Journal of Pediatric Gastroenterology and Nutrition
41:416–421 © October 2005 Lippincott Williams & Wilkins, Philadelphia

Evaluation of the Pediatric Crohn Disease Activity Index: A Prospective Multicenter Experience

*Jeffrey Hyams, †James Markowitz, ‡Anthony Otley, §Joel Rosh, ‖David Mack, ¶Athos Bousvaros, #Subra Kugathasan, **M. Pfefferkorn, ††Vasundhara Tolia, ‡‡Jonathan Evans, §§William Treem, ‖‖Robert Wyllie, ¶¶Robert Rothbaum, ##J. del Rosario, ***Aubrey Katz, †††Adam Mezoff, ‡‡‡M. Oliva-Hemker, *Trudy Lerer, and §§§Anne Griffiths, for the Pediatric Inflammatory Bowel Disease Collaborative Research Group

**Connecticut Children's Medical Center, Hartford, Connecticut; †NorthShore-Long Island Jewish Health System, New Hyde Park, New York; ‡IWK Health Centre, Halifax, Nova Scotia; §Morristown Memorial Hospital, Morristown, New Jersey; ‖Children's Hospital of Eastern Ontario, Ottawa, Ontario; ¶Children's Hospital, Boston, Massachusetts; #7) Medical College of Wisconsin, Milwaukee, Wisconsin; **Riley Hospital for Children, Indianapolis, Indiana; ††Children's Hospital of Michigan, Detroit, Michigan; ‡‡Nemours Children's Clinic, Jacksonville, Florida; §§Duke University, Durham, North Carolina; ‖‖Cleveland Clinic, Cleveland, Ohio; ¶¶St. Louis Children's Hospital, St. Louis, Missouri; ##AI DuPont Hospital for Children, Wilmington, Delaware; ***Floating Hospital for Children, Boston, Massachusetts; †††Children's Medical Center, Dayton, Ohio; ‡‡‡Johns Hopkins Hospital, Baltimore, Maryland; §§§Hospital for Sick Children, Toronto, Ontario*

ABSTRACT

Background and Objectives: Longitudinal assessment of disease activity is necessary for studies of therapeutic intervention in children with Crohn disease. The Pediatric Crohn Disease Activity Index (PCDAI) was developed a decade ago for such a purpose, but it function has only been examined in a small number of studies with a limited number of patients. The primary objectives of the present study were to develop cut scores reflecting disease activity as determined by physician global assessment (PGA) and to evaluate the responsiveness of the PCDAI to changes in patient condition after therapeutic interventions.

Methods: Data were derived from a prospective database of newly diagnosed children with inflammatory bowel disease established in 2002 at 18 pediatric gastroenterology centers in the United States and Canada. At diagnosis, at 30 days and 3 months after diagnosis, and quarterly thereafter, children (<16 years of age) with Crohn disease had disease assessment performed by PGA and PCDAI. Disease management was provided according to the dictates of the attending gastroenterologist and not by predetermined protocol.

Results: 181 patients had concomitant PGA and PCDAI performed at diagnosis, and 95 of these had similar assessment at short-term follow up. Mean ± SD PCDAI scores for mild, moderate, and severe disease by PGA at diagnosis were 19.5 ± 10.4, 32.2 ± 12.7, and 47.8 ± 14.9, respectively ($P < 0.001$ for all comparisons). Mean ± SD PCDAI for inactive disease after treatment was 5.2 ± 5.4. Receiver operating characteristic (ROC) curve analysis suggested that: 1) activity of moderate/severe disease was best reflected by a PCDAI of ≥30 points, 2) clinical response (moderate/severe disease improving to mild/inactive) was best reflected by a decrease in PCDAI of ≥12.5 points, and 3) a PCDAI < 10 best reflected inactive disease.

Conclusions: PCDAI scores accurately reflect disease activity as assessed by physician global assessment. A PCDAI score of ≥30 has acceptable sensitivity and specificity to indicate disease of moderate/severe activity. A PCDAI decrease of 12.5 points or greater following therapeutic intervention accurately reflects a clinically significant response. The PCDAI is an appropriate tool for intervention trials in Crohn disease in children. ***JPGN 41:416–421, 2005.***

Key Words: Crohn disease—children—activity—index—physician global assessment.

INTRODUCTION

Multicenter intervention trials in Crohn disease require validated disease activity instruments to assess response to treatment. No single laboratory parameter consistently and accurately reflects disease activity in Crohn disease (1) and lack of correlation between objective findings (e.g., radiographic features, endoscopy, and laboratory parameters) and subjective reporting of symptoms (e.g., abdominal pain, ability to carry on normal daily functioning) is frequently observed. This dilemma is particularly striking in the pediatric population where Crohn disease may have a profound impact on growth and development in the presence of minimal gastrointestinal symptoms.

Received September 16, 2004; accepted March 3, 2005.

Address correspondence and reprint requests to Jeffrey Hyams, M.D., Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT (e-mail: 06106jhyams@ccmckids.org).

Multi-item measures of disease activity have been developed to allow uniformity between observers in stratifying patients into those with inactive, mild, moderate, or severe activity (2–4). The Pediatric Crohn Disease Activity Index (PCDAI) was developed at a consensus meeting of pediatric inflammatory bowel disease (IBD) experts and subsequently validated at 12 pediatric centers in North America (4). This multi-item instrument consists of four general fields: history, physical examination, growth parameters, and common laboratory tests. The PCDAI differs from the adult Crohn Disease Activity Index (CDAI)(2) primarily in adding growth parameters and laboratory measures and by decreasing the weighting of subjective parameters and eliminating antidiarrheal agents as a variable. Directly comparative data are sparse, but one study, using physician global assessment as the gold standard, suggests that the PCDAI more accurately classifies disease activity in children (5). Although the PCDAI has hitherto not been used as the primary outcome variable in published pediatric studies, short-term responsiveness has nevertheless been demonstrated in a single-center study and in post hoc analysis of a multicenter trial, where the PCDAI was calculated as a secondary outcome variable (6).

We used a prospective multicenter patient registry (1) to reassess the validity and responsiveness of the PCDAI as a measure of disease activity, (2) to reevaluate previously recommended PCDAI cut scores (cut-off points) for inactive and moderate/severe disease, and (3) to reevaluate the PCDAI definition of both response and loss of response to therapeutic intervention.

METHODS

All data included in this report were generated from the database of the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. This Registry was initiated in January 2002 by 18 pediatric gastroenterology centers in the United States and Canada as a method of describing the contemporary natural history of inflammatory bowel disease in newly diagnosed patients who had not yet reached their 16th birthday. For each enrolled subject clinical and demographic characteristics, including type and extent of IBD, disease activity assessment, laboratory studies when performed, treatment, complications, and need for hospitalization or surgery are recorded at the time of initial diagnosis, 30 days and 3 months after diagnosis, and quarterly thereafter. All data are recorded on standardized forms and transmitted to a central data repository. Patients are managed according to the dictates of their physicians, not by standardized protocols. Approval for the registry has been received from the Human Subjects Review Committee at each participating institution. Informed consent is obtained from all families.

Disease Activity Assessment

The PCDAI includes three history items (abdominal pain, number of liquid stools, general wellbeing), five physical examination items (abdominal examination, perirectal disease, extraintestinal manifestations, weight, height), and three laboratory tests (hematocrit, albumin, erythrocyte sedimentation rate). Items are scored on a three-point scale (zero, 5, or 10 points) except for hematocrit and erythrocyte sedimentation rate which are scored as zero, 2.5 or 5 points. PCDAI scores can range from zero to 100 with higher scores indicating more active disease.

At the time of each patient visit the attending physician is asked to categorize disease activity as inactive, mild, moderate, or severe (physician global assessment or PGA). The historical and physical examination sections of the PCDAI form are completed at clinic visits by the attending physician. Values for hematocrit, ESR, and serum albumin, if measured at the time of clinical assessment, are added to the PCDAI form when they become available and a total PCDAI score is then determined.

The short-term responsiveness of the PCDAI to improvement in patient clinical status, as judged by physician global assessment, was made by comparing data at diagnosis to scores obtained at follow-up intervals ranging from 30 days to 3 months. Similarly, the responsiveness of the PCDAI to worsening of patient condition was evaluated by studying patients whose disease activity as reflected by PGA improved to inactive or mild following therapeutic interventions but who subsequently worsened during follow up to moderate/severe disease.

Statistical Methods

Mean PCDAI scores between patients grouped according to physician global assessment (PGA) were compared using analysis of variance followed by Scheffe's multiple comparisons test. Receiver operating characteristic curve (ROC) analysis was used to assist in determining optimal PCDAI cut scores for severity of disease activity and PCDAI change scores associated with clinically meaningful change in clinical status.

RESULTS

Complete PCDAI data at the time of diagnosis were available for 181 patients whose demographic characteristics are shown in Table 1. Ninety-five of these patients

TABLE 1. *Characteristics of study population (n = 181) (mean ± SD or frequency (%))*

Age at diagnosis	11.7 ± 3.0 yrs
Gender	
Male/female	59%/41%
Race	
White/nonwhite	88%/12%
Tanner stage	
I	53%
II	20%
III	13%
IV/V	15%
Disease location	
Large intestine	85%
Small intestine	70%
Esophagus-gastroduodenal	56%
Physician global assessment at diagnosis	
Mild	27%
Moderate	53%
Severe	21%

also had PCDAI and PGA completed at an early follow-up visit, either at 3 months or 30 days (57 at 3 months, 38 at 30 days but not at 3 months). Data for this subset of 95 patients were used to examine the relationship between change in PCDAI and change in PGA following initial therapeutic intervention (short-term clinical improvement). Since no patient had inactive disease by PGA at diagnosis, analyses involving inactive PGA were also based on the 30 day/3 month day. Preliminary data concerning PCDAI change with deterioration of clinical status were derived from 16 of the initial 181 patients who had subsequent worsening of disease following initial therapeutic improvement.

Relationship of PCDAI to Physician Global Assessment

The relationship between PCDAI and PGA at diagnosis in the 181 patients is shown in Table 2. PCDAI increases with increasing PGA of disease severity and all pairwise mean comparisons (mild vs. moderate, mild vs. severe, moderate vs. severe) were significantly different at the $P < 0.001$ level. To evaluate PCDAI scores for patients in whom disease was considered inactive by PGA, data from 30 day or 3 month visits were examined; 43 patients (45%) had inactive disease at the follow-up visit with a mean PCDAI of 5.2 ± 5.4 (95% confidence interval (CI) 3.6–6.9).

Determination of PCDAI Scores that Differentiate Disease Activity by PGA

Inactive vs. Mild Disease

Based on the 30 day/3month data, disease was inactive or mild as judged by PGA for 43 and 41 patients, respectively. Using very low PCDAI scores (5 or lower) improved specificity but decreased sensitivity for identifying inactive disease (Table 3, top). Conversely, using higher scores (12.5 or greater) improved sensitivity but decreased specificity. A PCDAI score <10 appeared to give the best balance between sensitivity and specificity in distinguishing between inactive and mild disease. Eleven of the 43 subjects with PGA inactive had a PCDAI of zero, while the remaining thirty-two had scores of 2.5 or greater. Fifteen of these latter subjects received points for a laboratory abnormality only, 2 for decreased height velocity only, 1 for decreased height velocity and laboratory values only, 6 for a sign or symptom (abdominal pain, loose stools, or perirectal disease) only, and 8 for a gastrointestinal symptom and either an abnormal laboratory value or decreased height velocity.

TABLE 2. *Relationship of Physician Global Assessment and PCDAI at diagnosis*

Physician Global Assessment (number of patients)	PCDAI (mean ± SD)
Mild (48)	19.5 ± 10.4*
Moderate (96)	32.2 ± 12.7*
Severe (38)	47.8 ± 14.9*

PCDAI, Pediatric Crohn Disease Activity Index.
*All pairwise comparisons significant at $P < 0.001$.

TABLE 3. *Sensitivity, specificity, and predictive value of cut scores for disease severity (PCDAI) by Physician Global Assessment*

Cut score	Sensitivity	Specificity	Predictive value of positive test
For inactive disease versus mild Crohn disease activity			
<5	0.47	0.85	0.77
<7.5	0.72	0.73	0.74
<10	0.81	0.68	0.73
<12.5	0.86	0.46	0.63
For moderate/severe disease versus mild Crohn disease			
≥20	0.88	0.52	0.84
≥22.5	0.84	0.63	0.86
≥25	0.81	0.75	0.90
≥27.5	0.78	0.79	0.91
≥30	0.71	0.83	0.92
≥32.5	0.62	0.90	0.93
≥35	0.53	0.90	0.93

PCDAI, Pediatric Crohn Disease Activity Index.

Mild vs. Moderate vs. Severe Disease

Despite significant differences in mean PCDAI values between moderate and severe patients, ROC analysis of severe PGA compared to moderate disease at diagnosis showed poor predictive value of high PCDAI in distinguishing severe from moderate disease (e.g., PCDAI cut score of 40 yields a positive predictive value of 0.48). Therefore, patients with moderate and severe disease were combined and then compared as a group to those with mild disease (Table 3, bottom). Lower PCDAI scores (e.g., 20, 22.5) were more sensitive but less specific. Conversely, higher scores (32.5, 35) were more specific but less sensitive. As increased specificity is important in assuring that a specific PCDAI score is more likely to accurately reflect greater disease severity, the data suggest that a PCDAI score of ≥30 maintains good sensitivity (0.71) while also providing acceptable specificity (0.83).

Relationship of PCDAI to Short-Term Clinical Improvement

Data were examined from the 95 patients with either 30 day or 3 month follow up to determine the magnitude of PCDAI changes that occur following initial therapeutic intervention. Patients were cross-classified by PGA at diagnosis and PGA at the short term follow-up visit (30 day or 3 month) and the change in PCDAI was determined. As can be seen in Table 4, large average decreases in PCDAI were observed for those patients

TABLE 4. *Relationship of changes in PCDAI* to changes in Physician Global Assessment following therapeutic intervention*

PGA at diagnosis	PGA at followup	n	Decrease in PCDAI	95% CI on change
Moderate/severe	Inactive	33	(33 ± 16)	27 to 38
Moderate/severe	Mild	30	(25 ± 15)	19 to 31
Mild	Inactive	10	(17 ± 7)	11 to 22
Moderate/severe	Moderate/severe	8	(6 ± 22)	12 to –25
Mild	Mild	11	(5 ± 9)	1 to 12
Mild	Moderate/severe	3	(5 ± 5)	17 to 7

PCDAI, Pediatric Crohn Disease Activity Index.

*Mean ± SD and 95% confidence interval (CI) for PCDAI at diagnosis minus PCDAI at short-term follow-up (30 day or 3 month). This represents the decrease in PCDAI from diagnosis to post-intervention level.

with moderate/severe disease by PGA at diagnosis who improved to either inactive or mild disease (33 ± 16 and 25 ± 15, respectively). Subgroup analysis for patients with severe disease at diagnosis showed a mean PCDAI decrease of 43 ± 19 (n = 10) for those improving to inactive and a mean decrease of 38 ± 12 (n = 8) for those improving to mild disease. Patients with moderate disease at diagnosis improving to inactive disease (n = 23) had a mean PCDAI decrease of 28 ± 12 points and for those improving to mild disease (n = 22) the mean PCDAI decrease was 20 ± 12 points.

Table 5 shows threshold incremental PCDAI changes that reflect clinically meaningful changes in PGA in response to therapy (moderate/severe disease becoming mild/inactive disease). Smaller decreases in PCDAI (10 or 12.5 points) identified higher proportions of patients who improved by PGA (improved sensitivity) than larger PCDAI changes (22.5 or 25 points) which were less sensitive but more specific. The data suggest a clinically significant change (decrease) in PCDAI of 12.5 points has excellent sensitivity (0.87) and acceptable specificity (0.73). Increasing the change to 17.5 or 20 points improves specificity (0.77, 0.82 respectively) but decreases sensitivity (0.76, 0.71, respectively).

Relationship of PCDAI to Clinical Deterioration

Clinical relapse occurred in 16 subjects whose PGA improved to inactive/mild and then deteriorated to moderate/severe over the study period. Overall, these patients had a mean increase in PCDAI of 23 ± 10 points, with the increments ranging from 10 to 47.5 points. For subjects whose disease activity had become inactive and then deteriorated to moderate/severe, the mean increase in PCDAI was 26 ± 11 (n = 9), and for those who went from mild to moderate/severe the mean increase in PCDAI was 18 ± 11 points (n = 7).

TABLE 5. *Sensitivity, specificity, and predictive value of incremental changes in PCDAI versus clinically significant improvement in Physician Global Assessment**

Incremental decrease in PCDAI	Sensitivity	Specificity	Predictive value of positive test
≥10	0.89	0.68	0.89
≥12.5	0.87	0.73	0.90
≥15	0.79	0.73	0.89
≥17.5	0.76	0.77	0.91
≥20	0.71	0.82	0.92
≥22.5	0.70	0.82	0.92
≥25	0.68	0.86	0.94

PCDAI, Pediatric Crohn Disease Activity Index.

DISCUSSION

As in previous validation studies (4,5) we found that the PCDAI correlates well with physician global assessment of disease. This confirms that the PCDAI is a valid measure of disease activity in children and adolescents with Crohn disease. Additionally, it is reassuring that our prospectively collected multicenter Registry data suggest PCDAI cut scores for moderate/severe disease and for inactive disease that are similar to those previously recommended (4,5).

Selection of optimal cut scores between different categories of disease activity is a balance between sensitivity and specificity. The cut score for moderate/severe disease is important, as it is used as the primary entry criterion in most therapeutic trials. Our population of exclusively newly diagnosed patients includes a large cohort of children with moderate or severe disease. Our data demonstrate that while no cut score defines moderate/severe versus mild disease with 100% sensitivity and specificity, a PCDAI ≥30 should provide an acceptable definition for at least moderate disease activity. The cut score of >30 described in the original PCDAI validation study (4) is only slightly altered, but recommendation is now made with greater confidence based on substantially more patients with moderately to severely active disease.

The achievement of remission is the most important goal of therapy, and therefore it has been recommended that the cut score for inactive disease should serve as the primary endpoint in most clinical trials (7). Analysis of data in the original PCDAI validation study (4) determined that a cut score of ≤10 most often correctly identified patients with PGA of inactive versus mildly active disease. The lower the PCDAI score the greater the

specificity, but the lower the sensitivity for inactive versus mild disease. In the original PCDAI validation study (4), the PGA was made without knowledge of laboratory test results. The Registry physicians in the present study were not specifically instructed and some may have assessed an asymptomatic patient as having mildly active disease because of elevated ESR or low serum albumin. This could have contributed to the loss of specificity versus mild disease observed with relatively low PCDAI values in this analysis in comparison to the original validation study (4).

The issue of defining remission becomes even more complex as abnormal laboratory values (1) (e.g., ESR) or growth impairment (8,9) are common in pediatric patients without gastrointestinal symptoms. The PCDAI includes laboratory parameters and height velocity, so that scores above zero might be anticipated even in subjects without gastrointestinal or extraintestinal signs and symptoms. Our present data suggest a PCDAI cut score of <10 (equivalent to ≤ 7.5) may be a reasonable target for at least long-term therapeutic trials in children. The authors hesitate, nevertheless, to recommend alteration of the originally proposed cut score for remission (4) in short-term trials based on this smaller data set of patients with inactive and mild disease. Indeed given that very slow linear growth can contribute 10 points to a child's score, an individual child with such growth impairment could never achieve clinical remission defined by a cut score of <10 following short term treatment with even the most effective therapy. Maintaining the originally recommended PCDAI cut score for remission of ≤ 10 in short term clinical trials seems like a reasonable compromise at the present time.

Data from which to determine the minimal change in PCDAI score that reflects a clinically significant response to therapy are limited (6,10). A recent consensus paper suggested a PCDAI decrease of at least 12.5 points be considered an appropriate change to reflect an improvement in patient condition (11). The large number of Registry patients with prospectively recorded baseline and short-term followup PCDAI data has provided an opportunity to reassess this recommendation. We considered a change of PGA from moderate/severe to mild/inactive to represent a clinically significant response. Our current observations confirm a PCDAI decrease of 12.5 points or greater reflects a significant improvement in patient condition. Greater decreases in PCDAI have greater specificity with a small drop-off in sensitivity.

The value of the PCDAI versus the CDAI as the primary endpoint for intervention trials in pediatric Crohn disease remains controversial (11). The CDAI is well-established in adult trials and when used in children in one study demonstrated responsiveness to short-term improvement in patient condition (5). Its use is hampered by the requirement for completion of a 7 day diary, the lack of well-established cut scores for disease activity in children, the concern that children and adolescents may underreport symptoms, and its lack of growth data as a scoring item. The PCDAI has been shown to reflect disease activity in children (4,5), has been used in pediatric intervention trials (6,10), and cut scores for disease activity and changes in disease activity have been established (4). Its inclusion of height velocity, a parameter unlikely to change over a short-term intervention trial, has raised concerns about its usefulness in such studies. However, previous data (5) as well as information from the present study demonstrate its ability to reflect short-term changes in patient condition. Long-term trials, where changes in growth parameters are more pertinent, would be reflected in the PCDAI rather than the CDAI.

The Inflammatory Bowel Disease Working Group in the context of the Second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition, recommended that further data were required to validate the utility and assess the performance characteristics of the PCDAI (12). Our prospective study conducted at multiple centers and examining a large number of patients confirms the role of this instrument in accurately reflecting physicianassessment of disease activity. The PCDAI has been shown to work well in the real world setting of a prospective collaborative multicenter research group database strengthening its utility for clinical trials and cohort studies.

ABBREVIATIONS

PGA, Physician Global Assessment
PCDAI, Pediatric Crohn Disease Activity Index
CDAI, Crohn disease activity index
IBD, inflammatory bowel disease
ESR, erythrocyte sedimentation rate
SD, standard deviation
CI, confidence interval
ROC, receiver operating characteristic

Acknowledgment: The authors are deeply indebted to the following research coordinators whose efforts greatly facilitated the performance of this study: Patricia Davis, Kathy Grancher, Valerie Grant, Annette Langseder, Ruth Singleton, Anna Zholudev, George Kay, Gail Waltz, Kim Boyer, Shari Huffman, Cathy Williams, Rebecca Abood, Rosemary Nagy, Carol Rudman, Myrna Miller, Vivian Abadom, and Laura Defaveri.

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