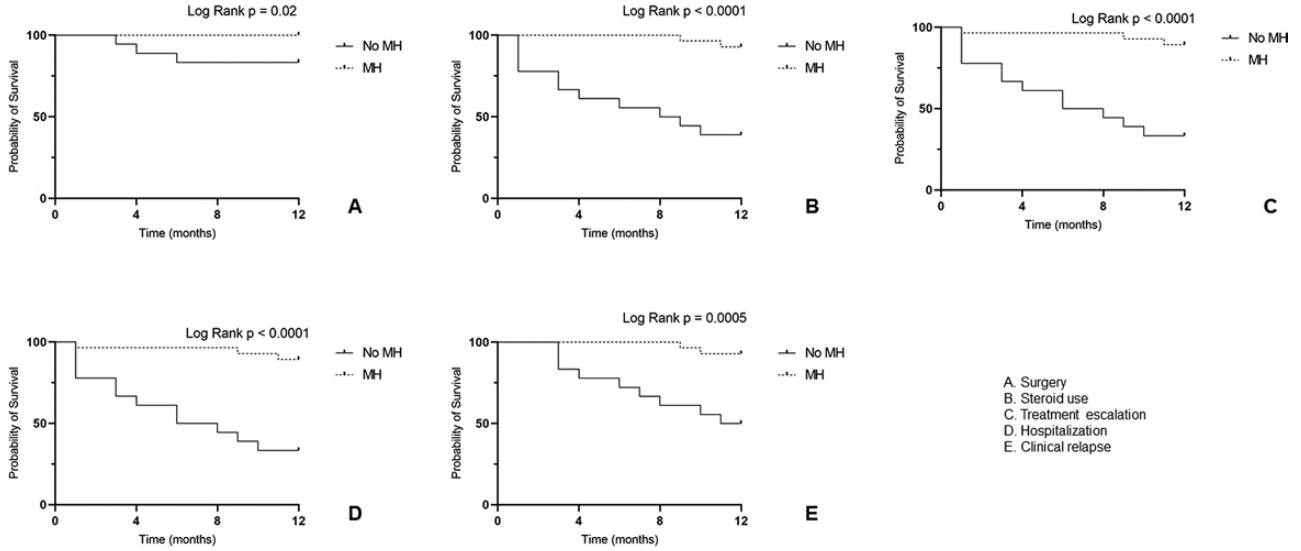

Figure 3. Kaplan-Meier survival analysis of (A) the risk of surgery, (B) need for steroids, (C) treatment escalation, (D) hospitalization, and (E) clinical relapse in the 2 groups. MH, mucosal healing.

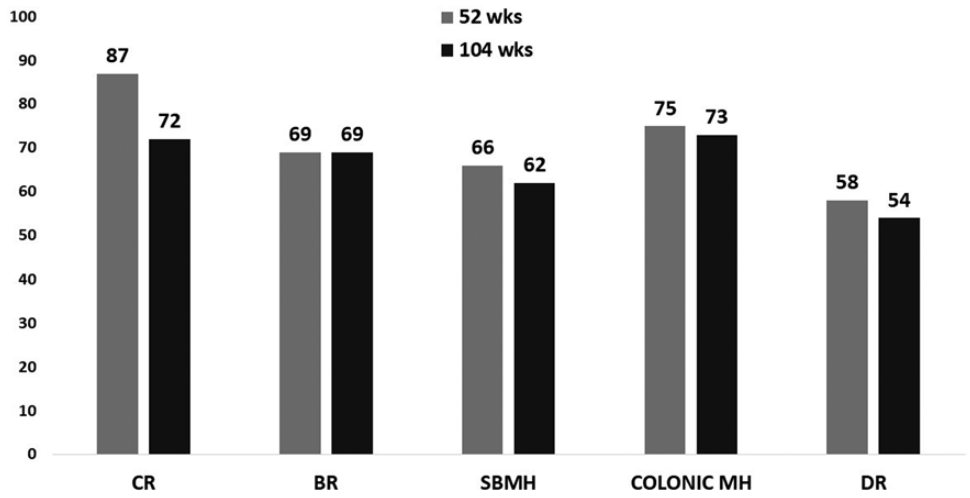

Figure 4. Comparison of the rates of complete remission (CR), biomarker remission (BR), small bowel mucosal healing (SBMH), colonic mucosal healing (MH), and deep remission (DR) at 52 and 104 weeks.

Discussion

Having demonstrated how a treat-to-target strategy guided by noninvasive mucosal assessment (including the SB) through the PCE can significantly increase MH and DR rates at 1-year follow-up, this extension study proves that achieving MH consistently improves patients' longer-term outcomes. Those who were able to restore normal mucosal appearance by 1 year had a significantly lower risk of use of steroids, treatment escalation, hospitalization, and clinical relapse during the subsequent year. Survival analysis demonstrated that patients with MH had a significant interval free from the same assessed outcomes compared with patients with persistent mucosal inflammation, regardless of baseline characteristics and treatment received.

Furthermore, the 2-year overall analysis of the effect of PCE-based treat-to-target strategy shows a significant persistence of the achieved goals (MH and DR) over the second year. The diagnostic yield of the PCE was higher in detecting persistently active disease compared with MRE and biomarkers.[12]

These results are important for several reasons as they contribute to the implementation of the treat-to-target strategy, which benefits not only from the selection of more ambitious targets, achievable thanks to newer therapeutic options, but also from the more advanced and less invasive diagnostic tools. The advent of such noninvasive techniques is rapidly increasing, thus supporting their wise introduction into the management algorithm.

The perspective from which we discuss our results is broad, as it encompasses the entire study time frame. In fact, thanks to this extension study, we have demonstrated the effectiveness of a PCE-based pediatric treat-to-target strategy, highlighting several key discussion elements.

First, the importance of carefully monitoring the SB is that more than half of the patients originally enrolled in the study had SB involvement and 25% had both SB and colonic lesions. In addition, most patients in clinical remission (62%) required treatment adjustment. Achieving MH in patients who would have escaped mucosal examination has significantly altered the long-term outcomes. Indeed, extensive proximal GI disease is extremely common in children, with a prevalence of up to 50% of cases.[13,14] Moreover, SB involvement as well as an extensive ileocolonic disease are among the risk factors for severe disease that mandate upfront anti-tumor necrosis factor therapy.[15] Our results confirm the risk of worsening disease progression for patients with persistent SB inflammation. A 2021 comprehensive review of the available literature, aiming to develop evidence-based guidelines on risk factors for severe pediatric CD, which could serve as a basis for tailored treatments, found an association between SB disease (ie, L1 or L3 ± L4b) and an increased risk of developing stricturing (B2) and/or penetrating complications (B3).[16] One of the main studies supporting this association was that published in 2010 by Gupta et al,[17] which reported a lower cumulative incidence of complicated disease at 1, 5, and 10 years in patients with colonic disease compared with patients with SB disease or SB disease combined with colonic disease. Another study by Attard et al[18] highlighted the severity of CD jejunoileitis (higher risk of surgery) and its therapeutic implications, noting that it more often requires an aggressive nutritional therapy with a nasogastric tube. Such patient stratification, which we are rapidly moving toward, must include not only the therapy, but also the monitoring phase, as rapid recognition of treatment failure, considering the availability of multiple therapeutic options, could ultimately change the disease course.

Second, our data support a treat-to-target strategy that can be applied to children, as it effectively improves outcomes. Tight monitoring is associated with better outcomes and a higher rate of MH. This was reported by the CALM study[19], in which the MH rate (the primary endpoint assessed) reached 46% (vs 30% in the conventional monitoring arm). With our results, we support the need to include mucosal assessment in this strategy.[19] According to our study, accompanying the clinical and laboratory assessment (as in the CALM study) with an instrumental technique helps improve such outcomes, as higher DR rates were observed (58% at 1 year and 54% at 2 years), and hence the long-term outcomes. Such data enrich the literature in support of the longer-term benefits of achieving MH, which are still scarce despite the importance of MH as major treatment goal. A meta-analysis of 10 studies found a significant association between MH and long-term clinical remission (odds ratio, 2.80; 95% confidence interval, 1.91-4.10) but not with a reduced risk of surgery (analysis performed on 3 studies; odds ratio, 2.22; 95% confidence interval, 0.86-5.69).[20]

Indeed, Ungaro et al,[21] in evaluating the follow-up data of a subcohort of the CALM study, demonstrated that the rapid achievement of DR (regardless of use of a tight control or conventional management strategy) in moderate-to-severe CD patients was alone associated with a lower risk of disease progression over a 3-year time frame. The same authors argued that endoscopic examination limited to the colon and terminal ileum could mask active inflammation proximal to the reach of a colonoscope (as well as transmural inflammation), underscoring the importance of SB evaluation and the value of our evaluation strategy.[21]

Of course, this extension study shares the same limitations of the first study phase, including the single-center nature, lack of randomization for different monitoring and treatment strategies, small sample size (larger cohorts might underestimate our results), and lack of validation of endoscopic scores (SES-CD) for PCE. Conversely, the previously highlighted strengths also remain and refer to the stringent definition of MH that was applied to avoid overestimating MH, the well-structured study design, the intention-to-treat analysis, and the proven expertise of the study group when interpreting the PCE findings.

Moreover, unlike the scenario in which capsule endoscopy is utilized for identifying bleeding or neoplastic lesions, the diagnostic effectiveness of the capsule in evaluating the extent and severity of inflammation in CD is relatively unaffected by low completion rates and insufficient cleanliness. This is primarily because inflammatory lesions can be detected with greater ease compared with small polyps.

Conclusions

Our study supports the role of PCE in the pediatric CD treat-to-target strategy. Certainly, our results need to be contextualized and confirmed by larger and prospective cohorts, which ideally also examine the ability of each therapeutic intervention to act synergistically with this monitoring approach. Because the child's clinical and biological remission (which are considered as minimum and short-term goals)

are no longer sufficient, a complete mucosal examination should be performed whenever possible, with the treatment adjusted accordingly. PCE, performed and interpreted by well-trained professionals, could serve this purpose perfectly, limiting the discomfort and risks associated with endoscopy, or overcoming the limitations of radiological techniques in assessing the mucosa when complications (such as strictures or a penetrating behavior) do not dictate other evaluation techniques. CD is a complex disease, and there is no single simple strategy (either therapeutic or monitoring) that can be applied universally. Again, a multidimensional assessment by the clinician and based on patient characteristics (and preferences) is crucial, and not only should stratification be related to the therapeutic phase, but also patients should ideally be assigned to different monitoring strategies based on their characteristics. Among others, PCE is a tool, whose value depends on how the physician uses it, backed by accumulated evidence of its safety and effectiveness.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflicts of Interest

C.H., S.O., and S.C. have served as consultants for Medtronic. All other authors have no disclosures related to the article to declare.

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