

# Assessing Clinical Activity in Crohn's Disease

## FACULTY

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Crohn's Disease (CD) is a complex illness that varies in presentation, anatomic location, clinical course, and response to treatment. Although it is accepted that acute and chronic inflammation contribute to the pathophysiology and symptomatology of CD, the etiology of the disease remains poorly understood. To minimize the effects of CD, clinicians must accurately assess disease activity and tailor therapy according to the many variations in severity, location, extraintestinal manifestations, and perception of disease reported among patients with CD. This approach may lead to different solutions for different patients with *identical* presentations. A separate but related challenge is to assess the effects of the same treatment in patients with *different* presentations.

The challenge of assessing the response to a single agent has led to the development of a variety of indices of disease activity.<sup>1</sup> An ideal chronic disease

index should consist of as few easily obtainable variables as possible, and it should be validated, objective, and reproducible.<sup>1</sup> The most frequently used CD indices are the Crohn's Disease Activity Index (CDAI), the Harvey-Bradshaw Index (HBI), and the Inflammatory Bowel Disease Questionnaire (IBDQ). All are clinical constructs that make it possible to evaluate the effects of treatment across a variety of patients with CD. Because of their "one-size-fits-all" orientation and often cumbersome nature, however, the use of these indices has been limited to the realm of clinical trials. Furthermore, in part because they attempt to glean generalizable information about any and all patients with CD, the indices lack specificity.<sup>1</sup> Patients with a variety of gastrointestinal illnesses may have "active" scores on these indices despite the absence of CD-related inflammation. Patients with symptoms related to CD that are not driven by

active inflammation, such as the increased frequency of bowel movements seen in patients who have undergone substantial intestinal resections, can have elevated scores without clinically important disease activity. Conversely, patients without extraintestinal manifestations and diarrhea (as is often seen in small-bowel disease) can have activity scores in the normal range despite the presence of significant active inflammation. Until a more accurate index is created that has greater specificity and a tighter correlation with active inflammation, however, clinical trials will employ one of the available multiple-component indices.

**TABLE 1.** Crohn's Disease Activity Index

CLINICAL OR LABORATORY VARIABLE	WEIGHTING FACTOR
<b>Number of liquid or soft stools (each day for 7 days)</b>	<b>x2</b>
<b>Abdominal pain</b>	<b>x5</b>
(0, none; 1, mild; 2, moderate; 3, severe)	
<b>General well-being</b>	<b>x7</b>
(0, generally well; 1, slightly under par; 2, poor; 3, very poor; 4, terrible)	
<b>Complications</b>	<b>x20</b>
arthritis/arthralgia	
iritis/uveitis	
erythema nodosum/pyoderma gangrenosum/apthous stomatitis	
anal fissure/fistula/abscess	
other fistula	
fever over 37.80°C (100°F)	
<b>Use of diphenoxylate or loperamide for diarrhea</b>	<b>x30</b>
(0, no; 1, yes)	
<b>Abdominal mass</b>	<b>x10</b>
(0, no; 2, questionable; 5, definite)	
<b>Hematocrit</b>	<b>x6</b>
(men, 47-Hct [%]; women, 42-Hct [%])	
<b>Body weight</b>	<b>x1</b>
<b>Total:</b>	

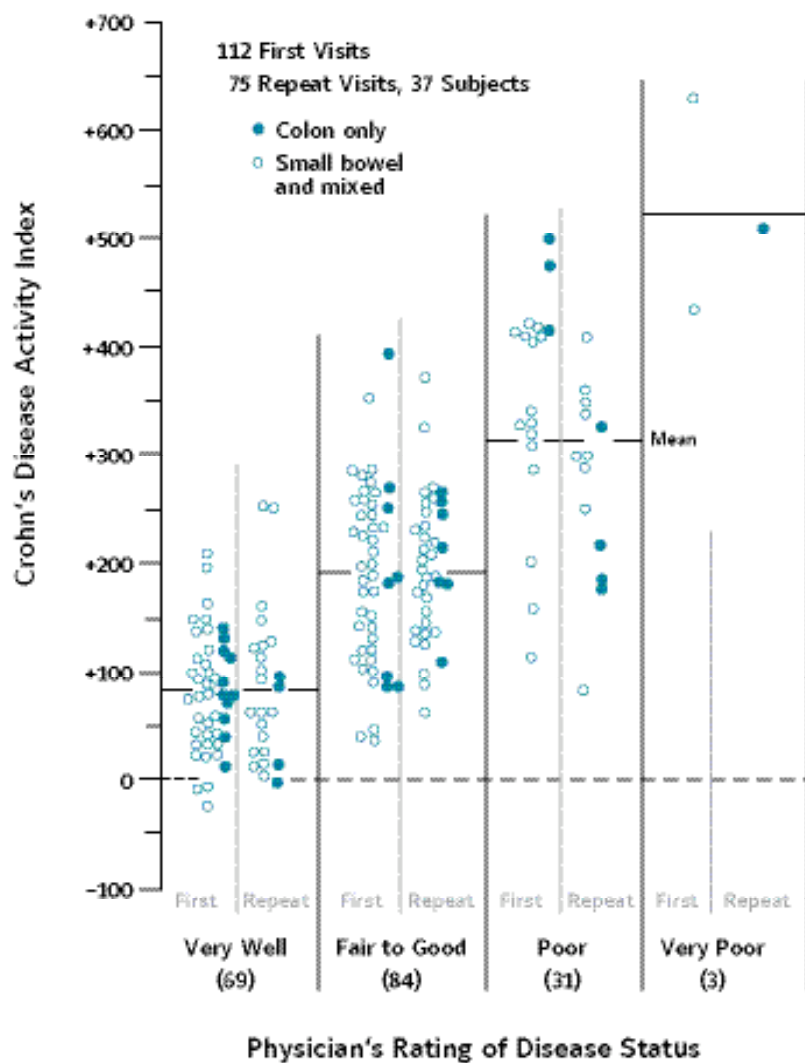
Adapted from reference 2.

**TABLE 2.** Harvey-Bradshaw Index

The first 3 items are scored for the previous day. Remission is defined by a score of less than 5.

<b>General well-being</b>	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
<b>Abdominal pain</b>	
None	0
Mild	1
Moderate	2
Severe	3
<b>Number of liquid stools per day (#)</b>	
<b>Abdominal mass</b>	
None	0
Dubious	1
Definite	2
Definite and tender	3
<b>Complications (additive)</b>	
Arthralgia	1
Uveitis	1
Erythema nodosum	1
Apthous ulcers	1
Pyoderma gangrenosum	1
Anal fissure	1
New fistula	1
Abscess	1

Adapted from reference 4.



**FIGURE 1.** Scatterplot comparing physician's rating of disease status with Crohn's Disease Activity Index.

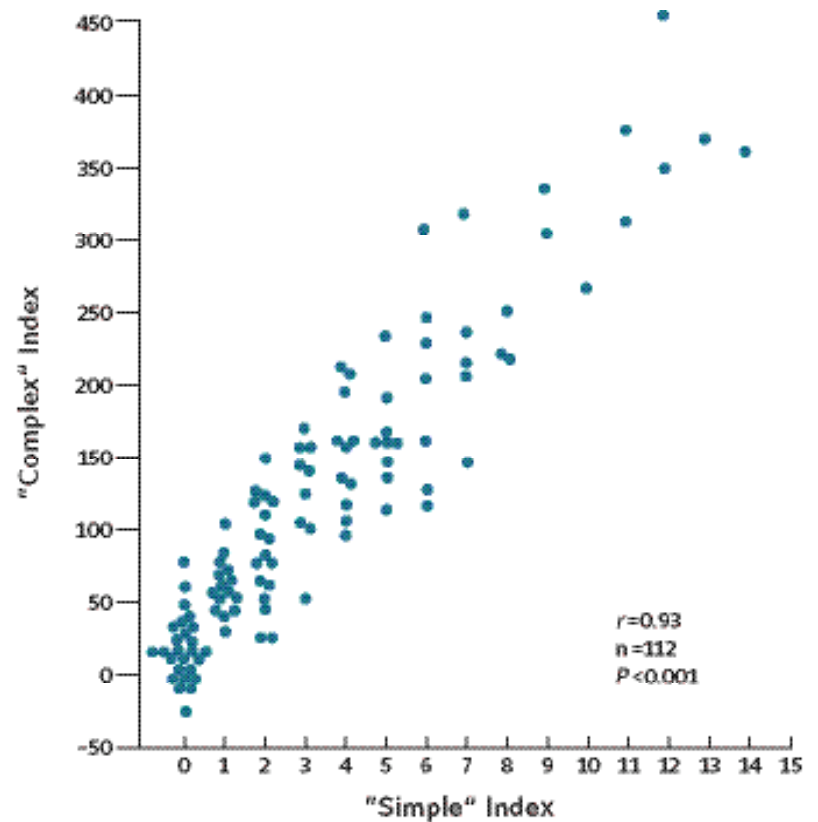
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## Indices of Clinical Disease Activity

### *Crohn's Disease Activity Index*

The CDAI<sup>2</sup> is the most widely used of the multiple-component CD indices.<sup>3</sup> It was developed in the 1970s by Best and colleagues for the National Cooperative Crohn's Disease Study to serve as a single, omnibus index for assessing a variety of therapies in CD.<sup>2</sup> The first step in the genesis of the CDAI was to determine which measurable elements of CD activity might logically be included in the index: What clinical features correlate with disease activity? Ultimately, the investigators entered clinical information by using 18 predictor variables based on 187 visits of 112 patients.<sup>2</sup> Then, with mathematical reduction formulas (multiple regression analysis), they were able to determine

which of these variables best correlated with their sense of clinical activity. Ultimately, 8 of the 18 variables examined were included in the index, the value of each was multiplied by a weighted coefficient, and the per-variable values were summed (Table 1).<sup>2</sup> On the CDAI, scores can be greater than 600 (scores can also be negative due to the hematocrit and weight subtotals). A score of 150 is used as a cutoff between remission and active disease.<sup>2</sup> By approaching the task of creating the CDAI in this fashion, the authors ensured that their index carried substantial *face validity*; it seemed to measure what it was supposed to measure. Curiously, however, the "gold standard" against which the CDAI was mathematically evaluated was the Physician's Global Assessment of these patients, an ordinal variable that allowed 4 possible ratings: "very well," whose value was set at 1;



**FIGURE 2.** Correlation between CDAI and HBI.

CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index

Reprinted from *Lancet*, 1(8167), Harvey RF, Bradshaw JM, A simple index of Crohn's-disease activity, 514, 1980, with permission from Elsevier.

"fair to good," valued at 3; "poor," valued at 5; and "very poor," valued at 7. Figure 1 is the scatterplot from this seminal work in which the CDAI was measured against the Physician's Global Assessment.<sup>2</sup>

Despite some obvious limitations (validation of the index against a 4-point physician's assessment, its requirement that patients keep a 7-day diary for the measure of stool frequency [which can result in patients filling out all 7 days' worth of information on a single day],<sup>4,5</sup> and the finding of a lack of uniformity when patients are evaluated with the instrument),<sup>6</sup> the CDAI has gained wide acceptance and is used in most large, multicenter trials.

### *Harvey-Bradshaw Index*

In an effort to better meet the ideal of parsimony in a multidimensional scale, Harvey and Bradshaw created a "simplified" index that incorporated fewer clinical variables (5 as opposed to 8), all of which could be measured easily in a single outpatient visit (Table 2).<sup>4</sup> Additionally, rather than summing the products of code values and coefficients, as the CDAI does, the HBI simply adds the code values together. In their initial description of the improved index for

calculating CD activity, Harvey and Bradshaw demonstrated a tight correlation ( $r=0.93$ ;  $P<0.001$ ) between scores on their index and scores on the CDAI (Figure 2).<sup>4</sup> When a linear regression analysis of their values is performed, an HBI score above 5 corresponds to a CDAI score above 150 and indicates active CD.<sup>4</sup>

Although it has been cited more than 400 times according to the Science Citation Index and is clearly an easier index to manage, the HBI, more than 2 decades after its initial publication, has yet to supplant the CDAI in clinical trials.<sup>3</sup> Like the CDAI, the HBI lacks direct markers of active inflammation and therefore exhibits some of the same limitations as the CDAI, such as a lack of specificity for CD inflammation. Additionally, like the CDAI, the HBI tells us very little about what is most bothersome to an individual patient and very little about the quality of life of an affected patient; instead, both indices provide a summed score of possible active symptoms in an "average" patient affected with CD.

### *Inflammatory Bowel Disease Questionnaire*

To better assess the quality of life of patients with CD, Irvine and colleagues

created the IBDQ,<sup>7</sup> a 32-item questionnaire comprising 4 domains: bowel function, emotional status, systemic symptoms, and social function.<sup>5</sup> In contrast to high CDAI and HBI scores, high IBDQ scores indicate a better quality of life. IBDQ scores have been demonstrated to correlate well (albeit inversely) with CDAI scores ( $r = -0.67$ ;  $P < 0.001$ ),<sup>5</sup> and although not specific for inflammatory bowel disease, the IBDQ is the accepted standard by which the quality of life of patients with CD or ulcerative colitis is measured.<sup>7</sup> The IBDQ can be self-administered, and a shortened 10-question version is also available,<sup>8</sup> as are validated versions in other languages. The IBDQ score is often used as a secondary end point in clinical trials to determine whether patients actually function better after an administered maneuver (usually, but not always, a pharmaceutical agent).<sup>5</sup> Yet, like the CDAI and HBI, the IBDQ lacks specificity in the active, objective measurement of CD-related inflammation.

## Other Scales for Measuring Disease Activity

In their search for better objective measures of active inflammation in CD, investigators have examined endoscopic, radiologic, serologic, and fecal markers of CD activity. Although a detailed review of the different measurements and their associated strengths and limitations is beyond the scope of this synopsis, a brief summary is warranted.

### Endoscopic and Radiologic Measures

Endoscopic measures of CD activity are born of the fact that directly observed mucosal lesions represent CD-related inflammation that may be the source of symptoms, a therapeutic target, or of prognostic significance. The Crohn's Disease Endoscopic Index of Severity (CDEIS), formulated in 1989 by Mary and Modigliani, was limited by its failure to correlate with the CDAI and by its cumbersome nature (not to mention its lack of applicability to patients with isolated small-bowel disease).<sup>9</sup> A revision of this index with "simplification" by Daperno and colleagues was also cumbersome because 4 independent scores still had to be recorded for each of 5 possible segments.<sup>10</sup> Although the simplification and its parent—the CDEIS—are used for research purposes, they are rarely applied in routine clinical practice. Rutgeerts and colleagues have developed a system for endoscopically evaluating the neoterminal

ileum postoperatively that has been demonstrated to be of prognostic value.<sup>11</sup>

Scales for evaluating the small bowel with wireless capsule endoscopy and the entire gastrointestinal tract with computed enterography and small-bowel barium examinations have been developed but also await acceptance in routine practice.

### Serum and Fecal Markers

A CD-specific serum marker for evaluating active inflammation remains elusive. Two nonspecific markers of inflammation, C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), are used in clinical practice because of their low cost and ubiquity, but they offer little by way of specificity or even sensitivity. In a Mayo Clinic study, a high CRP level in patients with CD correlated with moderately or severely active disease by a number of other direct and indirect measures of activity,<sup>12</sup> and Feagan and colleagues found that a low CRP level correlated with a high rate of placebo response in a trial of certolizumab pegol and anti-tumor necrosis factor therapy.<sup>13</sup> Similarly, an elevated ESR seems to correlate with active Crohn's colitis but not ileitis.<sup>14</sup> These markers are easy to obtain in practice, but their clinical utility is yet to be convincingly demonstrated.

Fecal markers of inflammation provide another opportunity for the direct measurement of disease activity, and although noninvasive, their collection can prove challenging. The most promising fecal tests involve the measurement of stable, neutrophil-derived proteins, such as the S100A proteins calprotectin and calgranulin, as well as lactoferrin. They have been used as secondary measures of activity in a number of clinical trials, but their use and acceptance will not become widespread for some time. Not surprisingly, although they correlate with active inflammation, they more closely correlate with colonic disease.

## Conclusion

Indices of clinical activity are essential tools for monitoring CD activity in clinical trials. Of the available indices, the CDAI is the most frequently used. However, it has been criticized as being difficult to use and is impractical in a clinical setting. The HBI is a simpler alternative that can be used to assess severity of disease at a single outpatient visit and is also a practical tool in clinical trials. For assessments of quality of life, the IBDQ is the instrument of choice.

Since the creation of the CDAI and its subsequent refinement, the HBI, a number of attempts have been made to find a simple, noninvasive measure of activity in CD. One can envision a future in which a simple serum or fecal measure will replace the cumbersome multidimensional indices currently used in clinical trials, but no such solution has yet been discovered and validated.

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