

A Case-Based Monograph Focusing on Pediatric IBD

MONITORING DISEASE ACTIVITY



IN PEDIATRIC IBD PATIENTS

FACULTY

Athos Bousvaros, MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Boston, MA

Dan Turner MD, PhD
Pediatric Gastroenterology Unit
The Hebrew University of Jerusalem
Shaare Zedek Medical Center
Jerusalem, Israel

Leanne Vitito, MS, RN, FNP-BC, CGRN
Department of Pediatric Gastroenterology
University of Nebraska Medical Center
Omaha, NE

CME CONTENT REVIEWER

Melanie K. Greifer, MD
Assistant Professor of Pediatrics
Albert Einstein College of Medicine
New Hyde Park, NY

MEDICAL WRITER

Jason Jenkins
TCL Institute, LLC
Cary, NC

Jointly sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC.

Release Date: December 15, 2009 Expiration Date: December 14, 2011

Estimated time to complete: 2.0 hours

Jointly sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC.

INTRODUCTION

Evaluating disease activity in children with inflammatory bowel disease (IBD) requires the use of outcomes that reflect pediatric-specific qualities of the disease. Monitoring pediatric ulcerative colitis (UC) and Crohn's disease (CD) is not limited to observing intestinal symptoms, but also involves assessing weight and height gains, sexual maturation, extraintestinal manifestations, and psychosocial well-being. Disease activity is best measured using multi-item indices, which incorporate clinical symptoms, laboratory parameters, and endoscopic findings. Indices are prediction rules used to measure the activity of disease, and use a combination of history, examination, and laboratory data to develop an objective score that is reproducible between different observers.

Currently, validated indices are utilized in clinical trials of pediatric IBD, but not widely used in everyday clinical practice because they are perceived by clinicians as being too difficult to learn and too time-consuming to administer and interpret. This may result in suboptimal management because the accurate determination of disease activity results in closer monitoring of the patient's progress, and allows for the adjustment of medical therapy as appropriate. This monograph focuses on teaching clinicians to incorporate validated indices into clinical practice.

TARGET AUDIENCE

This activity is designed for gastroenterologists, physician assistants, nurse practitioners, and other clinicians who will utilize indices to measure disease activity in children with IBD.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Identify validated indices to evaluate disease progression, severity of disease, and efficacy of pharmacotherapies for children with IBD
- Utilize appropriate indices for children with UC and CD based on their presenting symptoms
- Implement indices to monitor disease activity in appropriate children with IBD while understanding the advantages and disadvantages of each tool

PHYSICIANS

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), the Children's Digestive Health and Nutrition Foundation (CDHNF), and TCL Institute, LLC. NASPGHAN is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA STATEMENT

NASPGHAN designates this educational activity for a maximum of 2.0 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

STATEMENT OF DISCLOSURE

All faculty/speakers, planners, abstract reviewers, moderators, authors, coauthors, and administrative staff participating in the continuing medical education programs sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC are expected to disclose to the program audience any/all relevant financial relationships related to the content of their presentation(s).

Accordingly, the staff at NASPGHAN, CDHNF, and TCL Institute, LLC have reported no financial relationships with any commercial interests related to the content of this educational activity.

Dr. Bousvaros reported that he is a consultant to Millennium Pharmaceuticals, Inc.; receives research support from Abbott Laboratories and Merck & Co., Inc.; and is a speaker for Abbott Laboratories.

Dr. Greifer, Dr. Turner, and Ms. Vitito have nothing to disclose.

In accordance with ACCME Standards for Commercial Support of CME, NASPGHAN, CDHNF, and TCL Institute, LLC implemented mechanisms to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity. To resolve identified conflicts

of interest, the educational content was peer-reviewed by a physician member of the NASPGHAN Review Committee who has nothing to disclose. The resulting certified activity was found to provide educational content that is current, evidenced based, and commercially balanced.

DISCLOSURE OF UNLABELED OR INVESTIGATIONAL DRUGS

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, attendees/participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

MEDIUM OR COMBINATION OF MEDIA USED

This activity will consist of a mailed or Web-based newsletter and a posttest. To view a pdf of the monograph please visit <http://totalmeded.com/links/monographs/ibdindices>. This activity requires Adobe Acrobat to view a pdf of the monograph. If you encounter problems, please notify us at questions@TotalMedEd.com.

HOW TO RECEIVE CME CREDIT:

To receive CME credit for reviewing "Monitoring Disease Activity in Pediatric IBD Patients", participants must review the CME information (learning objectives, disclosures, etc), review the entire activity, and complete the activity posttest and evaluation questions.

To complete the activity posttest and evaluation, please visit: http://www.gotomylist.com/evaluator/evaluation_start.cfm?pk_event=520. Certificates will be provided immediately after completion of both posttest and evaluation.

Questions about receiving credit: Please e-mail Katie@cmehelp.com

PROVIDER CONTACT INFORMATION

Jointly sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC. For questions, please contact:

TCL Institute, LLC | 104 Towerview Court | Cary, NC 27513
Phone: (919) 467-0006, ext. 233 | Fax: (215) 243-7273

DISCLAIMER

The content and views presented in this educational activity are those of the authors and do not necessarily reflect those of NASPGHAN; CDHNF; TCL Institute, LLC; or Centocor, Inc. This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely upon the information contained within this educational activity.

POLICY ON PRIVACY AND CONFIDENTIALITY

NASPGHAN, CDHNF, and TCL Institute, LLC will make every effort to protect the privacy of every individual participant of this activity and will use information gathered only to maintain records as required by the American Medical Association (AMA) and ACCME.

This activity does not require readers to "register" to review the material with the exception of physicians and other health care providers who desire to receive CME credit for this activity. If an individual completes a CME for this activity, we are required by the AMA and ACCME to collect personal information on the individual, such as their name, address, and phone number, that will allow us to issue a CME certificate to them and to keep this information on file for up to 6 years.

Personal information gathered will not be released to any other company or organization for any purpose. This information remains totally confidential. If you have any questions about TotalMedEd.com or any of our policies, you may contact us at help@TotalMedEd.com.

© Copyright 2009 NASPGHAN, CDHNF, and TCL Institute, LLC.

OVERVIEW

Managing children with inflammatory bowel disease (IBD) and its 2 main subtypes – Crohn’s disease (CD) and ulcerative colitis (UC) – requires attention to issues unique to children. Monitoring children with UC and CD is not limited to observing symptoms; it also involves assessing weight and height gains, sexual maturation, extraintestinal manifestations, and psychosocial well-being.

As therapy for IBD evolves, physicians are recognizing the need to develop and standardize disease activity indices that enable their peers and other clinicians to monitor and adjust therapy.¹ Disease activity is a concept for which no gold standard exists. Therefore, disease activity indices often include a number of clinical variables (eg, abdominal pain, diarrhea, rectal bleeding) to generate a composite numerical score. Since each included item may have different importance in explaining disease activity, weight is typically assigned to each clinical factor of the index. For example, in the Pediatric Ulcerative Colitis Activity Index (PUCAI), rectal bleeding is weighted more heavily than other items.²

Disease activity indices for CD and UC have been developed for use in clinical studies, most notably drug trials. This monograph reviews currently available activity indices for children and assesses their utility for standard clinical practice in addition to research purposes.

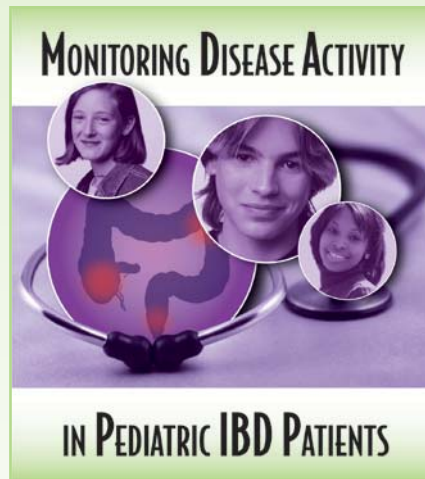
SHOULD PEDIATRIC IBD DISEASE ACTIVITY INDICES BE IMPLEMENTED IN ROUTINE CLINICAL PRACTICE?

On the surface, gathering and calculating a disease activity score in the clinical inpatient or outpatient setting may seem intimidating and cumbersome. However, incorporating disease activity indices into routine clinical practice has several potential advantages (Table 1).

Table 1. Reasons to Incorporate IBD Disease Activity Indices Into Practice

• Standardizes the gathering of clinical data at initial and follow-up visits
• Allows more objective assessment of disease activity
• Allows more objective assessment of response to drug therapy (response vs remission)
• Allows prediction of clinically important outcomes
• Facilitates communication between physicians caring for the patient
• Facilitates quality improvement measurements
• Facilitates a clinician’s participation in retrospective clinical studies

The calculated composite score should be reproducible between observers (ie, good reliability) and therefore allow comparisons between different physicians and centers. Clinicians who treat children with UC or CD may use these scoring systems to accurately characterize disease activity. In turn, the accurate



determination of disease activity results in closer monitoring of patient’s progress and allows for the adjustment of medical therapy.² When combined with an electronic medical record and/or database, a physician could track what percentage of his patients are in remission and focus to intensify monitoring and therapy on the patients who are not doing well. Groups intent on quality improvement initiatives could also use a well-validated index to institute improvement interventions that might improve overall health in their patients.

Currently, the use of indices in routine clinical practice is limited because they are perceived as difficult to learn and time consuming.³ In addition, clinicians using these measures may

be lulled into thinking that indices accurately describe the overall health of the patient. They do not. Indices only capture a limited portion of a patient’s overall health and are just another tool for clinicians to manage and use to follow a patient with chronic disease. For example, while the Pediatric Crohn’s Disease Activity Index (PCDAI) may capture symptoms of abdominal pain and anemia, it does not capture problems such as prolonged corticosteroid exposure, osteopenia, or depression. Therefore, gathering the data needed to complete an activity index score sheet does not equate to performing a thorough history and physical examination on a patient. While many indices can be completed in 1-2 minutes, others take longer. In the discussion of the various indices below, the authors will attempt to grade the indices, both with respect to general acceptance and ease of use.

By providing semiquantitative measures of response and remission, pediatric IBD disease activity indices have proven critical in determining whether new therapies are effective. They allow researchers to conduct clinical trials while minimizing invasive tests such as blood drawing and endoscopy, which is of a particular interest in children. Clinical indices may be used in everyday practice for assessing disease activity in IBD. In fact, indices represent the most practical, cost-efficient, and noninvasive way to determine whether or not a UC or CD pediatric patient is getting better.

CONCEPTS OF INDICES DEVELOPMENT AND VALIDATION

For disease evaluation in clinical trials, objective, validated, and reproducible disease activity indices are necessary to allow interpretations of results across trials.¹ An index may be developed for discriminative purposes to distinguish different categories of disease state at one point in time; evaluative purposes for measuring longitudinal change, for which responsiveness assessment is crucial; and for predicting clinically important outcomes. Hence, predictive validity is required.

INDEX DEVELOPMENT

The methodology utilized to develop activity indices has been refined over the last 20 years when the clinimetric field was introduced by Wright and Feinstein.⁴ The development of activity indices combines input from both experts in the field and statistical modeling. As an example for the multistep process required for formulating a valid clinical index, the development of the PUCAI by Turner and colleagues utilizes 2 large prospective cohorts of children with UC, as shown in Table 2.²

Table 2. Process of Developing the PUCAI²

Step	Description
Item generation	Using a Delphi process, [*] a panel of experts generated a broad list of potentially clinically significant variables that might impact disease activity (eg, number of daily stools, urgency, hemoglobin, radiographic appearance, and others).
Reduction	The list was reduced to include only the most pertinent items.
Grading	The responses for each item were graded to maximize discriminant validity, reliability, and responsiveness.
Weighting	Each item was weighted according to its importance in explaining disease activity using multivariate regression analysis on a cohort of UC patients.
Defining cut-off scores	Cut-off scores of the index were determined using data from the UC cohort, which correspond to clinically important disease states (eg, remission and mild-to-severe disease activity).
Evaluation	The final product, the clinical index, was then evaluated to assess validity, reliability, and responsiveness (defined within the text).

* A Delphi process involves obtaining a consensus agreement on a defined issue between many experts who are not present in the same room (using e-mail, for instance)

Evaluation

Once an index has been developed, it must be evaluated for validity, reliability, responsiveness, and feasibility.⁵⁻⁷

- **Validity** is the degree to which the instrument measures the concept that it means to measure and includes face, content, construct, and criterion validity.⁸
 - Face and content validity - Most experts in the field will judge the sensibility of the index and the importance of included items
 - Construct validity - The measure acts the way it is expected based on the concept it represents (eg, high correlation between disease activity index and the need for hospitalization)
 - Criterion validity - Determines the relationship between the measure and a gold standard
- **Reliability** of an index reflects whether an index is reproducible between different raters at the same time (interobserver reliability) and whether a score is reproducible at different times under stable conditions (test/retest reliability).²
- **Responsiveness** is a reflection of an index’s ability to identify change in disease state over time when it occurs.⁵⁻⁷ This is a very important property for clinical trials because it allows researchers to conduct the trial with a smaller sample size.⁹
- **Feasibility** encompasses respondent and administrative burden.⁵⁻⁷ Respondent burden is the participant’s contribution to the completion of the instrument while the administrative burden is the researcher’s involvement. An instrument is feasible if the participant and researcher report that the instrument is completed within reasonable limits of participant discomfort and both participant and researcher time constraints.⁸

INDICES TO EVALUATE PEDIATRIC CD

In adult patients with CD, the primary index used to assess patients in clinical trials is the Crohn’s Disease Activity Index (CDAI); in children with IBD, the primary index utilized is the PCDAI.^{10,11}

The adult CDAI, developed by statistical modeling on adult CD patients, measures 8 weighted factors: number of soft stools, abdominal pain, general well-being, presence of complications, the use of antidiarrheal medication, presence of an abdominal mass, hematocrit (HCT), and weight loss.¹²

The outcome of the CDAI varies between 0 and 600 points. In most studies, complete remission is defined by a value of < 150 points and clinical response is characterized by a decrease in CDAI of > 70 to 100 points.¹

The next widely used adult CD index is the Harvey-Bradshaw Index (HBI) (Table 3), which includes 5 of the main components of the CDAI and is easier to calculate.¹³

Table 3. HBI¹³

	Score
1. Patient’s general well-being (for the previous day) (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)	
2. Abdominal pain (for the previous day) (0 = none, 1 = mild, 2 = moderate, 3 = severe)	
3. Number of liquid stools per day (for the previous day) (score 1 per movement)	
4. Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)	
5. Complication (score 1 per item)	
Arthralgia	
Uveitis	
Erythema nodosum	
Aphthous ulcers	
Pyoderma gangrenosum	
Anal fissure	
New fistula	
Abscess	
Please insert the value of the total score in the appropriate area in either sections 5 or 7 on the form HLTH 5368.	TOTAL

PEDIATRIC ULCERATIVE COLITIS ACTIVITY INDEX (PCDAI)

Development and Use of the PCDAI

In 1990, the PCDAI was developed and validated solely by a group of experts without the involvement of statistical modeling. The PCDAI, specifically designed for use in children, has several benefits over the CDAI for this population:

- Calculation of the PCDAI does not require a 1-week diary and the historical items can be assessed during the clinic visit
- The PCDAI includes a child-specific item: the height velocity variable
- The PCDAI includes the addition of 2 additional laboratory parameters: erythrocyte sedimentation rate (ESR) and albumin level
- The scoring of HCT is adjusted based on age and gender

The PCDAI score can range from 0-100, with higher scores signifying more active disease (Table 4).¹¹ A score of < 10 is consistent with inactive disease, 11-30 indicates mild disease, and > 30 is moderate-to-severe disease. A decrease of 12.5 points is taken as evidence of improvement.

Table 4. PCDAI¹¹

History (Recall, 1 week)			
Abdominal Pain			Score
0 = None	5 = Mild: Brief, does not interfere with activities	10 = Moderate/ Severe: Daily, longer lasting, affects activities, nocturnal	
Patient Functioning, General Well-Being			Score
0 = No limitation of activities, well	5 = Occasional difficulty in maintaining age-appropriate activities, below par	10 = Frequent limitation of activity, very poor	
Stools (per day)			Score
0 = 0-1 liquid stools, no blood	5 = Up to 2 semiformed with small blood, or 2-5 liquid	10 = Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	
Laboratory			
HCT			Score
< 10 years (Male and Female):		11-14 years (Male):	
0 = > 33%	2.5 = 28%-32%	5 = < 28%	0 = $\geq 35\%$
			2.5 = 30%-34%
			5 = < 30%
11-19 years (Female):		15-19 years (Male):	
0 = $\geq 34\%$	2.5 = 29%-33%	5 = < 29%	0 = $\geq 37\%$
			2.5 = 32%-36%
			5 = < 32%
ESR			Score
0 = < 20 mm/hr	2.5 = 20-50 mm/hr	5 = > 50 mm/hr	
Albumin			Score
0 = ≥ 3.5 g/dL	5 = 3.1-3.4 g/dL	10 = ≤ 3.0 g/dL	
Examination			
Weight			Score
0 = Weight gain or voluntary weight stable/loss	5 = Involuntary weight stable, weight loss 1%-9%	10 = Weight loss $\geq 10\%$	
Height at Diagnosis			Score
0 = < 1 channel decrease	5 = ≥ 1 , < 2 channel decrease	10 = > 2 channel decrease	
Height at Follow-Up			Score
0 = Height velocity ≥ -1 SD	5 = Height velocity < -1 SD, > -2 SD	10 = Height velocity ≤ -2 SD	
Abdomen			Score
0 = No tenderness, no mass	5 = Tenderness or mass without tenderness	10 = Tenderness, involuntary guarding, definite mass	
Perirectal Disease			Score
0 = None, asymptomatic tags	5 = 1-2 indolent fistula, scant drainage, no tenderness	10 = Active fistula, drainage, tenderness, or abscess	
Extraintestinal Manifestations			Score
(Fever $\geq 38.5^\circ\text{C}$ for 3 days over past week, definite arthritis, uveitis, <i>E. nodosum</i> , <i>P. gangrenosum</i>)			
0 = None	5 = 1	10 = ≥ 2	
Total Score:			

The limitation of activity should be based on the most significant limitation during the past week, even if it is only for 1 day.¹⁰ For example, if a volleyball player with CD missed 1 of her games that week because of abdominal pain, the patient should still be scored as having limited activity, even if she might have felt better later in the week. However, if the activity limitation is due to another illness (eg, upper respiratory infection), the illness period should be excluded from the patient's PCDAI score.

Calculating Height Velocity

Perhaps the most challenging aspect of the PCDAI for the practicing clinician is calculating the height subsection.⁸ Height velocity requires a 1-year (and at least 9 months) follow-up. Upon diagnosis, previous accurate heights are commonly unavailable and thus the item is scored based on whether the child crossed "channels" (ie, major centiles) on the growth charts from his/her premorbid time. The following percentiles are considered channels: > 90%, 75%, 50%, 25%, and < 10%. If there has been no fall off in height, or the fall off in height is less than 1 channel, the PCDAI height score is 0. If there is a fall off of only 1 channel, the score is 5 points and a fall off of 2 channels (eg, 75% channel to 25% channel) is scored as 10 points.

After the diagnosis or at the time of follow-up, the height variable involves the calculation of height velocity in cm/year.^{14,15} To calculate the height velocity, 2 heights are obtained, ideally 6-12 months apart. Height velocity is then calculated using the formula:

$$\text{Height velocity} = \frac{\text{Current height} - \text{previous height (cm)}}{\text{Time (year)}}$$

The height velocity is then transformed into the Z score, which can be compared directly to an age- and gender-matched reference curve.^{14,15}

$$\text{Z score} = \frac{\text{Observed height velocity} - \text{Mean height velocity for age and sex (cm/yr)}}{\text{Standard deviation (SD) of the mean height velocity (for age and sex)}}$$

The Z score corresponds to the SD of the child's height velocity.^{14,15} Points are allocated to the number of SDs below normal, defined as ≥ -1 SD. As a much easier alternative, Table 5 and Table 6 list the height velocity Z score cut off values by age and gender for calculating the PCDAI for males and females, respectively.¹⁴

Table 5. Height Velocity Reference Values for Calculating the PCDAI: Males¹⁴

Age (years)	Height Velocity in cm/yr (Males)		
	- 2 SD	- 1 SD	Mean
2.5	5.7	7.0	8.3
3.0	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4.0	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5.0	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6.0	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7.0	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8.0	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9.0	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10.0	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11.0	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12.0	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13.0	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14.0	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15.0	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16.0	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17.0	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Courtesy of Thomas D. Walters, MD.

Table 6. Height Velocity Reference Values for Calculating the PCDAI: Females¹⁴

Age (years)	Height Velocity in cm/yr (Females)		
	- 2 SD	- 1 SD	Mean
2.5	5.9	7.3	8.6
3.0	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4.0	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5.0	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6.0	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7.0	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8.0	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9.0	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10.0	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11.0	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12.0	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13.0	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14.0	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Courtesy of Thomas D. Walters, MD.

How Well Does the PCDAI Perform?

The PCDAI has been evaluated in several studies of children with CD. Otley and colleagues showed that the PCDAI was highly correlated with physician global assessment of disease activity and was superior to the CDAI and HBI.¹⁶ The researchers also showed interobserver reliability by comparing concurrent calculation of the PCDAI by 2 independent gastroenterologists. Kundhal and colleagues demonstrated only fair responsiveness to change in disease activity.¹⁷

The optimal PCDAI score representative of disease remission has been a matter of debate. The initial study found that a PCDAI score of ≤ 10 points discriminated active from quiescent disease.¹¹ Recent studies, however, have found that PCDAI scores of < 10 were more accurate than a score of ≤ 10 points for disease remission.^{18,19} In the REACH study, evaluating infliximab in CD, clinical response was defined as a PCDAI decrease of ≥ 15 points, but it is customary to use 12.5 points to define response.²⁰

Overall, the PCDAI is an activity index that has accepted use in clinical trials. The PCDAI completion requires a physician assessment and laboratory tests that are routinely ordered as part of standard medical care.⁸ Scoring the height velocity requires some practice, but can be quickly learned by a physician or nurse in practice. Calculating a PCDAI requires < 5 minutes of physician or nursing time.

Using the Abbreviated PCDAI as an Alternative to PCDAI

While the PCDAI remains the most widely used index to measure disease activity in pediatric CD patients, it has been criticized by researchers for including laboratory tests and items that may not change fast enough during therapy to make them useful to detect change over time (eg, growth velocity).¹⁶

The abbreviated PCDAI (abbrPCDAI) omits the growth and 3 laboratory items from the PCDAI, thereby increasing its feasibility (Table 7). AbbrPCDAI scores range from 0 to 70. While the correlation with the full PCDAI is good, cut points for disease activity levels have not been established.²¹

Table 7. Abbreviated PCDAI

History (Recall, 1 week)			
Abdominal Pain			Score
0 = None	5 = Mild: Brief, does not interfere with activities	10 = Moderate/Severe: Daily, longer lasting, affects activities, nocturnal	
Patient Functioning, General Well-Being			Score
0 = No limitation of activities, well	5 = Occasional difficulty in maintaining age appropriate activities, below par	10 = Frequent limitation of activity, very poor	
Stools (per day)			Score
0 = 0-1 liquid stools, no blood	5 = Up to 2 semiformed with small blood, or 2-5 liquid	10 = Gross bleeding, ≥ 6 liquid, or nocturnal diarrhea	
Examination			
Abdomen			Score
0 = No tenderness, no mass	5 = Tenderness, or mass without tenderness	10 = Tenderness, involuntary guarding, definite mass	
Perirectal Disease			Score
0 = None, asymptomatic tags	5 = 1-2 indolent fistula, scant drainage, no tenderness	10 = Active fistula, drainage, tenderness, or abscess	
Weight			Score
0 = Weight gain or voluntary weight stable/loss	5 = Involuntary weight stable, weight loss 1%-9%	10 = Weight loss $\geq 10\%$	
Extraintestinal Manifestations			Score
(Fever $\geq 38.5^\circ\text{C}$ for 3 days over past week, definite arthritis, uveitis, <i>E. nodosum</i> , <i>P. gangrenosum</i>)			
0 = None	5 = 1	10 = ≥ 2	
Total Score:			

It has been suggested that laboratory tests do not improve the ability of the subjective parts of the index to classify patients as being in remission or relapse.²² Indeed, the abbrPCDAI was found to be highly correlated with the full PCDAI.²¹

INDICES TO EVALUATE PEDIATRIC UC

Existing Indices to Measure UC Activity

Direct examination of the colonic mucosa has become the preferred method of measuring disease activity in adult UC trials, but most pediatric patients and their parents consider this to be too invasive, especially since endoscopy involves general anesthesia in most centers.² Multiple noninvasive clinical indices have been developed to reflect disease activity in UC as shown in Table 8²³:

Table 8. Indices to Reflect Disease Activity in UC^{2,8,23-28}

	Powell-Tuck	ECCI	Mayo Score	Rachmilewitz	Lichtiger	Seo	Beattie	SCCAI	PUCAI
Stool frequency									
Stool form									
Urgency									
Nocturnal diarrhea									
Antidiarrheal prescription									
Blood per rectum									
Abdominal pain/tenderness									
Well-being									
Extraintestinal									
Rectal prolapse									
Fever									
Laboratory tests									
Endoscopy/x-ray									
MD assessment									

Table 8 Items measured by the following UC indices: Powell-Tuck Index, Endoscopic Clinical Correlation Index (ECCI), Mayo Score, Rachmilewitz Index, Lichtiger Index, Seo Index, Beattie Index, Simple Clinical Colitis Activity Index (SCCAI), and PUCAI

Most of these indices did not undergo comprehensive psychometric evaluation of validity, reliability, and responsiveness, but they have been used in multiple clinical studies in adults where cut-off values for remission and response were proposed.²³ Two invasive indices, the Mayo Score and the Powell-Tuck Index, have noninvasive versions: the partial Mayo Score (which excludes the mucosal appearance item from the 4-item index) and the partial Powell-Tuck Index (which excludes all items pertaining to endoscopy or physical examination).

In a head-to-head comparison of all noninvasive UC disease activity indices among adult patients, the PUCAI and the SCCAI proved to have the highest combined psychometric properties, including validity, reliability, and responsiveness.^{2,25} Although the PUCAI was developed in pediatrics, the lack of included items exclusive to children also allowed good performance in adults. Both of these indices are noninvasive and easy to score. In children, the PUCAI is the only existing validated disease activity index.

PUCAI: A Useful Index for Children With UC

The PUCAI was developed using a combined judgmental and statistical approach, utilizing 2 prospectively accrued cohorts of 205 children with UC. Item generation, reduction, and grading were performed using a Delphi technique among 36 experts in pediatric UC. To minimize interobserver variability, the group established logical gradations and clear definitions of items. Proposed gradation schemes for each item of the PUCAI were distributed to the Delphi group, with the final instrument reflecting consensus opinion. The final version of PUCAI is composed of 6 clinical items (Table 9).² Weights of the included items were assigned according to a multivariate regression analysis of 157 children with UC, in which rectal bleeding assumed the highest weight.

Index Evaluation

Once developed, the PUCAI was evaluated using a second prospective cohort of 48 children undergoing complete colonoscopy. In this validation cohort, the PUCAI showed excellent correlation with physician global assessment of disease activity, colonoscopic appearance, and the adult-invasive Mayo Score. Correlations were higher than 2 noninvasive adult indices, the Seo and Lichtiger indices, calculated concurrently. Interobserver

and test/retest reliability were excellent. The PUCAI differentiated well the categories of disease activity of none, mild, moderate, and severe. Responsiveness was shown to be high at repeated visits of 74 children. The laboratory items did not improve the validity or responsiveness of the PUCAI, making it attractive for pediatric use.

The PUCAI can be used to both differentiate disease activity states and assess change over time without the use of a colonoscopy. The correlation of the PUCAI with mucosal inflammation seems strong enough to allow measurement of disease activity in children without endoscopy.

Since its introduction, the good performance of the PUCAI has been replicated in independent studies.^{29,31} However, while the data on the usefulness of the PUCAI are promising, it should be noted that the PUCAI has a ceiling effect and does not effectively differentiate the very severe from the fulminant presentation. Also, since Turner and colleagues excluded ulcerative proctitis patients from their validation study of the PUCAI, the tool's ability to ascertain disease activity in these patients is still unknown.

PUCAI Implementation

The historical parameters should reflect a daily average of the patient's last 48 hours. However, if the patient's condition is changing rapidly, the last 24 hours may be used. The PUCAI score ranges from 0 to 85; a score of < 10 denotes remission, 10-34 mild disease, 35-64 moderate disease, and 65-85 severe disease. A clinically significant response is defined as a PUCAI change of ≥ 20 .²

Table 9. PUCAI²

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in < 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
> 8	15
5. Nocturnal stools (any episode causing waking)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
TOTAL MAXIMUM SCORE	85

Children with UC commonly experience ≥ 1 severe exacerbation and the PUCAI may be used to predict response. In a 2008 study, Turner and colleagues retrospectively reviewed admissions of 99 children and adolescents with active UC who were hospitalized for intravenous corticosteroid therapy over a 10-year period. The authors determined that children with UC often experience ≥ 1 severe exacerbation that requires intravenous steroid therapy. The PUCAI, determined at day 3 (> 45 points) should be used to screen for patients likely to fail corticosteroids (ie, infectious screen, surgical consult) and at day 5 ($> 65-70$ points) to dictate the introduction of second-line therapies, since these children are very unlikely to respond even when prolonging steroid therapy.³²

Practical Use of the PCDAI

CASE 1: DONNA



Donna, an 11-year-old girl with CD of the terminal ileum and cecum, comes in for her assessment, 3 months after her previous visit. She was diagnosed 2 years ago and her current medication is 6-mercaptopurine. Two weeks ago, she had some abdominal cramping for 3 consecutive days, but she has had no pain since. She is having 2 formed stools daily, with no visible blood in the stool. She states she “feels tired,” and missed a day of school this week from fatigue. She also complains of mouth sores and knee pain.

On examination, you identify a small oral ulcer and a mildly tender abdomen. The perianal, joint, skin, and neurologic examinations are normal. Review of her weight and height demonstrates she has gained 1.5 kg and 3 cm in 8 months. Her HCT is 33%, ESR is 25 mm/hour, and albumin is 4.0 g/dL.

Is her PCDAI score consistent with remission, mild disease, or moderate-to-severe disease?

Assessment of Donna Using PCDAI

- **History (Recall, 1 Week)**
 - **Abdominal pain:** While Donna had abdominal pain 2 weeks ago, the PCDAI only incorporates symptoms from the last week; thus, the abdominal pain score is 0.
 - **Patient Functioning, General Well-Being:** Donna has missed 1 day of school this week from fatigue and therefore warrants a 5 on the well-being assessment.
 - **Stools (per day):** Donna is passing 2 stools per day, but they are formed rather than semiformal, thus, the score on bowel movements is a 0.
- **Laboratory**
 - **HCT:** The HCT of 33% scores 2.5 for a female aged 11-19 years.
 - **ESR:** The ESR of 25 mm/hour scores 2.5.
 - **Albumin:** The albumin score of 4.0 g/dL scores 0.
- **Examination**
 - **Weight:** She has gained weight, which scores 0.
 - **Height at diagnosis:** Not applicable

- **Height at follow-up:** Donna has significant growth failure (height velocity: 4.5 cm per year), which is 2 SDs below the expected growth rate of 7.7 cm per year for an 11-year-old girl (see Table 6). The growth delay gives her a score of 10 on the height velocity PCDAI subsection.
- **Abdomen:** Donna’s physical examination reveals mild abdominal tenderness upon moderate palpation, for a score of 5.
- **Perirectal disease:** There are no signs of perirectal disease; thus, a score of 0.
- **Extraintestinal manifestations:** While Donna has arthralgias and mouth ulcers, these are not scored as extraintestinal manifestations on the PCDAI; thus, her extraintestinal score is 0.

• DONNA’S COMPOSITE PCDAI SCORE: 25

- A score of 25 is consistent with mild disease activity, but close to the moderate-to-severe disease activity cut off (≥ 31).

Practical Use of the abbrPCDAI

CASE 2: MARK



Mark, a 14-year-old male outpatient with CD of the ileum, ascending colon, and descending colon, returns for his first visit in 3 months. He has been prescribed methotrexate injections 20 mg/week and admits to missing some doses, but cannot state how many. He has had 4 mushy bowel movements per day, without blood. He denies abdominal pain, has not missed any school, and is active in sports.

Examination demonstrates no abdominal mass or tenderness. There is a small perianal fistula with active purulent drainage. Review of his growth curve demonstrates a 2-lb weight loss, but he states he has lost weight because of his track workouts. He has gained 4.2 cm of height in 8 months. You recommend blood work to Mark’s parents, but Mark refuses.

- **What is Mark’s abbrPCDAI score?**
- **Is Mark in remission, have mildly active CD, or moderate-to-severe CD?**

Assessment of Mark Using abbrPCDAI

- **History (Recall, 1 Week)**
 - **Abdominal pain:** Mark denies abdominal pain; thus, he scores 0.
 - **Patient functioning, general well-being:** Mark has not missed any school and is active in sports; thus, he scores 0.
 - **Stools (per day):** Mark has 4 mushy bowel movements per day; thus, his score is 5.
- **Examination**
 - **Abdomen:** Examination demonstrates no abdominal mass or tenderness; thus, Mark’s score is 0.
 - **Perirectal disease:** Because Mark has an actively draining fistula, his perianal disease score is 10.
 - **Weight:** Because he has lost the weight voluntarily with his sports training, his score is 0.

• MARK'S COMPOSITE abbrPCDAI SCORE: 15

Loonen suggested that a cut-off score of < 10 in the abbrPCDAI should define remission, although no further studies are available to validate this finding.²² Mark is not in remission, but, in view of the low composite score, has mild disease activity.

Practical Use of the PUCAI

CASE 3: LAKISHA

PART 1



Lakisha is a 18-year-old female with a 2-year history of UC involving the entire colon. She is admitted to the hospital for intravenous steroid therapy for treating an acute attack of bloody diarrhea, unresponsive to oral prednisone. She has been taking mesalamine since her diagnosis.

She states that earlier in the week, she was having 7 bowel movements per day, but in the last 2 days she has been having 5 bowel movements per day. The stools are completely liquid and look like they are filled with blood. She has mild abdominal cramping that does not make her run to the bathroom. She is getting up at night to go to the bathroom. She has a swollen, tender left knee. She has also had low-grade fevers to 101°F. She has missed the last 3 days of school and has trouble getting out of bed. Despite these symptoms, she is keeping up with her homework.

- According to parameters of the PUCAI score, does she have inactive, mild, moderate, or severe disease?

Assessment of Lakisha Using PUCAI

1. **Abdominal pain:** Lakisha has mild abdominal cramping that may be ignored; thus, she would score 5.
2. **Rectal bleeding:** Lakisha has a large amount of blood (> 50% of the stool content); thus, her score would be 30.
3. **Stool consistency of most stools:** Because Lakisha's stools are liquid, her score would be 10.
4. **Number of stools per 24 hours:** Lakisha reports 5 stools per day; thus, her score would be 5.
5. **Nocturnal stools (any episode causing waking):** Lakisha does not report nocturnal stools or any episode causing waking; thus, her score is 10.
6. **Activity level:** Lakisha has missed the last 3 days of school and has trouble getting out of bed; thus, her score is 10.

LAKISHA'S TOTAL PUCAI SCORE is 80, which is consistent with severe disease. The arthritic joint and fevers, while important clinical signs, are not factored into the calculation of the PUCAI.

- Lakisha is treated for 3 days with methylprednisolone 40 mg IV once daily.
- At day 3, her total PUCAI score is at 70. Because this is > 45 points, her score warrants planning of second-line therapy. A surgeon is consulted and a test for tuberculosis and a chest x-ray are ordered.

- On day 5, the PUCAI is once again administered and Lakisha scores 75. Furthermore, she now has nocturnal diarrhea. A PUCAI score at day 5 > 70 has a positive predictive value of 87% and is thus sufficient to initiate second-line therapy.

- Lakisha's family decides to proceed to infliximab therapy at that stage, after discussing this regimen with the gastroenterologist, and cyclosporine, tacrolimus, or colectomy.

Lakisha is a model example of how and when to utilize the PUCAI accurately in managing acute severe UC. Screening these patients ahead of time and understanding the predictive values indicated can provide clearer direction of implementation of second-line therapy when steroid use is failing.³²

CASE 3: LAKISHA

PART 2

Seven days following the infliximab infusion, Lakisha is now having 3 stools per day. The stools remain liquid and there is still blood in every stool, but the amount of blood in the stool has decreased to less than a tablespoon in each stool. She no longer has abdominal cramping and is not getting up at night to have bowel movements. She remains tired and is undergoing physical therapy in the hospital to maintain strength. The left joint is no longer swollen.

- According to the criteria in the PUCAI, does Lakisha have a clinically significant response to the infliximab infusion?

Using PUCAI to Evaluate Response

1. **Abdominal pain:** After 7 days of therapy, Lakisha's abdominal pain has resolved; thus, her score changed from 5 (7 days ago) to 0.
2. **Rectal bleeding:** The blood in Lakisha's stool has decreased to a small amount in each stool. Her score decreased from 30 (7 days ago) to 20.
3. **Stool consistency of most stools:** Lakisha's stool consistency is unchanged from 7 days ago; thus, her score stays at 10.
4. **Number of stools per 24 hours:** The number of stools per day has decreased from 5 to 3, but this does not affect the PUCAI score, which remains 5.
5. **Nocturnal stools (any episode causing waking):** Lakisha does not report nocturnal stools or any episode causing waking; thus, her score remains 0.
6. **Activity level:** Lakisha still reports fatigue, thus her score remains 10.

LAKISHA'S UPDATED TOTAL PUCAI SCORE: 45

The infliximab treatment had a meaningful response, as the PUCAI score reduced by > 20 points (from 70 to 45). However, a score of 45 is still considered moderate disease, despite 13 days of intravenous corticosteroids. Since some improvement has been noticed with infliximab therapy, the option of a second infusion has been discussed with the family. However, they eventually elected to proceed to colectomy.

ENDOSCOPIC INDICES OF DISEASE ACTIVITY IN IBD

Gastrointestinal Endoscopy Indices

While clinical assessment of patients is helpful, the symptoms of patients do not always accurately represent the severity and extent of the disease.^{1,33,34} Invasive endoscopic assessment of disease activity more accurately reflects the severity of intestinal inflammation and allows the clinician to ascertain mucosal healing. Another advantage of endoscopy is it affords the opportunity for clinicians to obtain biopsies or dysplasia in patients with long-standing disease.¹

The role of upper endoscopy and colonoscopy in assessing patients with IBD remains in evolution. Endoscopic procedures have an accepted role in establishing the type of IBD, in determining disease location, and screening for dysplasia in patients with colitis duration for over 8-10 years. Endoscopy is also useful if the clinician is trying to decide whether or not to intensify treatment in a patient with a challenging clinical picture. Endoscopy may identify strictures in the colon or at the ileocecal valve and determine whether or not to recommend surgery. In CD that has undergone ileocecal resection, endoscopy can assess for asymptomatic recurrence and guide prophylactic treatment. Nonetheless, the interpretation of the degree of mucosal inflammation is subjective and has shown to have poor interobserver reliability. Moreover, mucosal improvement lags after clinical response and thus does not always reflect current status. It is thus accepted that, at the least, clinical variables must accompany endoscopic grading.

Other modalities (magnetic resonance imaging, computed tomography, and capsule endoscopy) have yet to replace standard endoscopy for these patients. Capsule endoscopy may mitigate the invasive nature of standard endoscopy. Clinicians may consider capsule endoscopy for patients who³⁵:

- Have indeterminate colitis
- Are failing medical therapy or may require colectomy
- Have truly unexplained symptoms based on standard endoscopy and radiography
- Have IBD and obscure bleeding

Although capsule endoscopy identifies small bowel pathology with greater sensitivity than other methods, the implications of these lesions are not fully understood. At present, capsule endoscopy as a tool for evaluating mucosal healing or for predicting postoperative recurrence remains investigational.

CD Endoscopy Indices

Assessment of gastrointestinal mucosal disease is important in CD research because mucosal healing is associated with better long-term outcomes.³⁶ The Groupe d'Études Thérapeutiques des Affections Inflammatoires du Tube Digestif designed the Crohn's Disease Endoscopic Index of Severity (CDEIS) by incorporating endoscopic findings that have been shown to have high inter-rater reliability into a regression model, using the physician global assessment of endoscopy severity as the dependent variable.^{37,38} The index was found to have high inter-rater reliability and validity ($r = 0.81$), but has been criticized for its complexity.³⁹

In response to this criticism, Daperno and colleagues developed the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), shown in Table 10.³⁹

Table 10. SES-CD*

Variable	Score per Segment			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1-0.5 cm [†])	Large ulcers (0.5-2.0 cm [†])	Very large ulcers (> 2 cm [†])
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected segment	< 50%	50%-75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

*SES-CD = Total score from each segment (rectum, sigmoid and left colon, transverse colon, right colon, and ileum)

[†] Diameter

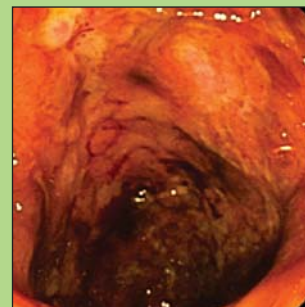


Figure 1. Active CD of the descending colon. There are large ulcers encompassing 30%-75% of the surface of the colon. More than 75% of the colon is affected by inflammation. Thus, the simplified endoscopic activity score for this segment would be 2 (large ulcers) + 3 (> 30% ulcerated surface) + 3 (> 75% affected surface) = 8.



Figure 2. CD in remission, transverse colon. There is no evidence of inflammation, ulceration, or narrowing. The endoscopic score for this segment is 0.

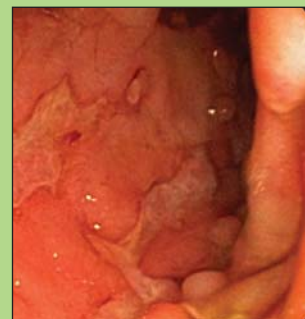


Figure 3. Active CD, terminal ileum. There are linear ulcers ranging from 0.5 to 2.0 cm in length, encompassing 10%-30% of the ileal surface. The lumen is not narrowed and the affected surface is < 50%. The endoscopic score for this segment would be 2 (large ulcers) + 2 (ulcerated surface, between 10%-30%) + 1 (affected surface < 50%) = 5.

The SES-CD had high inter-rater reliability (intraclass correlation coefficient = 0.98) and was highly correlated with the CDEIS ($r = 0.92$).³⁹ Lower correlations were found between both the SES-CD and CDEIS and other parameters of disease activity, including the CDAI (0.39 and 0.36, respectively) and

C-reactive protein ($r = 0.47$ and 0.45 , respectively). These data confirm that in IBD, mucosal findings do not necessarily reflect a patient's current clinical status. Examples of SES-CD assessment are provided in Figures 1-3.

There is no standardized endoscopic instrument for pediatric CD.⁸ However, there is no evidence that endoscopic characteristics differ in children. Although the CDEIS is the most widely employed instrument in adult clinical trials, the SES-CD seems to be a valid alternative to its more complicated counterpart. The use of either instrument in pediatric studies should be supplemented with a physician global endoscopy assessment until further assessment in pediatric CD is available.

In pediatric UC patients, no endoscopic index has been rigorously developed and evaluated. The lack of an evaluated measure is troublesome, especially when taking into account the low reliability of some endoscopic assessments.

SUMMARY

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. Of the current indices, the PUCAI is both validated and easy to use and has proven its utility in managing severe pediatric UC. The PCDAI can also be used in practice, but it requires both the calculation of height velocity and the incorporation of certain clinical laboratory measurements (HCT, ESR, and albumin levels). The abbrPCDAI omits height velocity and laboratory measurements, but needs further evaluation. New indirect biomarkers are constantly emerging which may further aid in the clinical decision-making process in children with IBD.

REFERENCES

- Naber AH, de Jong DJ. Assessment of disease activity in inflammatory bowel disease; relevance for clinical trials. *Neth J Med.* 2003;61:105-110.
- Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology.* 2007;133:423-432.
- Pardi DS, Sandborn WJ. Predicting relapse in patients with inflammatory bowel disease: what is the role of biomarkers? *Gut.* 2005;54:321-322.
- Wright JG, Feinstein AR. A comparative contrast of clinimetric and psychometric methods for constructing indexes and rating scales. *J Clin Epidemiol.* 1992;45:1201-1218.
- Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res.* 2002;11:193-205.
- Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology.* 1994;106:287-296.
- Yoshida EM. The Crohn's Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: a review of instruments to assess Crohn's disease. *Can J Gastroenterol.* 1999;13:65-73.
- Noble A, Turner D. Clinical indices for pediatric inflammatory bowel disease research. In: Mamula P, Markowitz JE, Baldassano RN, eds. *Pediatric Inflammatory Bowel Disease.* 1st ed. New York, NY: Springer US; 2008:507-530.
- Beaton DE, Bombardier C, Katz JN, et al. A taxonomy for responsiveness. *J Clin Epidemiol.* 2001;54:1204-1217.
- Griffiths AM, Otley AR, Hyams J, et al. A review of activity indices and end points for clinical trials in children with Crohn's disease. *Inflamm Bowel Dis.* 2005;11:185-196.
- Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr.* 1991;12:439-447.

- Best WR, Beckett JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* 1976;70:439-444.
- Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet.* 1980;1:514.
- Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107:317-329.
- Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. *Arch Dis Child.* 1966;41:613-635.
- Otley A, Loonen H, Parekh N, et al. Assessing activity of pediatric Crohn's disease: which index to use? *Gastroenterology.* 1999;116:527-531.
- Kundhal PS, Critch JN, Zachos M, et al. Pediatric Crohn Disease Activity Index: responsive to short-term change. *J Pediatr Gastroenterol Nutr.* 2003;36:83-89.
- Hyams J, Markowitz J, Otley A, et al. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. *J Pediatr Gastroenterol Nutr.* 2005;41:416-421.
- Otley A. Evaluating health utilities in adolescents: raising the profile of an alternative method for assessing health-related quality of life. *J Pediatr.* 2009;154:476-478.
- Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology.* 2007;132:863-873.
- Shepanski MA, Markowitz JE, Mamula P, et al. Is an abbreviated Pediatric Crohn's Disease Activity Index better than the original? *J Pediatr Gastroenterol Nutr.* 2004;39:68-72.
- Loonen HJ, Griffiths AM, Merkus MP, et al. A critical assessment of items on the Pediatric Crohn's Disease Activity Index. *J Pediatr Gastroenterol Nutr.* 2003;36:90-95.
- D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology.* 2007;132:763-786.
- Seo M, Okada M, Yao T, et al. An index of disease activity in patients with ulcerative colitis. *Am J Gastroenterol.* 1992;87:971-976.
- Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut.* 1998;43:29-32.
- Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ.* 1989;298:82-86.
- Azzolini F, Pagnini C, Camellini L, et al. Proposal of a new clinical index predictive of endoscopic severity in ulcerative colitis. *Dig Dis Sci.* 2005;50:246-251.
- Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet.* 1990;336:16-19.
- Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis.* 2009;15:1218-1223.
- Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol.* 2009;7:1081-1088.
- Turner D, Schünemann HJ, Griffith LE, et al. The minimal detectable change cannot reliably replace the minimal important difference [published online ahead of print September 30, 2009]. *J Clin Epidemiol.* doi:10.1016/j.jclinepi.2009.01.024.
- Turner D, Walsh CM, Benchimol EI, et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. *Gut.* 2008;57:331-338.
- Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *BMJ.* 1964;1:89-92.
- Walsh AJ, Brain AOS, Keshav S, et al. Which activity index for ulcerative colitis (UC)? Evaluation of inter-observer variation in clinical, endoscopic and composite indices. *J Crohn Colitis.* 2009;3:545.
- Legnani P, Abreu MT. Use of capsule endoscopy for established Crohn's disease. *Gastrointest Endosc Clin N Am.* 2006;16:299-306.
- Stange EF, Travis SP, Lémann M, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut.* 2006;55(suppl 1):i16-i35.
- Modigliani R, Mary JY. Reproducibility of colonoscopic findings in Crohn's disease: a prospective multicenter study of interobserver variation. *Dig Dis Sci.* 1987;32:1370-1379.
- Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut.* 1989;30:983-989.
- Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc.* 2004;60:505-512.

THANK YOU FOR PARTICIPATING IN THIS ACTIVITY.

To take the posttest and evaluation and receive credit, please go to: http://www.gotomylist.com/evaluator/evaluation_start.cfm?pk_event=520, or review page 2 under "How to Receive CME Credit" for further details.

Improve Your IBD Patient Outcomes



This activity is part of an ongoing educational series on pediatric IBD.

- Topics include:
- Diagnosis
 - Monitoring disease activity
 - Treatment Safety
 - Transitioning Care
 - More to come...



Click here to visit www.pedibd.org