Changing Paradigms for Assessing Response to Therapy in Crohn's Disease

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**Introduction**

Historically, assessing disease response to therapy in Crohn’s disease placed emphasis on symptom resolution as the ultimate treatment goal; however, the correlation between clinical symptoms, endoscopic improvement, and indicators of biological activity (i.e., C-reactive protein [CRP]) is not robust. As such, there is ongoing investigation and controversy as to the best means to assess response.

There are many different methods to evaluate disease and measure treatment response. These include clinical indices, endoscopic indices, magnetic resonance enterography scoring systems, capsule endoscopy, and development and study of noninvasive biomarkers (i.e., CRP and fecal calprotectin), which will all be discussed in this newsletter.

**Target Audience**

This activity is designed for pediatricians, pediatric and adult gastroenterologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who are interested in treating children and young adults with CD.

**Learning Objectives**

Participants completing this activity should be better able to:

- Recognize the need to differentiate between a patient in clinical remission and a patient who has achieved laboratory and endoscopic remission
- Understand the benefits of using disease assessment tools in different clinical scenarios
- Identify gaps in knowledge that stand in the way of moving toward a standardized approach to monitoring disease activity following change in therapy or surgical resection

**Physicians**

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**Introduction**

Historically, assessing disease response to therapy in Crohn’s disease (CD) placed emphasis on symptom resolution as the ultimate treatment goal; however, the correlation between clinical symptoms, endoscopic improvement, and indicators of biological activity (ie, C-reactive protein [CRP]) is not robust.\(^1\)\(^2\) As such, there is ongoing investigation and controversy as to the best means to assess response.

Currently, the patient’s response to therapy can be accurately defined in the following terms:

- clinical response (symptoms are improved, but patient is not completely well)
- clinical remission (patient feels well)
- clinical and laboratory remission (patient feels well and laboratory values are normal)
- clinical, laboratory, and endoscopic remission (patient feels well, laboratory values are normal, and mucosal ulceration is absent)

There are many different methods to evaluate disease and measure treatment response. These include clinical indices, endoscopic indices, magnetic resonance (MR) enterography scoring systems, capsule endoscopy (CE), and development and study of noninvasive biomarkers (ie, CRP and fecal calprotectin), which will all be discussed in this newsletter.

**Clinical Indices**

Clinical indices have long been available to monitor CD. Indices represent the most practical, cost-efficient, and noninvasive ways to determine whether or not a pediatric ulcerative colitis (UC) or CD patient is getting better.\(^3\) Activity indices have been widely accepted as research tools but remain underused in clinical practice. The incorporation of some activity indices into clinical practice may improve patient care and facilitate quality improvement. Currently, the use of indices in routine clinical practice is limited because they are perceived as difficult to learn and time consuming.\(^4\) Comprehensive (multi-item) CD indices have been developed for use in adults (ie, CD Activity Index [CDAI]), and a pediatric CD activity index (PCDAI)\(^5\) has undergone multiple revisions in order to make it more practical for use in the clinic.

**Physician’s Global Assessment**

The Physician’s Global Assessment (PGA) continues to be the easiest and most commonly used method for classifying a patient’s severity of disease. The PGA is typically used as the standard of comparison in the design of CD clinical indices.\(^5\)\(^6\)

The PGA measures disease severity on a scale of inactive (quiescent), mild, moderate, and severe. The definitions of these disease severities are subjective and can vary among clinicians.

**PCDAI**

The PCDAI was developed in 1990 and validated by a group of experts.\(^5\) The PCDAI includes a child-specific item: the height velocity variable. The PCDAI score can range from 0–100, with higher scores signifying more-active disease. Cutoff values for inactive, mild, and moderate-severe disease are shown below. The PCDAI highly correlates with PGA and is superior to the CDAI and Harvey–Bradshaw Index.\(^6\) The PCDAI requires a physician assessment and laboratory tests that are routinely ordered as part of standard medical care.\(^7\) The PCDAI’s major limitation is the limited ability to complete it in the context of routine clinical care.\(^8\)
PCDAI Parameters

History (recall: 1 week)
- Abdominal pain
  - None: 0
  - Mild—brief, does not interfere with activities: 5
  - Moderate-to-severe—daily, longer lasting, affects activities, nocturnal: 10
- Stools (per day)
  - 0–1 liquid stools without blood: 0
  - ≤2 semiformed with small blood or 2–5 liquid: 5
  - Gross bleeding, ≥6 liquid, or nocturnal diarrhea: 10

Patient function/general well-being (recall: 1 week)
- No activity limitations/well: 0
- Occasional difficulty maintaining age-appropriate activities/subpar: 5
- Frequent activity limitations/very poor: 10

Laboratory
- Hematocrit (Hct) [%]
  - <10 years [male or female]
    - ≥33: 0
    - 28–32: 2.5
    - <28: 5
  - 11–19-year-old female
    - ≥34: 0
    - 29–33: 2.5
    - <29: 5
  - 11–14-year-old male
    - ≥35: 0
    - 30–34: 2.5
    - <30: 5
  - 15–19-year-old male
    - ≥37: 0
    - 32–36: 2.5
    - <32: 5
- Erythrocyte sedimentation rate (ESR) (mm/hour)
  - <20: 0
  - 20–50: 2.5
  - >50: 5
- Albumin (g/dL)
  - ≥3.5: 0
  - 3.1–3.4: 5
  - ≥3.0: 10

Examination
- Weight
  - Gain or voluntary weight stable/loss: 0
  - Involuntary weight stable or loss of 1%–9%: 5
  - Loss of ≥10%: 10
- Height
  - Diagnosis
    - <1 channel decrease: 0
    - ≥1 to <2 channel decrease: 5
    - ≥2 channel decrease: 10; or
  - Follow-up
    - Height velocity ≥ –1 standard deviation (SD): 0
    - Height velocity < –1 SD to > –2 SD: 5
    - Height velocity ≤ –2 SD: 10
- Abdomen
  - No tenderness or mass: 0
  - Tenderness/mass without tenderness: 5
  - Tenderness/involuntary guarding/definite mass: 10
- Perirectal disease
  - None/asymptomatic tags: 0
  - 1–2 indolent fistula/scant drainage/no tenderness: 5
  - Active fistula/drainage/tenderness/abscess: 10
- Extraintestinal manifestations (fever ≥38.5°C for 3 days in past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)
  - None: 0
  - 1: 5
  - ≥2: 10

Scoring
- Score can range from 0–100, with higher scores signifying more active disease
- <10 is consistent with inactive disease
- 11–30 indicates mild disease
- >30 is moderate-to-severe disease
- A decrease of 12.5 points is taken as evidence of improvement
Modified Versions of the PCDAI

abbrPCDAI. The PCDAI has been modified over the last 24 years. The Abbreviated PCDAI (abbrPCDAI) omits growth and 3 laboratory items, thereby increasing its feasibility of use in the clinic.9 The abbrPCDAI is limited in that the remaining scored items are not reweighted, leading to low face validity (face validity pertains to how much the index makes sense and is a subjective assessment of whether the measure leaves out any items that most experts would agree are important).

Short PCDAI. The short PCDAI was developed by Kappelman and colleagues in 2010 for use in quality improvement and observational studies to increase feasibility.9 Its major advantage over the PCDAI and abbrPCDAI is less time with no laboratory values, growth velocity, or perianal disease to be assessed. However, the limitation of low face validity remains.9

Modified PCDAI. The Modified PCDAI was developed by Leach and colleagues in 2010,10 combining the 3 laboratory parameters from the PCDAI (Hct, ESR, and albumin) with CRP. This index does not use any history or physical examination parameters. Whereas the Modified PCDAI provides an objective measure of inflammation that may have applications in the setting of research focusing on the state of inflammation, its responsiveness and discriminant validity have been proven inferior to the PCDAI and Suggested Mathematically Weighted PCDAI (wPCDAI).9 Discriminant validity in this study was the ability to differentiate patients in remission from those with active disease and from the different disease activity states (mild, moderate, and severe).

wPCDAI. The wPCDAI was developed by Turner and colleagues in 2012 in order to add weight to the items in the PCDAI and make it more feasible.9 In the wPCDAI, growth velocity, abdominal examination, and Hct are removed.

wPCDAI Parameters:

**History** (recall: 1 week)
- Abdominal pain
  - None: 0
  - Mild—brief, does not interfere with activity: 10
  - Moderate-to-severe—daily, longer lasting, affects activity, nocturnal: 20
- Patient function/general well-being
  - No limitation of activity/well: 0
  - Occasional difficulty maintaining age-appropriate activity/subpar: 10
  - Frequent limitation/very poor: 20
- Stools (per day)
  - 0–1 liquid, no blood: 0
  - ≤2 semiformal with small blood or 2–5 liquid: 7.5
  - Gross bleeding, ≥6 liquid, or nocturnal diarrhea: 15

**Laboratory**
- ESR (mm/hour)
  - <20: 0
  - 20–50: 7.5
  - >50: 15
- Albumin (g/dL)
  - ≥3.5: 0
  - 3.1–3.4: 10
  - ≤3.0: 20

**Examination**
- Weight
  - Gain or voluntary stable/loss: 0
  - Involuntary stable or loss of 1%–9%: 5
  - Loss ≥10%: 10
- Perirectal disease
  - None/asymptomatic tags: 0
  - 1–2 indolent fistula/scant drainage/no tenderness: 7.5
  - Active fistula/drainage/tenderness/abscess: 15
- Extraintestinal manifestations (fever ≥38.5°C for 3 days in past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)
  - None: 0
  - ≥1: 10

**Total Score:** 0–125

**Scoring**
- <12.5 remission
- 12.5–40 mild
- >40 moderate
- >57.5 severe
- A decrease of 17.5 points is taken as evidence of improvement
**Case Study 1: Nicky**

Nicky is an 8-year-old boy with CD involving the terminal ileum (TI) as well as pancolitis who comes in for assessment 3 months after his last appointment. He was diagnosed 1 year ago and was placed on 6-mercaptopurine (6-MP) 6 months ago after becoming steroid dependent. He was successfully weaned off prednisone 3 months ago and, at that time, was having no abdominal pain, 1 formed BM daily without blood, and no limitation of activities. At today’s appointment, it is described that he has mild, brief abdominal pain episodes twice a week. His BMs are 2–3 times per day and semiformed, and he has noticed blood twice per week for the last month. He continues to have no limitation of activities. He has no extraintestinal manifestations.

On examination today, there is mild lower-abdominal tenderness. Head, eyes, ears, nose, and throat; musculoskeletal; skin; and perianal examination are normal. Weight is the same as it was 3 months ago. Over the last 12 months, Nicky has grown 0.5 cm and has fallen from the 50th percentile for height to between the 10th and 25th percentiles. His Zscore for his height velocity is –1.06. His Hct is 30%, ESR is 25, and albumin is 3.2.

**Assessment: PCDAI points**

**History:**
- Abdominal pain: 5
- General well-being: 0
- Stools: 5

**Examination:**
- Abdomen: 5
- Perianal disease: 0
- Weight: 5
- Height: 5
- Extraintestinal manifestations: 0

**Laboratory:**
- Hct: 2.5
- ESR: 2.5
- Albumin: 5

Nicky’s Composite PCDAI Score: 35 (previous PCDAI 3 months ago was 5)

A score of 35 is consistent with moderate-to-severe disease, where it was inactive 3 months ago.

Based on the wPCDAI (weighted):

**Assessment: wPCDAI points**

**History:**
- Abdominal pain: 10
- General well-being: 0
- Stools: 7.5

**Examination:**
- Perianal disease: 0
- Weight: 5
- Extraintestinal manifestations: 0

**Laboratory:**
- ESR: 7.5
- Albumin: 10

wPCDAI score of 40 is consistent with upper limit of mild disease (previous wPCDAI 3 months ago was 0).

**Discussion Points and Unanswered Questions**

- There is a discrepancy in disease severity, with the PCDAI measuring Nicky’s disease as moderate-severe disease and the wPCDAI measuring Nicky’s disease as mild. Does the PCDAI or wPCDAI score better reflect this patient’s disease severity?
  - The absence of growth velocity in the wPCDAI score may lead to underestimation of a pediatric patient’s disease severity.
Endoscopic or visual evaluation of intestinal mucosa is essential in diagnosing CD, identifying disease location and severity, and monitoring for dysplasia. Endoscopy may also play an important role in surveillance of disease activity, though few guidelines exist regarding how and when to use endoscopic surveillance in CD. Recent European guidelines suggest endoscopy in cases of relapse, refractoriness, new symptoms, or when surgery is being considered. The value of routine endoscopy during periods of symptom remission is not well studied and is often debated, both in the United States and Europe.

There is growing evidence that early healing of the intestinal epithelium is associated with decreased likelihood of a flare, progression to complications, and need for hospitalization and surgery in both UC and CD. Though unproven, the argument may be made for achieving mucosal healing as the targeted therapeutic goal in children, given the observation of improved clinical outcomes and decreased need for surgery and hospitalization in adults. Reassessment of mucosal inflammation following treatment, particularly when using a “step-up” therapeutic approach, is termed the “treat to target” strategy. Data show the strategy of repeat colonoscopy within 6 months of starting therapy, with a target of mucosal healing, is useful and feasible in adults with UC. However, optimal timing of follow-up endoscopy and optimal degree of improvement in mucosal appearance following therapy remain unclear. The feasibility and benefit of the treat-to-target approach in pediatric UC and pediatric and adult CD is unknown. Prospective studies are needed to answer questions about the most cost-effective and risk-averse strategies to achieve targeted therapeutic goals in pediatric CD. In general, pediatric studies regarding endoscopic response are lacking.

Complete absence of mucosal ulcers may be an unachievable goal in many cases with currently available therapies. However, if a measurable improvement in the appearance of the mucosal inflammation is a therapeutic goal, scoring systems can help to make serial evaluation more precise. Two such endoscopic scores developed in adults are the CD Endoscopic Index of Severity (CDEIS) and the Simplified Endoscopic Activity Index for CD (SES-CD). In a post hoc analysis of the Study of Biologic and Immunomodulator Naïve Patients in CD (SONIC) trial, a decrease in baseline CDEIS or SES-CD by at least 50% at week 26 correlated with corticosteroid-free remission at week 50. However, further studies are needed to determine the optimal score improvement to predict better longer-term outcomes. The CDEIS has a high inter- and intrarater reliability and validity but is complex and not realistic for implementing in clinical practice. The SES-CD is more feasible for use in daily practice and also has a high level of inter- and intrarater reliability. Another example of predictive endoscopic scoring is the Rutgeert’s score, developed for predicting recurrence of CD activity after ileocolonic resection by evaluating the appearance of the neoterminal ileum 6 months after ileocolonic resection. For future studies, more precisely defining what is meant by “mucosal healing” and endoscopic response will be critical in determining the degree of improvement needed to affect outcomes in pediatric CD patients. A possible limitation of endoscopic evaluation is that the mucosa represents <15% of the entire bowel wall and it does not evaluate inflammation at deeper layers of the bowel wall. Although histologic scores exist for diagnosis of inflammatory bowel disease (IBD), there is no histologic scoring system validated for serial evaluation of inflammatory activity in CD. Although it may be more feasible in UC, histologic assessment of disease assessment may prove to be difficult in CD because of the patchy nature of the disease, limited ability to assess the small intestine, and potential for sampling error.

### Rutgeert’s Score

**Grade 0:** No lesions in distal ileum

**Grade 1:** ≤5 aphthous lesions

**Grade 2:** >5 aphthous lesions with normal mucosa between lesions or skip larger lesion areas or lesions confirmed to ileocolonic anastomosis (<1 cm long)

**Grade 3:** Diffuse aphthous ileitis with diffusely inflamed mucosa

**Grade 4:** Diffuse inflammation with already large ulcers, nodules, and/or narrowing
### SES-CD

**Size of ulcers**
- None: 0
- Aphthous ulcers (0.1–0.5 cm): 1
- Large ulcers (0.5–2.0 cm): 2
- Very large ulcers (>2 cm): 3

**Ulcerated surface**
- None: 0
- <10%: 1
- 10%–30%: 2
- >30%: 3

**Affected surface**
- Unaffected segment: 0
- <50%: 1
- 50%–75%: 2
- >75%: 3

**Presence of narrowing**
- None: 0
- Single, can be passed: 1
- Multiple, can be passed: 2
- Cannot be passed: 3

**SES-CD score is the total of each section, with higher scores indicating worse histology**

### CDEIS

**Total 1: deep ulceration** *(12 if present; 0 if absent)*
- Rectum
- Sigmoid and left colon
- Transverse colon
- Right colon
- Ileum

**Total 2: superficial ulceration** *(6 if present; 0 if absent)*
- Same segments as in Total 1

**Total 3: surface involved by disease (cm)*
- Same segments as in Total 1

**Total 4: Ulcerated surface (cm)*
- Same segments as in Total 1

**Scoring**
- Total 1 + Total 2 + Total 3 + Total 4 = Total A
- Total A ÷ number of segments totally or partially explored = Total B
- C: 3 if ulcerated stenosis anywhere; 0 if not
- D: 3 if nonulcerated stenosis anywhere; 0 if not
- Total B + C + D = CDEIS

* 10 cm linear scale represents surface effectively explored for partially explored segments and for ileum

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### Noninvasive Biomarkers of Disease Activity

Whereas endoscopic assessment of the mucosa may be the gold standard of disease assessment, serial colonoscopies with repeat bowel preparation and anesthesia are a significant risk and cost burden, particularly in pediatrics. An accurate, noninvasive biomarker of disease activity, defined as a characteristic or test that is objectively measured as an indicator of disease response, is of great interest in CD. However, biomarkers have little value in measuring treatment response unless there is a clearly defined therapeutic target that translates into improved patient outcomes, and optimal timing of posttreatment disease evaluation must also be considered.  

The two noninvasive biomarkers currently being studied and most widely used clinically are fecal calprotectin and serum CRP. Fecal calprotectin is a neutrophil protein secreted by intestinal epithelial cells in response to inflammatory cytokines like interleukin 1 (IL-1) and bacterial lipopolysaccharide. Fecal calprotectin correlates with endoscopic and histologic assessment of disease activity in adults and children. A cutoff of 200–250 µg/g seems to be the most sensitive and specific for inflammation in both UC and CD when compared with the Mayo score and the SES-CD. Levels of 250–300 µg/g have been shown to predict relapse of CD involving the colon. In CD, fecal...
calprotectin is significantly higher in patients with more-severe disease as defined by SES-CD.\(^{32}\)

In a study of 140 ileocolonoscopies in CD patients, SES-CD correlated more closely with fecal calprotectin and CRP than CDAI. The overall accuracy for detecting endoscopically active disease was 87% for calprotectin (70 µg/g), 66% for CRP, and 40% for CDAI ≥ 150.\(^{33}\) The correlation with mucosal healing is imperfect, and appropriate timing of follow-up fecal calprotectin assessment after therapy is unknown. Also, there is a weaker correlation of fecal calprotectin to mucosal healing in the small bowel (SB) than in the colon.\(^{34}\) It should be noted that use of nonsteroidal anti-inflammatory drugs (NSAIDs), infection, and malignancy can all increase fecal calprotectin and can be important confounders.\(^{29}\) These drawbacks make it difficult to rely on fecal calprotectin alone as a monitoring tool. However, it could potentially be studied for use in conjunction with another biomarker, such as CRP, or in patients with a known elevation at baseline.

Serum CRP is an acute phase reactant secreted by the liver in response to the circulating proinflammatory cytokine IL-6.\(^{35}\) In a trial of 200 children with CD treated with a variety of standard therapies, only 14% of patients in corticosteroid-free remission (as defined by PCDAI < 10 or PCDAI < 7.5 without the height component) by week 12 were in corticosteroid-free remission by week 52.\(^{36}\) In a subgroup analysis of 104 children with an elevated CRP at baseline and corticosteroid-free remission at 12 weeks, normal serum CRP at 12 weeks was a significant predictor of sustained remission at 1 year. Although 60% of the subgroup patients achieved a normal serum CRP by week 8, only 33% achieved remission and normal CRP by week 12. Poor outcomes were not correlated with increased disease severity at diagnosis. Other studies have shown a normal CRP to be a good predictor of disease outcome, including the A CD Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen I (ACCENT1) study, where CRP < 0.5 at week 14 was predictive of maintenance of response to infliximab.\(^{37}\)

In summary, CRP and fecal calprotectin are promising as noninvasive biomarkers of disease activity, but further research is needed to define a therapeutic target to correlate with noninvasive biomarkers. To become a surrogate of disease response, the biomarker must then be correlated with longer-term patient outcomes.

**Case Study 2: Samantha**

Samantha is a 14-year-old girl with a history of ileocolonic CD. Her older sister has a history of ileal CD and stricture requiring resection. Samantha was treated with corticosteroids and 6-MP but, upon taper of prednisone, rapidly developed symptoms of SB obstruction. MR enterography (MRE) revealed enhancement and bowel-wall thickening of the TI and cecum, with dilatation proximal to the TI. Due to concerns about fixed stricture, the patient underwent ileectomy with negative margins. The patient was treated with 6-MP postoperatively, but due to complaints of nausea, her mother stopped giving the drug. Colonoscopy 6 months postsurgery showed normal bowel with no aphthous ulcerations at the anastamosis or in the neoterminal ileum (Rutgeert’s score 0). Postoperatively, a baseline fecal calprotectin was normal at 45 µg/g of feces. The parent and patient opted to not take postoperative prophylaxis. The fecal calprotectin was monitored every 6 months. One year postoperation, the fecal calprotectin increases to 335 µg/g of feces. The patient denies any NSAID use or symptoms. Colonoscopy reveals diffuse aphthous ulcerations with ileal inflammation (Rutgeert’s score 3). After discussion with the family and patient regarding risk of symptom recurrence and further need for surgery, the patient is started on a biologic.
Several radiologic studies may be useful in pediatric CD, including upper gastrointestinal (GI) series with SB follow through, computed tomography (CT) enteroclysis, and contrast-enhanced ultrasound. However, given concerns for ionizing radiation, recent European Crohn’s and Colitis Organisation (ECCO) guidelines recommend MRE be done where available.\textsuperscript{17, 38–40} The absence of ionizing radiation makes MRE especially appealing in the pediatric population and for patients who require serial imaging. High-resolution ultrafast sequences are particularly suitable in the study of the SB by MRE, providing sharp images of the anatomy of the intestine. Among other methods of disease evaluation, MRE is the only method available for assessing structural changes of the bowel wall (ie, bowel-wall thickness, full thickness inflammation, or enhancement). Engorgement of the vasa recta with the addition of elevated T2 signal within or adjacent to the bowel wall (caused by the presence of fluid) is indicative of an active inflammatory process.\textsuperscript{41, 42} This feature can help to distinguish inflammatory from fibrostenotic bowel.\textsuperscript{43} Because SB CD (more so than colonic disease) is more likely to progress from an inflammatory to a stenotic or fistulizing phenotype in a shorter period of time, re-evaluation of disease progression may be most important in this group of patients.\textsuperscript{16, 17}

Newly developed indices, such as the MR Index of Activity (MaRIA), provide a step forward for the robust evaluation of imaging findings associated with CD, because they include characteristics such as wall thickness, relative contrast enhancement, edema, and ulceration. The MaRIA index is calculated by [1.5 x wall thickness [mm]] + [0.02 x relative contrast enhancement] + [5 x edema] + [10 x ulcers]. The global MaRIA score is calculated by summing the scores from the TI, ascending colon, transverse colon, descending colon, sigmoid, and rectum. Mucosal healing is defined as a MaRIA score of <7, and ulcer healing is defined as a score of <11, because this cut-off point has a 90% sensitivity and 94% specificity to detect the presence of ulcers.\textsuperscript{44} The MaRIA index is shown to correlate well with endoscopic response to adalimumab therapy.\textsuperscript{45} However, this index has not been used in children. An obstacle to the use of MRE in CD monitoring is that adequate bowel distension is necessary to facilitate evaluation of mucosal enhancement and bowel-wall thickening.\textsuperscript{43, 46} Collapsed bowel-wall segments can be mistaken for pathologic bowel-wall thickening.\textsuperscript{43} Tolerance of a large amount of contrast material may be limited, especially in children who are prone to vomiting and abdominal pain from active CD. Rectal contrast may be difficult for children to tolerate. Other downsides include limited availability of MR imaging and steep costs associated with these studies.

The Lemann score is under development by the International Program to develop New Indices in Crohn’s Disease group. The main objective of this multicenter, cross-sectional study is to develop an instrument that can measure the cumulative bowel damage at a specific point in time, as assessed by history, endoscopy, and imaging techniques. The index score will take into account damage location, extent, and severity based on a comprehensive assessment of structural bowel damage, including stricturing lesions, penetrating lesions (fistulas and abscesses), and surgical resection. The goal is to determine if this score will identify patients at high or low risk of disease progression. The imaging modalities MRE and CT enterography (CTE) are emphasized as critical to evaluate tissue damage, unlike upper GI endoscopy and colonoscopy, which can identify mucosal lesions that more accurately reflect disease activity (inflammation) than bowel damage.\textsuperscript{47}


CASE STUDY 3: Ryan

Ryan is a 15-year-old, well-nourished boy who presented with acute onset of vomiting and abdominal pain. Initial CT scan from outside the emergency department showed narrowing of the TI with bowel-wall thickening and air fluid levels indicative of partial SB obstruction. Infectious workup was negative. With bowel rest and gastric decompression, symptoms resolved and his diet was advanced without further vomiting. Despite lack of ongoing symptoms, laboratory values were obtained and CRP noted to be elevated 1 month postadmission. MRE was ordered, revealing 1.5 cm of bowel-wall thickening/enhancement. Esophagogastroduodenoscopy (EGD)/colonoscopy revealed no active colitis, but scattered granulomas were present throughout the colon and mild chronic active ileitis with granulomas was also present. The patient was treated with budesonide and subcutaneous methotrexate, with improvement in the CRP and weight gain. Follow-up MRE several months later reveals ongoing narrowing in the TI and the presence of bowel-wall enhancement, indicating ongoing active disease and prompting discussion about escalation of therapy despite lack of symptoms.

DISCUSSION POINTS AND UNANSWERED QUESTIONS

- MRE sometimes reveals a lack of correlation between structural changes in the bowel wall and symptom reports
- Is use of MRE appropriate to stratify patients at high risk of complications, regardless of symptoms?
  - MRE offers a potential for noninvasive monitoring of disease activity, particularly in SB CD, but there are no guidelines supporting use of this modality to monitor pediatric patients with CD

CAPSULE ENDOSCOPY

CE is a noninvasive method of endoscopic imaging that can be swallowed by the patient or delivered into the SB with endoscopic assistance. CE was US Food and Drug Administration approved in 2001 as an adjunctive tool in evaluation of SB diseases and is now indicated for patients aged 2 years and older and for monitoring CD. The capsule is approximately the size of a large multivitamin (1.1 × 2.6 cm or 1 × 0.5 in.). The main advantage of CE is the ability to visualize the entire SB with minimal discomfort to the patient and no radiation.

CD confined to the SB can be detected in up to 30% of a pediatric population. CE has made evaluation of the SB more sensitive, and many cases of unclassified IBD are reclassified as CD when SB involvement is detected. CE has been shown to improve the diagnostic yield in adults with IBD. At this time, pediatric reports are few, mostly retrospective, or include a small number of patients.

Indications/Limitations

As recommended by the Organisation Mondiale d’Endoscopie Digestive-ECCO consensus, CE should be performed in children or adolescents with a high suspicion of CD when conventional upper and lower GI endoscopy and SB imaging are inconclusive.

Clinicians may consider CE for patients who:
- have unclassified IBD
- are failing medical therapy or may require colectomy
- have truly unexplained symptoms based on standard endoscopy and radiography
- have IBD and obscure bleeding
Although CE identifies SB pathology with greater sensitivity than other methods, the implications of identified lesions are not fully understood. Small bowel endoscopy, CTE, and MRE usually provide the information needed to guide therapy in patients with known CD. However, in cases where management decisions are not clear despite the use of these modalities, CE can be an invaluable tool and worth the potential risk of capsule retention. There is no consensus about patient preparation for CE. Each practice uses a different combination of dietary fasting, laxatives, and medications to stimulate peristalsis.

There are several limitations to CE, including a lack of therapeutic capabilities, the inability to control the movement along the SB, the potential to miss single lesions, as well as the high rate of incidental findings. A major complication is potential retention, which precludes its use in patients with suspected obstruction or strictures.

**Interpreting Results**

A diagnosis of CD should not rely on CE features alone, because there are many false positives and no validated diagnostic criteria. The presence of >3 ulcerations in the absence of NSAIDs ingestion is the most commonly used CE diagnostic criteria for CD; however, there is not sufficient evidence to confirm this score.

**Risk of Retention**

A diagnosis of CD is associated with an increased risk of capsule retention. The risk of SB capsule retention in CD patients has been reported between 6.7% and 13% for all age groups and mainly in those with documented intestinal stenosis or previous surgery. In children with CD, the rate of capsule retention is closer to 5%. In a pediatric cohort of 207 patients, the risk of capsule retention with a history of known IBD was 5.2%, and certain disease characteristics significantly increased this risk. A SB series demonstrated that SB CD is associated with a 37.5% retention risk and body mass index <50 percentile with known IBD is associated with a 43% retention risk. Capsule retention requiring intervention has been reported in <1% of pediatric subjects. In order to reduce the risk of retention, a "patency" capsule can be used to assess the risk of capsule retention, because a patency capsule will dissolve and not require removal if it becomes stuck in the SB. However, timely passage of the patency capsule is not 100% sensitive for adequate passage of the capsule for CE. If the capsule does become retained in the SB, it can often be removed by deep SB enteroscopy, such as double-balloon enteroscopy.

**Future Considerations**

There is limited experience with the use of CE, especially in children with IBD. There has been 1 clinical trial by Di Nardo et al. in Italy, where CE and SB imaging were compared among 117 children with established or suspected IBD. This study concluded that CE was valuable in revealing SB lesions in children with a previous diagnosis of CD, was helpful in unclassified IBD patients, and could influence the management and course of IBD. There are considerations for CE to be used for postoperative surveillance to help evaluate mucosal healing or diagnose postoperative recurrence. As there is a strong movement towards endoscopic healing representing remission, if evidence shows that aggressive treatment of CD for endoscopic healing positively affects the natural history of the disease, then CE may become an even more important tool in assessing the extent of disease.
A repeat prednisone course, colectomy, and changing from 6-MP to a biologic are discussed. The patient is very resistant to the thought of going back on a prednisone course because of the adverse effects.

It is decided to repeat an EGD and colonoscopy. Her stomach shows scant aphthous ulcers that come back as chronic gastritis without granulomas. Colonoscopy shows quiescent to mild active colitis (improved from previous colonoscopy 5 years ago). She has a normal TI. An MRE is performed because of the concern for possible CD and because the family is considering colectomy over biologic treatment. The MRE does not show any signs of active inflammation in the SB.

A CE is ordered. The capsule study shows 4 discrete ulcerations in the jejunum with additional areas of erythematous, granular-appearing mucosa. The patient’s Asacol® is changed to Pentasa®. The patient has a mild improvement in symptoms over the next few months, but despite adding ciprofloxacin and metronidazole, she continues to have symptoms and is placed on infliximab. The patient currently has inactive disease and a normal ESR.

**Case Study 4: Sara**

Sara is a 12-year-old girl who was diagnosed with UC when she was 7 years old. She presented with chronic diarrhea with rectal bleeding. She also showed poor weight gain at diagnosis. Her colonoscopy showed pancolitis with normal biopsies of the TI. Her upper endoscopy showed aphthous ulcers in the stomach, which was reported as chronic inactive gastritis. There were no granulomas reported in any of the biopsies. Her SB series was normal. Her IBD serology was not consistent with IBD (the entire serologic profile was negative).

Sara was initially treated with Asacol®, and after developing two flares that required oral prednisone, she had 6-MP added to her Asacol® regimen. On the 6-MP, she has had intermittent mild disease over the last 2 years with occasional loose stools and abdominal pain. She denies blood and reports only occasional mucus in the stool. Over the previous 6 months, her appetite has decreased and her loose stools and abdominal pain have worsened. Her weight and height have been stable at the 5th–10th percentiles. Her ESR has been between 20 and 30 mm/hour over the last 2 years and is now 40 mm/hour. Her stool is negative for *C. diff* and culture.

**Discussion Points and Unanswered Questions**

- CE is a valuable tool for this patient who has indeterminate colitis, is failing medical therapy, and may have undergone colectomy
- The CE diagnostic criteria for SB CD has been suggested as “The presence of >3 ulcerations, in the absence of NSAIDs ingestion” in an adult study, however, this may not be applicable to the pediatric age group
Monitoring disease activity in CD is particularly important, given the lack of correlation between symptoms and endoscopic findings, particularly if a more-conservative step-up approach is taken. Currently, there are several methods to assess disease response, all providing slightly different information about CD activity. A more evidence-based approach to evaluating disease activity and response to medications is needed, including appropriate and cost-effective intervals and methods of testing. The long-term therapeutic goals—to minimize likelihood of a flare of symptoms, minimize progression of disease from an inflammatory to a penetrating phenotype, minimize hospitalization and surgery, and promote normal growth and development—are clear. These factors go into the improvement of a patient’s health-related quality of life. However, clarification of short-term physiologic goals is needed to help guide therapeutic decisions effectively, particularly as more medical options become available.

**References**


