

## SPECIAL REPORTS AND REVIEWS

# A Review of Activity Indices and Efficacy Endpoints for Clinical Trials of Medical Therapy in Adults With Crohn's Disease

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Advances in immunology, biotechnology, and pharmaceutical science have resulted in an unprecedented number of medications with potential application to the treatment of Crohn's disease. Clinical development of these drugs requires that adequate and well-controlled trials be conducted to demonstrate safety and efficacy. Experience in clinical trial design for Crohn's disease over the last 25 years has led to the creation of a number of disease-specific instruments to measure disease activity. In addition, an enhanced understanding of the natural history of Crohn's disease has allowed the classification of patients into subpopulations based on disease pattern, disease activity, and prolonged treatment with corticosteroid or immunosuppressive therapy to develop. Recently regulatory agencies in multiple jurisdictions, with variable input from expert panels, have ruled on optimal measures of response and treatment indications in Crohn's disease. Important variations exist in the conclusions of these groups. This article presents the consensus of an international group of experts on the current state of the art with respect to disease activity measurements, classification, treatment indications, and clinical trial efficacy endpoints for the medical therapy of Crohn's disease.

### The Consensus Process

The need for a systematic evaluation of the outcomes used for clinical trials in Crohn's disease came about from perceived inconsistencies in regulatory decision-making. This was identified as an issue by a small number of individuals who are regularly involved in the design and implementation of randomized controlled trials of therapy for this disorder. The clinical trials task force of the International Organization of Inflammatory Bowel Disease (IOIBD) began the process of developing

a systematic review on this topic in 1999. The task force group met initially in person for discussion. That discussion was summarized in a draft manuscript by the primary author (W. J. S.). The draft manuscript was extensively edited and revised by other members of the task force followed by a second in person meeting for discussion in 2000. The discussion from that meeting was again summarized by the primary author in a further revision of the manuscript, followed by extensive editing and revision by members of the task force. The manuscript was then circulated to the entire membership of the IOIBD, as well as representatives from 3 groups of investigators who conduct clinical trials in Crohn's disease in the United States (the clinical alliance of the Crohn's and Colitis Foundation of America), Canada (the clinical network of the Crohn's and Colitis Foundation of Canada), and France (the Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives), and from pharmaceutical companies who are conducting clinical trials in Crohn's disease including AstraZeneca, Falk Pharma, Procter & Gamble, Ferring Pharmaceuticals, Centocor, Axcan Pharma, and Giuliani SPA. The manuscript was again extensively edited and revised, and then discussed by the entire membership of the IOIBD in 2001. Following that meeting, additional revisions were made and the review was submitted for publication. External peer review by the journal GASTROENTEROLOGY

*Abbreviations used in this paper:* CDEIS, Crohn's Disease Endoscopic Index of Severity; EMA, Evaluation of Medicinal Products; FDA, Food and Drug Administration; IOIBD, International Organization of Inflammatory Bowel Disease; NCCDS, National Cooperative Crohn's Disease Study; OMGE, Organisation Mondiale de Gastroenterologie; PDAI, Perianal Disease Activity Index.

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

Variable no.	Variable description	Multiplier	Total
1	No. of liquid or soft stools (each day for 7 days)	×2	
2	Abdominal pain, sum of 7 daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe)	×5	
3	General well-being, sum of 7 daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	×7	
4	Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8°C [100°F])	×20	
5	Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes)	×30	
6	Abdominal mass (0 = no, 2 = questionable, 5 = definite)	×10	
7	Hematocrit (males, 47-Hct [%], females, 42-Hct [%])	×6	
8	Body weight (1-weight/standard weight) × 100 (add or subtract according to sign)	×1	
CDAI score			

Adapted with permission from Best WR, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979;77:843–846.

led to a final revision that is presented below. Consensus statements can be classified with respect to the strength of the evidence supporting the conclusions (level 1, randomized controlled trials; level 2, well-designed cohort and case control studies; level 3, expert opinion based on observational data).<sup>1</sup> There have been no randomized controlled trials or subexperimental studies that have compared the utility of the different measures of outcome. Thus, the evidence summarized in this review is all level 3.

## Instruments for Measuring Disease Activity

### Clinical Disease Activity

Before 1979, few placebo-controlled clinical trials were performed that evaluated new treatments for Crohn's disease.<sup>2–10</sup> These studies were relatively small and none used rigorously developed and validated instruments to measure disease activity. In 1971, the National Cooperative Crohn's Disease Study (NCCDS) was initiated to assess the efficacy of prednisone, sulfasalazine, and azathioprine for the treatment of Crohn's disease.<sup>11</sup> Before beginning this placebo-controlled trial, the investigators developed and validated an instrument to measure disease severity, the Crohn's disease activity index (CDAI).<sup>12</sup> The investigators identified 18 potential predictor variables that were prospectively collected in 187 patient visits. A multivariable regression analysis was used to develop an equation that best predicted the investigators' overall rating for each patient. Eight variables determine the CDAI score: the number of liquid stools, the extent of abdominal pain, general well-being, the occurrence of extraintestinal symptoms, the need for antidiarrheal drugs, the presence of abdominal masses, hematocrit, and body weight (Table 1). Scores range

from 0 to approximately 600. In defining the limit between remission and active disease, the investigators believed that various cutoff values between 100 and 200 points could be selected such that most patients rated by physicians as "very well" would fall below and most others would fall above. They chose the midpoint of this range, 150 points, as a reasonable compromise. Ninety percent of patients rated by physicians as "very well" fell below this cutoff, as compared with 31% of patients rated as "fair to good," 6% of patients rated as "poor," and 0% of patients rated as "very poor." Conversely, the limit between active and very severe disease was defined as a cutoff value of 450 points. Zero percent of patients rated by physicians as "very well" or "fair to good" fell above this cutoff, as compared with 6% of patients rated as "poor" and 67% of patients rated as "very poor." Subsequently, investigators have arbitrarily designated CDAI scores of 150–219 as mildly active disease and scores of 220–450 as moderately active disease. The CDAI variables were rederived at completion of the NCCDS and little difference between the original and rederived equation was found, so the original version was recommended.<sup>13</sup> Several criticisms of this metric have been raised. First, substantial variability exists when different observers review the same case histories and calculate the CDAI score. However, this interobserver variability can be considerably reduced after discussion and education about the terminology.<sup>14</sup>

Secondly, a substantial portion of the total score is derived from the "general well being" and the "intensity of abdominal pain" items, which are relatively subjective and reflect the patients' perception of their disease (in this respect there is overlap between the CDAI and both the bowel symptoms domain and the systemic symptoms domain of the Inflammatory Bowel Disease Questionnaire

**Table 2.** Harvey Bradshaw Index (HBI, Simple Index)

Variable no.	Variable description	Total
1	General well being (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)	
2	Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)	
3	Number of liquid stools daily	
4	Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)	
5	Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcer, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item)	
HBI Score		

Adapted with permission from Harvey RF, Bradshaw JM. A simple clinical index of Crohn's disease activity. *Lancet* 1980;1:514.

[IBDQ]). However, these aspects of the disease are arguably important to patients. There is the potential for these symptoms to overlap with symptoms of irritable bowel syndrome in patients with Crohn's disease in remission. The authors are not aware of any large-scale population-based data on the frequency of concomitant diagnoses of Crohn's disease and irritable bowel syndrome. The limited data available suggests that patients with inflammatory bowel disease have decreased, not increased, pain perception to visceral stimuli.<sup>15-17</sup> One study reported an increased frequency of symptoms of irritable bowel syndrome in patients with ulcerative colitis in remission.<sup>18</sup> In randomized controlled trials enrolling patients with symptoms of active inflammatory Crohn's disease, patients whose symptoms are primarily functional in origin should be randomly distributed between treatment groups. Thus, any overlap of functional and organic symptoms in these patients should be a source or random error rather than bias.

Thirdly, the calculation of the CDAI score is based in part on a symptom diary maintained by the patient for 7 days before evaluation. This requirement essentially precludes the use of the CDAI to assess Crohn's disease activity in clinical practice. Although often not disclosed in the Methods section of published clinical trials in patients with Crohn's disease, some investigators and study coordinators assist patients in retrospectively completing the 7-day symptom diary at the time of a study evaluation visit. There are no data in the literature that assess the prevalence of this practice in controlled trials, and thus it is difficult to understand how great an effect this "real world" modification of the CDAI has on the operating properties of the instrument. Until studies are conducted to determine how this practice affects the "measurement noise" and the degree to which bias is introduced, the authors recommend that patients prospectively maintain a symptom diary for 7 days before each measurement of the CDAI as recommended in the original description of this measure. The other disease activity indexes which have been proposed include the Harvey Bradshaw index or "simple index" (Table 2),<sup>19</sup>

the Organisation Mondiale de Gastroenterologie (OMGE) index,<sup>20</sup> and the Cape Town index.<sup>21</sup> These 4 validated "clinical" indices all correlate with each other.<sup>14</sup> Another measure, the "Therapeutic Goals" score (Present/Korelitz index) was not rigorously developed or prospectively validated.<sup>22</sup> The van Hees or Dutch Index is a combined clinical and laboratory index that has been prospectively validated.<sup>23</sup> This index correlates poorly with the CDAI, the Harvey Bradshaw Index, the OMGE Index, and the Cape Town Index probably as a result of its extensive incorporation of laboratory-based items.<sup>14</sup> The CDAI is the most frequently used clinical index. For patients with predominantly inflammatory Crohn's disease (symptoms of diarrhea and abdominal pain), the CDAI has been used to evaluate the therapeutic efficacy of corticosteroids,<sup>24,25</sup> budesonide,<sup>26-29</sup> mesalamine,<sup>30</sup> azathioprine,<sup>31,32</sup> methotrexate,<sup>33,34</sup> cyclosporine,<sup>35-37</sup> metronidazole,<sup>38,39</sup> and infliximab.<sup>40</sup> Controlled trials that used the CDAI to measure disease activity led to regulatory approval in North America and Europe for budesonide and infliximab. Because the CDAI was rigorously developed and validated, and because it has been widely used in clinical trials over a 25-year period and led to regulatory approval of several drugs, this measure is currently the gold standard for evaluation of disease activity. The authors recommend that the CDAI be used as the primary outcome measure of clinical disease activity in patients whose symptoms are or have been predominantly inflammatory in nature (see below for patients with primarily fistulizing disease). Nevertheless, the need for physical examination and laboratory assessment to calculate the CDAI is cumbersome. Studies should be undertaken to determine if the CDAI can be simplified to include only patient symptoms without significantly altering the operating characteristics of the index.<sup>41,42</sup>

Patients whose primary symptom is drainage of enterocutaneous fistulas often have relatively low CDAI scores,<sup>43</sup> presumably because the presence of an actively draining fistula only contributes 20 points to the CDAI score.<sup>12</sup> Thus, the CDAI is not an appropriate instrument for assessing the activity of draining abdominal or peri-

**Table 3.** Perianal Crohn's Disease Activity Index

Categories affected by fistulas	Score
Discharge	
No discharge	0
Minimal mucous discharge	1
Moderate mucous or purulent discharge	2
Substantial discharge	3
Gross fecal soiling	4
Pain/restriction of activities	
No activity restriction	0
Mild discomfort, no restriction	1
Moderate discomfort, some limitation of activities	2
Marked discomfort, marked limitation	3
Severe pain, severe limitation	4
Restriction of sexual activity	
No restriction sexual activity	0
Slight restriction sexual activity	1
Moderate limitation sexual activity	2
Marked limitation sexual activity	3
Unable to engage in sexual activity	4
Type of perianal disease	
No perianal disease/skin tags	0
Anal fissure or mucosal tear	1
<3 Perianal fistulae	2
≥3 Perianal fistulae	3
Anal sphincter ulceration or fistulae with significant undermining of skin	4
Degree of induration	
No induration	0
Minimal induration	1
Moderate induration	2
Substantial induration	3
Gross fluctuance/abscess	4

Reprinted from Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. *J Clin Gastroenterol* 1995;20:27-32.

anal enterocutaneous fistulas. Therefore, investigators have proposed other indices. In 1980, Present and Korlitz reported the use of a therapeutic goals score to assess fistula closure in a clinical trial of 6-mercaptopurine.<sup>22</sup> Five items were scored using a 7-point scale. Although this instrument has the advantages of incorporating clinically sensible items and is easy to score, it has not been validated and was not widely used in subsequent studies. In 1995, Irvine described an instrument to measure the severity of perianal Crohn's disease called the Perianal Disease Activity Index (PDAI) (Table 3) and its validation in patients undergoing treatment with metronidazole.<sup>44</sup> The PDAI incorporates 5 items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4). A higher score indicates more severe disease. The PDAI has been used as a secondary endpoint in a placebo-controlled trial of infliximab for the closure of perianal fistulas.<sup>43</sup> It is likely that the PDAI will become the perianal Crohn's

disease equivalent of the CDAI. Additional research is needed to determine the minimum clinically significant difference (potentially the value may be 3 points because the mean difference in the CDAI score of improved patients was 3 points) and a "cut off" value that indicates remission (potentially, remission could be defined as a score of 0). Most recently, a fistula drainage assessment (Table 4) has been used to classify enterocutaneous or perianal fistulas as being either open and actively draining, or closed.<sup>43</sup> A fistula is open if the investigator can express purulent material from the fistula with the application of gentle pressure. This instrument served as the primary endpoint for a placebo-controlled trial of infliximab for abdominal and perianal enterocutaneous fistulas that led to regulatory approval of the drug in the United States and Europe. Additional placebo-controlled trials with infliximab, tacrolimus, and the humanized anti-tumor necrosis factor antibody CDP571 have used the fistula drainage assessment as a primary measure of outcome. We speculate that in the future, the fistula drainage assessment may become the de facto standard for assessing fistula closure. However, additional studies are needed to determine the reproducibility of this endpoint as compared with the PDAI and other alternative assessments such as standardized photography. The authors recommend that the fistula drainage assessment be used to measure fistula closure in patients whose symptoms are predominantly because of actively draining enterocutaneous or perianal fistulas. However, once additional prospective trials have been performed with the PDAI score as a secondary endpoint, and the minimum clinically significant difference in the PDAI and the cut-off value indicating remission have been determined, the PDAI may become the preferred instrument to measure the disease activity of perianal fistulas.

**Table 4.** Fistula Drainage Assessment

Endpoint	Definition
Improvement	Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Improvement defined as a decrease from baseline in the number of open draining fistulas of ≥50% for at least 2 consecutive visits (i.e., at least 4 weeks)
Remission	Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Remission defined as closure of all fistulas that were draining at baseline for at least 2 consecutive visits (i.e., at least 4 weeks)

Modified with permission from Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.

## Quality of Life

Disease-specific quality of life instruments for patients with Crohn's disease include the Rating Form of IBD Patient Concerns<sup>45–52</sup> and the IBDQ.<sup>53–56</sup> The IBDQ is a 32-item questionnaire with 4 dimensions (bowel function, emotional status, systemic symptoms, social function); the total score on this index ranges from 32–224, with higher scores indicating better quality of life. The scores of patients in remission usually range from 170–190.<sup>56</sup> The IBDQ can be self-administered<sup>57</sup> and a shortened 10-question version has been validated.<sup>58</sup> The IBDQ has been used extensively as a secondary endpoint in clinical trials,<sup>27,28,33–35,40</sup> and correlated with health utility states<sup>59</sup> in patients with Crohn's disease. A relatively good correlation exists between the IBDQ and the CDAI ( $r = -0.67$ ;  $P < 0.001$ ).<sup>56</sup> These studies have been performed in patients with inflammatory Crohn's disease, and there is no published data on the IBDQ scores of patients with primarily fistulizing Crohn's disease. An alternative measure, the Rating Form of Patient Concerns, quantifies disease-related patient concerns. Little experience exists using this instrument as a measure of outcome in randomized controlled trials. For these reasons, the IBDQ has evolved as the de facto standard for measuring disease-specific quality of life in patients with Crohn's disease. The authors recommend that the IBDQ be used to measure disease-specific quality of life

in patients with Crohn's disease, and that the IBDQ be routinely used as a secondary outcome measure in all prospective randomized controlled trials to ensure that quality of life is improved in medically treated patients with this chronic disease. Additional studies to validate the IBDQ in subpopulations of patients, such as those with primarily fistulizing disease, should be undertaken.

## Endoscopic Disease Activity

Early versions of endoscopic activity indices were not validated for use in clinical trials.<sup>60,61</sup> The Crohn's Disease Endoscopic Index of Severity (CDEIS) is a prospectively developed instrument that has been validated (Table 5).<sup>62–66</sup> The CDEIS has been used as a secondary endpoint in clinical trials to show endoscopic healing after treatment with corticosteroids and infliximab.<sup>65,67</sup> Scores range from 0–44 with higher scores indicating more severe disease. A minimum clinically important change in score and a specific cutoff value, which defines remission, has not been determined. For patients with ileal or ileocolonic Crohn's disease who undergo surgical resection of all evident disease with ileocolonic anastomosis, the Rutgeerts Score has been used to measure the presence and severity of endoscopic postoperative recurrence in the neoterminal ileum (Table 6).<sup>68,69</sup> Scores range from 0 to 4. Rutgeerts Scores of 3 or 4 are associated with a greater likelihood of clinical relapse.<sup>69</sup> The

**Table 5.** Crohn's Disease Endoscopic Index of Severity

Variable no.	Variable description	Weighing factor	Total
1	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that deep ulcerations are seen in divided by the number of segments examined	12	
2	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that superficial ulcerations are seen in divided by the number of segments examined	6	
3	Segmental surfaces involved by disease. The degree of disease involvement in each segment is determined by examining each segment for the following 9 lesions (pseudopolyps, healed ulcerations, frank erythema, frank mucosal swelling, aphthoid ulcers, superficial ulcers, deep ulcers, nonulcerated stenosis, ulcerated stenosis) and estimating the number of cm of involvement (1 or more lesions present) in a representative 10 cm portion from each segment. The average segmental surface involved by disease is calculated by dividing the sum of each of the individual segmental surfaces involved by disease by the number of segments examined	1	
4	Segmental surfaces involved by ulcerations. The degree of ulceration in each segment is determined by examining each segment for ulceration (aphthoid ulcers, superficial ulcers, deep ulcers, ulcerated stenosis) and estimating the number of cm of intestine involved by ulceration in a representative 10 cm portion from each segment. The average segmental surface involved by ulceration is calculated by dividing the sum of each of the individual segmental surfaces involved by ulceration by the number of segments examined	1	
5	Presence of a nonulcerated stenosis in any of the segments examined	3	
6	Presence of an ulcerated stenosis in any of the segments examined	3	
Total CDEIS			

Adapted with permission from Groupe D'Etudes Therapeutiques Des Affections Inflammatoires Du Tube Digestif (GTEAID) presented by Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Gut 1989;30:983–989.

**Table 6.** Endoscopic Scoring System for Postoperative Recurrence (Rutgeerts Score)

Grade	Endoscopic findings
0	No lesions in the distal ileum
1	≤5 aphthous lesions
2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to ileocolonic anastomosis (i.e., <1 cm in length)
3	Diffuse aphthous ileitis with diffusely inflamed mucosa
4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Reprinted with permission from Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;99:956–963.

Rutgeerts Score has been used to evaluate the efficacy of several drugs, including metronidazole,<sup>39</sup> budesonide,<sup>70,71</sup> mesalamine,<sup>72–75</sup> and 6-mercaptopurine.<sup>76</sup> One limitation of this index is that some investigators have found it difficult to differentiate between anastomotic ulceration from ischemia or staples and ulceration from recurrent Crohn's disease, and further clarification of this issue is needed. We conclude that the CDEIS and the Rutgeerts score are the de facto standards for assessing endoscopic healing of Crohn's disease and documenting the endoscopic recurrence of Crohn's disease in the neoterminal ileum after surgical resection. Endoscopic activity indices should be studied prospectively in further studies to validate their prognostic relevance. Until such studies are completed, assessment of endoscopic disease activity as a primary endpoint is not recommended. In studies in which assessment of endoscopic activity is desired, the authors recommend that the CDEIS be used to measure endoscopic disease activity except for studies where the goal is to prevent endoscopic postoperative recurrence of Crohn's disease. In studies in which the goal of the study is to prevent endoscopic postoperative recurrence of Crohn's disease, the authors recommend that the Rutgeerts Score be used to measure endoscopic activity and that endoscopic recurrence be defined as a Rutgeerts score of 3 or 4.

### Histologic Disease Activity

Two indexes have been used to quantitatively measure the histologic activity of Crohn's disease.<sup>77,78</sup> The scoring system for histologic abnormalities in Crohn's disease mucosal biopsy specimens (Table 7)<sup>78</sup> has been used to demonstrate histologic healing in patients treated with azathioprine<sup>79</sup> and infliximab.<sup>67,80</sup> Correlation between histological improvement and other assessments of disease severity is poor. Thus, the significance of histologic disease activity is uncertain and the potential for sampling error with bias in either direction (of greater

or lesser severity) is high because of the focality of Crohn's disease and the inherent variability of mucosal biopsy techniques. In general, the authors do not recommend assessment of histologic disease activity as a treatment endpoint because they do not believe that histologic activity can accurately represent a global response criteria and they are uncertain of its clinical relevance. If measurement of histologic disease activity is desired, then the scoring system for histologic abnormalities in Crohn's disease mucosal biopsy specimens should be used. However, additional research to prospectively validate this index, and to consider the development of additional histologic indices, is needed.

### Definitions of Patient Subpopulations

#### Classification According to Anatomy and Disease Course

The initial attempt to define subgroups of patients with Crohn's disease from the Cleveland Clinic was based on disease location.<sup>81</sup> Among 615 patients, 41% had ileocolitis, 29% had ileitis, and 27% had isolated

**Table 7.** Scoring System for Histologic Abnormalities in Crohn's Disease Mucosal Biopsy Specimens

Histologic findings	Score
Epithelial damage	0, Normal 1, Focal pathology 2, Extensive pathology
Architectural changes	0, Normal 1, Moderately disturbed (<50%) 2, Severely disturbed (>50%)
Infiltration of mononuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Polymorphonuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Polymorphonuclear cells in epithelium	1, In surface epithelium 2, Cryptitis 3, Crypt abscess
Presence of erosion and/or ulcers	0, No 1, Yes
Presence of granuloma	0, No 1, Yes
No. of biopsy specimens affected	0, None (0 of 6) 1, ≤33% (1 or 2 of 6) 2, 33%–66% (3 or 4 of 6) 3, >66% (5 or 6 of 6)
Total	

NOTE. Each topic should be scored independently. Moderate increase, up to twice the number of cells that can normally be expected; severe increase, more than twice the normal of cells. Reprinted with permission from D'Haens GR, Geboes K, Peeters M, Baert F, Penninx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology* 1998;114:262–267.

Crohn's colitis. This anatomic classification has implications for prognosis<sup>82</sup> and is useful for selecting appropriate patients for treatment with targeted delivery systems for the administration of medications such as mesalamine and budesonide directly to a specific anatomic location. Subsequently, it was suggested that patients might also be subdivided according to clinical behavior, i.e., perforating or nonperforating disease.<sup>83</sup> This concept was incorporated into the Rome Classification, which took into account disease location (stomach/duodenum, jejunum, ileum, colon, rectum, anal/perianal), disease extent (localized, diffuse), disease behavior (primarily inflammatory, fistulizing, or fibrostenotic), and operative history (primary, recurrent).<sup>84</sup> The reliability of this classification system has been challenged because classification of Crohn's disease by pattern of disease behavior yielded only fair interrater agreement.<sup>85</sup> As a consequence, the Vienna Classification modified the Rome Classification, taking into account age at diagnosis (< 40 years, ≥ 40 years), location (terminal ileum, colon, ileocolon, upper GI), and behavior (nonstricturing, nonpenetrating, stricturing penetrating).<sup>86</sup> The biologic relevance and validity of these classification systems is unclear. However, from the standpoint of selecting patients for participation in clinical trials, it seems useful to classify patients in 1 of 3 groups; predominantly inflammatory (nonstricturing nonpenetrating), predominantly obstructive (fibrostenotic, stricturing), or predominantly fistulizing (perforation, includes abscesses, includes perianal disease). At present, no criteria are available to define disease location (radiographic, endoscopic, histologic), inflammatory activity (distinguishing an inflammatory stricture from a fibrostenotic stricture), or how to assess changes in patterns over time (e.g., a patient who develops fistula after presentation).

## **Treatment Indications Based on Disease Patterns and Activity**

### **Inflammatory Crohn's Disease (Nonstricturing Nonpenetrating)**

Patients with inflammatory (nonstricturing nonpenetrating) Crohn's disease have a spectrum of disease severity ranging from remission to severely active. The CDAI score measures clinical disease activity. As discussed previously, clinical remission has been defined as a CDAI score < 150 points, indicating such a low level of disease activity that this cutoff is consistent with clinical remission. The CDAI score can also be used to further subclassify patients as being in remission (CDAI < 150 points), or having disease that is mildly active (CDAI scores 150–219), moderately active (CDAI

scores of 220–450), and severely active (CDAI scores > 450). In addition, remission can be subdivided into medically and surgically induced remissions. Previous studies have evaluated the following treatment indications for patients with inflammatory (nonstricturing nonperforating) Crohn's disease: treatment of signs and symptoms or induction of remission for active Crohn's disease, maintenance of a medically induced remission, and postoperative maintenance of remission.

The Food and Drug Administration (FDA) draft guidelines for the clinical evaluation of drugs for Crohn's disease indicate that potential indications are: treatment of acute disease, induction of remission (includes a requirement for endoscopic healing), and maintenance of remission.<sup>87</sup> The European Agency for the Evaluation of Medicinal Products (EMA) draft of points to consider on clinical investigation of medicinal products for the management of Crohn's disease indicates potential indications as: Acute Active Crohn's Disease (active disease [acute relapse] followed by symptom-free periods [remission] and managed on an outpatient basis using systemic/oral aminosalicylates [acute/maintenance therapy] and/or a short course of steroids [acute therapy]); Chronic Active Crohn's Disease (patients showing signs and symptoms with evidence of active inflammation well defined by biological criteria [C-reactive protein, erythrocyte sedimentation rate] over a period of 3 to 6 months while on steroids alone or in combination with other immunosuppressive agents or when termination of steroids/immunosuppressive medication is followed by a prompt reactivation of disease; this group includes 2 categories [steroid-dependent Crohn's disease and refractory Crohn's disease]).<sup>88</sup> The authors recommend that the treatment indications for patients with predominantly inflammatory Crohn's disease should be induction of clinical remission (see below for definition) for active Crohn's disease, maintenance of a medically induced remission, and prevention of postoperative recurrence. Response to treatment of active Crohn's disease, i.e., a reduction in signs and symptoms (see below for definition) should only be used as a secondary endpoint. The authors disagree with the provision of the FDA that endoscopic healing is required for induction of clinical remission because the correlation with clinically relevant outcomes may be poor. Similarly, the authors disagree with the provision of the EMA that patients be defined as acute or chronic based on response to concomitant medications (some of which are of unproven benefit).

### **Fistulizing Crohn's Disease**

Patients with fistulizing Crohn's disease may have internal or external fistulas that may be open (actively

draining) or closed. External (enterocutaneous) fistulas may involve the perianal region or the abdominal wall. Internal fistulas may involve adjacent loops of bowel (enteroenteric), the vagina (enterovaginal, rectovaginal), the bladder (enterovesical), or the peritoneal cavity (intra-abdominal abscess). Patients with actively draining external fistulas have been arbitrarily classified as having moderate to severe Crohn's disease, regardless of their CDAI score.<sup>43</sup> Treatment indications for patients with fistulizing Crohn's disease include inducing complete closure of all actively draining external fistulas, and maintenance of fistula closure. Complete closure of some ( $\geq 50\%$ ) actively draining fistulas has also been used as a treatment indication. The clinical importance of this endpoint is contentious. The FDA has recognized closure of some or all draining fistulas as treatment indications,<sup>43,87</sup> whereas the EMA has said that while fistula closure may be a response variable or outcome measure of the treatment of active disease or maintenance of remission, it should not be mentioned in the indication.<sup>88</sup> The term "closure" essentially applies to cessation of drainage as (1) imaging studies such as MRI demonstrate persistence of fistula tracts (or possibly scars) despite absence of drainage, and (2) many fistulas resume drainage after initial treatment that improves or ceases fistula output. The authors recommend that the treatment indications for patients with predominantly fistulizing Crohn's disease should be induction and maintenance of complete cessation of drainage from all actively draining external fistulas. Cessation of drainage from some ( $\geq 50\%$ ) actively draining fistulas should only be used as a secondary endpoint. The authors disagree with the EMA that fistula closure should not be mentioned as a treatment indication.

### Obstructive Crohn's Disease

Obstructive Crohn's disease results from luminal narrowing caused by irreversible fibrosis, edema, or a combination of the two.<sup>89</sup> For this reason, patients with compatible symptoms confirmed by endoscopy (impassable stricture) or barium radiograph (stenosis and prestenosis dilation) are typically excluded from clinical trials of medical therapy, and are instead treated with surgical resection or stricturoplasty. One caveat exists in patients with laboratory and clinical signs of inflammation, where an inflammatory stricture is suspected. Such patients may benefit from medical therapy, but this syndrome is difficult to define and diagnose. For this reason, these patients are not ideal candidates for clinical trials of medical therapies. For patients with clear-cut obstruction, it is reasonable to speculate that measurement of disease activity with the CDAI score and health-

related quality of life with the IBDQ score would be responsive to a procedural intervention to relieve obstruction, such as balloon dilation, surgical resection, or stricturoplasty. Thus, although patients with obstructive disease should be excluded from trials of medical therapy, they would be good candidates for trials assessing the safety and efficacy of procedural interventions to relieve obstruction.

### Steroid-Dependent Crohn's Disease

Patients who are unable to discontinue corticosteroids without a symptomatic relapse (disease flare) are considered to be steroid-dependent. This condition is a variation of active inflammatory Crohn's disease. Munkholm et al.<sup>90</sup> reported on the clinical course in a population-based cohort of 109 consecutive patients with Crohn's disease from Copenhagen County, Denmark, who received an initial course of corticosteroid therapy. A steroid-responsive state was defined as complete or partial clinical response to 40–60 mg/day of prednisone and no regression of clinical symptoms 30 days after prednisone treatment was completed. A steroid-dependent state was defined as partial or complete clinical response to treatment with prednisone 40–60 mg/day and relapse within 30 days after prednisone treatment was completed or relapse with a dose reduction of prednisone resulting in the use of prednisone at doses less than or equal to 15–25 mg/day for at least 6 months. A steroid-refractory state was defined as no response to prednisone at doses of 40–60 mg/day within 30 days. Another population-based study from Olmsted County, MN, used similar definitions.<sup>91</sup> The European Agency for the Evaluation of Medical Products draft of points to consider on clinical investigation of medicinal products for the management of Crohn's disease defines steroid-dependent Crohn's disease as patients requiring daily steroids to control symptoms (including those treated with azathioprine for steroid-sparing purposes). It should be recognized that steroid-responsiveness requires (1) an adequate dose of steroids (e.g., 1 mg/kg according to the EMA), and (2) an adequate duration of treatment (e.g., 4–8 weeks). The term steroid-dependency applies to individual patients whose disease flares at individual doses of steroids. This is in contrast to a maintenance therapy that prevents relapse in a proportion of patients.

### Refractory Crohn's Disease

The European Agency for the Evaluation of Medical Products draft of points to consider on clinical investigation of medicinal products for the management of Crohn's disease defines refractory Crohn's disease as patients who are uncontrolled on 1 mg/kg prednisolone

daily and who require additional immunosuppressive agents to adequately control the activity of the disease, or patients who have not responded to immunosuppressive drugs. The authors believe the following caveats must also be considered. For patients with ileal disease or previous ileal resection, a trial of therapy with a bile acid binding agent such as cholestyramine is required to exclude bile salt diarrhea before designating the patient as refractory. Similarly, intestinal obstruction must be excluded in patients with symptoms compatible with partial bowel obstruction before designating the patient as refractory.

### Endpoints Based on Treatment Indications

#### Response to Treatment and Induction of Clinical Remission for Active Inflammatory Disease

The endpoints based on the CDAI that have been used for clinical trials in patients with active inflamma-

tory Crohn's disease are summarized in Table 8. Initial trials had minimal or no CDAI-based eligibility criteria. This omission led to the inclusion of heterogeneous patient populations in early studies. Trials that are more recent have typically restricted entry CDAI scores to select patients with mild to moderate, moderate, or moderate to severe Crohn's disease. The minimal clinically important differences in the CDAI and Harvey Bradshaw scores are not entirely clear. When the CDAI was originally developed and validated, the relationship between change in the CDAI score over 2 successive visits and the physician's overall rating of change in the patient's disease activity ("much better, slightly better, the same, slightly worse, much worse") was determined. The difference between the mean CDAI values for "slightly better" versus "the same" and for "the same" versus "slightly worse" were each about 50 points.<sup>12</sup> In contrast, when the investigators examined the degree of inpatient variation over 1 month under stable conditions, the pooled standard deviation of replication of the CDAI score was 46 points.<sup>12</sup> Various clinical studies have

**Table 8.** Endpoints for Response to Treatment and Induction of Remission for Active Inflammatory Disease

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Summers <sup>24</sup>	Sulfasalazine Prednisone	Mild to severe	CDAI > 150	Induction of remission, CDAI < 150
Malchow <sup>25</sup>	Azathioprine Sulfasalazine	Mild to severe	CDAI ≥ 150	Induction of remission, CDAI < 150
Singleton <sup>30</sup>	6-Methyl-prednisolone Mesalamine	Mild to moderate	CDAI 151–400	Induction of remission, CDAI < 150 and decrease in CDAI > 50,
Tremaine <sup>95</sup>	Mesalamine	Mild to moderate	CDAI 150–450	Therapeutic benefit, decrease in CDAI > 50 Induction of remission, CDAI < 150 and decrease in CDAI > 70, Partial success, decrease in CDAI > 70
Prantera <sup>96</sup>	Mesalamine	Mild to moderate	CDAI 180–350	CDAI ≤ 150
Thomsen <sup>97</sup>	Mesalamine Budesonide	Mild to moderate	CDAI 200–400	Induction of remission, CDAI ≤ 150, Improvement, decrease in CDAI ≥ 100 or CDAI ≤ 150
Greenberg <sup>27</sup>	Budesonide	Mild to severe	CDAI ≥ 200	CDAI ≤ 150
Rutgeerts <sup>26</sup>	Budesonide Prednisolone	Mild to severe	CDAI ≥ 200	Induction of remission, CDAI ≤ 150, Success, decrease in CDAI ≥ 100 or CDAI ≤ 150
Campieri <sup>98</sup>	Budesonide Prednisolone	Mild to severe	CDAI ≥ 200	CDAI ≤ 150
Bar-Meir <sup>99</sup>	Budesonide Prednisolone	Mild to moderate	CDAI 150–350	Response, CDAI < 150 or decrease in CDAI ≥ 60 if baseline CDAI < 210
Gross <sup>100</sup>	Budesonide	Mild to moderate	CDAI > 150 ≤ 350	Response, CDAI < 150 or decrease in CDAI ≥ 60 if baseline CDAI < 210
Sutherland <sup>38</sup>	6-methyl-prednisolone Metronidazole	Mild to moderate	281–449	Change in CDAI (not defined for individual patients), Induction of remission, CDAI < 150
Feagan <sup>35</sup>	Cyclosporine	Remission to severe	No limit on CDAI score	Increase in CDAI ≥ 100
Stange <sup>36</sup>	Cyclosporine	Remission to severe	No limit on CDAI score	Complete success, CDAI < 150, Partial success, CDAI 150–200, Failure, CDAI > 200
Targan <sup>40</sup>	Infliximab	Moderate disease	CDAI 220–400	Response, decrease in CDAI ≥ 70 points, Induction of remission, CDAI < 150

defined a clinical response as a decrease in the CDAI of 50, 60, 70, or 100 points. A decrease of 70 points led to regulatory approval by the FDA with corroboration of end-points of remission and fistula closure (see below).<sup>40</sup> More recently, the FDA and EMA have suggested that a meaningful decrease in the CDAI score is a decrease of 100 points.<sup>88</sup> Virtually all studies have defined remission as a CDAI score <150 points. Accordingly, a Harvey Bradshaw score of <5 points would also indicate remission. The authors recommend the primary endpoint for therapeutic trials in patients with active inflammatory Crohn's disease be induction of remission, defined as a CDAI score <150 points. The authors also recommend that response to treatment of active disease (i.e., a reduction in signs and symptoms), defined as a decrease from baseline in the CDAI score  $\geq 70$ –100 points, only be used as a secondary endpoint.

### Maintenance of Medically Induced Remission

The endpoints based on the CDAI that have been used for clinical trials in patients with Crohn's disease with medically induced remission are summarized in

Table 9. Initial trials defined relapse as an increase in the CDAI to a value >150 points. Studies that are more recent have defined a relapse as both a CDAI score >150 points and an increase in the CDAI score of 50, 60, or 100 points. In other disease settings, the time to relapse (survival analysis) has been used as to measure maintenance of remission. Such an approach may be reasonable in patients with Crohn's disease, but the absolute increase in the time to relapse that would be clinically significant has not been determined. The authors recommend the primary endpoint for therapeutic trials in patients with Crohn's disease and a medically induced remission should be relapse, defined as both a CDAI score  $\geq 150$  points and a minimum increase in the baseline CDAI score  $\geq 70$  points. Studies evaluating maintenance of a medically induced remission should be at least 1 year in duration.

### Prevention of Postoperative Recurrence

The endpoints for prevention of postoperative recurrence can be either clinical or endoscopic. The endpoints that have been used in clinical trials for prevention

**Table 9.** Endpoints for Maintenance of Medically Induced Remission

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Summers <sup>24</sup>	Sulfasalazine Prednisone Azathioprine	Medical remission	CDAI $\leq 150$	CDAI > 150 and increase in CDAI $\geq 100$ from baseline
Malchow <sup>25</sup>	Sulfasalazine 6-Methyl-Prednisolone	Medical remission	CDAI < 150	CDAI > 150
Sutherland <sup>101</sup>	Mesalamine	Medical and postoperative remission	CDAI < 150	CDAI > 150 and increase in CDAI $\geq 60$ from baseline
Brignola <sup>102</sup>	Mesalamine	Medical remission	CDAI < 150 and laboratory activity score > 100	CDAI > 150 and increase in CDAI $\geq 100$ from baseline
Prantera <sup>103</sup>	Mesalamine	Medical remission	CDAI < 150	CDAI > 150 and increase in CDAI $\geq 100$ from baseline
Gendre <sup>104</sup>	Mesalamine	Medical remission	CDAI < 150	CDAI > 250 or CDAI 150–250 and increase in CDAI $\geq 50$ from baseline
Thomson <sup>105</sup>	Mesalamine	Medical remission	CDAI < 150	CDAI > 150 and increase in CDAI $\geq 60$ from baseline
Greenberg <sup>28</sup>	Budesonide	Medical remission	CDAI $\leq 150$	CDAI > 150 and increase in CDAI $\geq 60$ from baseline
Lofberg <sup>29</sup>	Budesonide	Medical remission	CDAI $\leq 150$	CDAI > 150 and increase in CDAI $\geq 60$ from baseline
Feagan <sup>35</sup>	Cyclosporine	Medical remission to severe	No limit	Increase of CDAI $\geq 100$
Stange <sup>36</sup>	Cyclosporine	Medical remission to severe	No limit	Complete success, CDAI < 150, Partial success, CDAI 150–200, Failure, CDAI > 200
Feagan <sup>34</sup>	Methotrexate	Medical remission	CDAI $\leq 150$	Increase of CDAI $\geq 100$
Rutgeerts <sup>106</sup>	Infliximab	Medical remission	Clinical response (decrease in CDAI $\geq 70$ points) in a patient with active disease (CDAI 220–400)	Maintenance of clinical response (decrease in CDAI $\geq 70$ points), Maintenance of remission (CDAI < 150)

**Table 10.** Endpoints for Prevention of Postoperative Recurrence

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Lochs <sup>75</sup>	Mesalamine	Postoperative remission	Resecting surgical procedure within 10 days	Increase in CDAI above 250 or CDAI 200–250 and increase in CDAI $\geq$ 60 from baseline, Rutgeerts score 2–4
Sutherland <sup>101</sup>	Mesalamine	Medical and postoperative remission	CDAI < 150	CDAI > 150 and increase in CDAI $\geq$ 60 from baseline
McLeod <sup>107</sup>	Mesalamine	Postoperative remission	Surgical resection within 8 weeks	Symptomatic recurrence, Total recurrence (includes clinical, endoscopic, or radiologic recurrence)
Floret <sup>74</sup>	Mesalamine	Postoperative remission	Surgical resection within 15 days	Rutgeerts score 1–4
Brignola <sup>73</sup>	Mesalamine	Postoperative remission	Surgical resection within 1 month	Change in Rutgeerts score (not defined for individual patients), Severe endoscopic recurrence (Rutgeerts score of 3–4), CDAI > 150 and increase in CDAI $\geq$ 100 from baseline
Caprilli <sup>72</sup>	Mesalamine	Postoperative remission	Surgical resection within 2 weeks	Rutgeerts score 2–4, CDAI > 150 and increase in CDAI $\geq$ 100 from baseline
Hellers <sup>70</sup>	Budesonide	Postoperative remission	Surgical resection within 2 weeks	Rutgeerts score 2–4, Change in CDAI (not defined for individual patients), Physician's global evaluation
Ewe <sup>71</sup>	Budesonide	Postoperative remission	Surgical resection within 4 weeks	Rutgeerts score 2–4, Increase in CDAI above 200 or CDAI $\leq$ 200 and increase in CDAI $\geq$ 60 from baseline
Rutgeerts <sup>39</sup>	Metronidazole	Postoperative remission	Surgical resection within 1 week	Rutgeerts score 3–4, Rutgeerts score 1–4
Korelitz <sup>76</sup>	Mesalamine 6-mercaptopurine	Postoperative remission	Surgical resection	Clinical relapse, Rutgeerts score 1–4, Rutgeerts score 3–4, Radiologic relapse

of postoperative recurrence are summarized in Table 10. Endoscopic recurrence precedes clinical recurrence and a Rutgeerts score of 3–4 predicts a poor prognosis.<sup>92,93</sup> Thus, endoscopic recurrence has been used as a surrogate for clinical recurrence, leading to shorter duration of clinical trials and small sample sizes. However, while it is clear that endoscopic recurrence precedes clinical recurrence by some variable period of time, it is not yet accepted as a matter of fact that the prevention of endoscopic recurrence as the primary endpoint for a trial proves that the drug is clinically efficacious. Endoscopic relapse has been defined as Rutgeerts scores of 1–4, 2–4, or 3–4. Clinical relapse has typically been defined as a CDAI > 150 points and an increase in the CDAI of 60 or 100 points. However, the CDAI scoring system has not been reproduced or validated in postoperative (post-resection) Crohn's disease patients (nevertheless, this is the only clinical instrument that has been used to date to assess disease activity in this setting). It is also unclear whether the CDAI is reliable in the immediate postoperative period. Furthermore, postsurgical relapse criteria

have not been evaluated for patients after ostomy surgery (either ileostomy or colostomy). Patients whose indication for operation is inflammatory (nonstricturing nonpenetrating) disease or abdominal abscess/fistula may have a different postoperative course than patients whose indication for surgery is stenosis with obstruction as do patients after creation of a stoma. A majority of the authors recommend the primary endpoint for therapeutic trials in patients with Crohn's disease and a surgically induced remission should be clinical relapse, defined as both a CDAI score  $\geq$  150 points and an increase in the CDAI score  $\geq$  70 points. Studies evaluating prevention of postoperative recurrence should be at least 1 year in duration, and should indicate the indication for the operation (inflammatory [nonstricturing nonpenetrating] disease, stricture, abdominal abscess, or fistula). Although it is clear that endoscopic recurrence precedes clinical recurrence, a majority of the authors believe that the use of endoscopic recurrence determined by the Rutgeerts score is investigational and should not, in the absence of further data that support its clinical relevance,

**Table 11.** Endpoints for Corticosteroid Sparing

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Modigliani <sup>108</sup>	Mesalamine	Steroid-induced remission	CDAI < 150 and decrease in CDAI > 100 from presteroid baseline after 4 weeks of induction therapy with prednisolone	Failure to discontinue steroids or CDAI > 150 and increase in CDAI > 100 from poststeroid baseline
Cortot <sup>109</sup>	Budesonide	Steroid-dependent	CDAI < 200 and prednisone 10–30 mg and unable to taper prednisolone	Increase in CDAI above 200 and increase in CDAI $\geq$ 60 from baseline
Gross <sup>110</sup>	Budesonide	Steroid-dependent or -refractory	Prednisolone 5–30 mg	CDAI < 150 and discontinuation of prednisolone
Gross <sup>111</sup>	Budesonide	Steroid-induced remission	CDAI < 150 and prednisone 5–10 mg/day after prednisolone induction	Increase in CDAI above 150 for 2 consecutive visits or at the end of the study
Ewe <sup>32</sup>	Azathioprine	Steroid-induced remission	CDAI > 150 and induction treatment with prednisolone	Decrease in CDAI below 150 and decrease in CDAI > 60 and prednisolone 10 mg/day
Candy <sup>31</sup>	Azathioprine	Steroid-induced remission	CDAI > 200 and induction treatment with prednisolone	Decrease in CDAI below 175 and discontinuation of prednisolone
Markowitz <sup>112</sup>	6-Mercaptopurine	Steroid-induced remission	Harvey Bradshaw Index $\geq$ 5 and induction treatment with prednisone	Harvey Bradshaw Index $\leq$ 3 and discontinuation of prednisone
Sandborn <sup>113</sup>	Azathioprine	Steroid-refractory	CDAI 150–450 and prednisone $\geq$ 20 mg/day for $\geq$ 4 weeks	CDAI < 150 and discontinuation of prednisone
Feagan <sup>33</sup>	Methotrexate	Steroid-dependent, steroid-refractory	$\geq$ 3 months of symptoms despite prednisone $\geq$ 12.5 mg/day and at least one attempt to discontinue prednisone	CDAI $\leq$ 150 and discontinuation of prednisone
Feagan <sup>114</sup>	CDP571	Steroid-dependent	CDAI < 150 and prednisone 15–40 mg/day or budesonide 9 mg/day for >8 weeks and failed attempt to discontinue steroids within 8 weeks	Failure to discontinue steroids or increase in CDAI above 220

be used as a surrogate for clinical relapse. However, the Rutgeerts score should continue to be studied prospectively in further studies to validate its prognostic relevance. The authors also believe that additional studies are warranted for patients who have undergone ileostomy or colostomy procedures (until these studies are undertaken, patients with ostomies should be excluded from clinical trials).

### Corticosteroid Sparing

The endpoint of corticosteroid sparing is difficult to define. Studies that have enrolled patients with corticosteroid-induced remission, corticosteroid-dependent disease, corticosteroid-refractory disease, and both corticosteroid-dependent and corticosteroid-refractory disease are summarized in Table 11. Distinguishing between corticosteroid dependence and symptoms of adrenal insufficiency may be difficult in some patients who have received prolonged treatment with corticosteroids. For

patients with corticosteroid-induced remission or corticosteroid-refractory disease, corticosteroid sparing requires clinical remission (CDAI < 150) after combination induction therapy with corticosteroids and the investigational medication, and then maintenance of clinical remission despite complete corticosteroid withdrawal. For patients with corticosteroid-dependent disease, corticosteroid sparing requires that clinical remission be maintained despite complete corticosteroid withdrawal. The minimum duration of corticosteroid-free time after corticosteroid withdrawal that is clinically significant is a subject of debate. It appears that the FDA has indicated that a minimum of 6 months without the need to reintroduce corticosteroids is required,<sup>94</sup> whereas the EMA has suggested that a minimum of 3 months may be sufficient.<sup>88</sup> The authors recommend that the primary endpoint for therapeutic trials in patients who have a steroid-induced remission should be complete removal of corticosteroid therapy without the develop-

ment of clinical relapse – defined by both a CDAI score  $\geq 150$  points and an increase in the CDAI score  $\geq 70$  points. A minimum period of 6 months without this event is considered clinically meaningful.

### Refractory Crohn's Disease

The endpoint of refractory disease is difficult to define. To date, there are no studies that have limited enrollment to patients who are refractory to steroids (uncontrolled despite prednisolone 1 mg/kg or equivalent for 4–8 weeks) and/or immunosuppressives (azathioprine 2–3 mg · kg · day or 6-mercaptopurine 1.5 mg · kg · day for 12 weeks or methotrexate 25 mg/week for 8 weeks). Infliximab received regulatory approval in the United States for patients unresponsive to conventional therapy, which was not specifically defined, and in the European Union for patients who had failed a “full and adequate course of steroids and or immunosuppressive therapy.” However, the pivotal studies of infliximab included heterogenous patient populations that did not uniformly meet the EMA definition of refractory Crohn's disease. The authors believe that targeting refractory Crohn's disease is problematic because the definition is always susceptible to change. For example, now that infliximab is proven to be efficacious, must the definition of refractory disease also include patients refractory to infliximab? The authors recommend that if a refractory population of patients is targeted for study enrollment, then the drug that the study population is refractory to must be specified in the entry criteria. Furthermore, the entry criteria must require that patients take a dose of the drug proven to be effective for a duration that exceeds the time to onset of action of the drug. Finally, all patients enrolled in the study must be refractory to the specified drug.

### Closure of Enterocutaneous Fistulas

The endpoints based on the Fistula Drainage Assessment and/or the PDAI for fistula closure, which have

been used for clinical trials in Crohn's disease patients with actively draining enterocutaneous fistulas are summarized in Table 12. The endpoints of fistula closure for 4 weeks using the Fistula Drainage Assessment led to approval in the United States and Europe by the FDA and the EMA. Studies to maintain fistula closure have not been reported to date. The authors recommend that the primary endpoint for induction trials in patients with Crohn's disease and actively draining enterocutaneous or perianal fistulas be complete cessation of drainage from all fistulas at a specific point in time. The authors also recommend the primary endpoint for maintenance trials in patients with Crohn's disease and medically induced fistula closure of enterocutaneous or perianal fistulas be defined as complete absence of drainage from all fistulas and the absence of any new or reopened fistulas or abscesses for at least 6 months.

### Endoscopic Remission

The endpoints for endoscopic response and remission that have been used in clinical trials of patients with active Crohn's disease are summarized in Table 13. The endpoints based on the CDEIS for endoscopic response and remission for individual patients have not been defined. That is, a specific “cutoff value,” which defines remission in an individual patient, has not been determined. Instead, studies have reported the mean or median decrease in a population of patients. This is not optimal and ultimately studies seeking to demonstrate endoscopic healing will need to define a priori, and then show, the occurrence of endoscopic response or remission in a significant proportion of individual patients. The clinical significance of endoscopic remission has not been established. The authors do not recommend that endoscopic remission be used as the primary endpoint for a therapeutic trial in patients with Crohn's disease until endoscopic remission has been defined and correlated with clinical remission and natural history.

**Table 12.** Endpoints for Closure of Enterocutaneous Fistulas

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Irvine <sup>44</sup>	Metronidazole	Perianal fistulas	Active perianal disease (? PDAI $\geq 5$ )	Decrease in PDAI $\geq 2$
Present <sup>43</sup>	Infliximab	Perianal and abdominal enterocutaneous fistulas	Fistula drainage with gentle compression, drainage present for $\geq 3$ months	Improvement, closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Improvement defined as a decrease from baseline in the number of open draining fistulas of $\geq 50\%$ for at least 2 consecutive visits (i.e., at least 4 weeks). Remission, closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Remission defined as closure of all fistulas that were draining at baseline for at least 2 consecutive visits (i.e., at least 4 weeks).

**Table 13.** Endpoints for Endoscopic Remission

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
Modigliani <sup>64</sup> Landi <sup>65</sup>	Prednisolone	Moderate to severe	CDAI $\geq$ 200 and induction treatment with prednisolone	Clinical induction of remission—CDAI $\leq$ 150 and decrease in CDAI $\geq$ 100, Endoscopic change—based on change in the CDEIS (significant change not defined for individual patients), Endoscopic remission based on 6 grade global assessment (no lesion at all, scarred lesions only, minor, moderate, severe and very severe lesions)—remission is no lesion at all, scarred lesions, or minor lesions only
D'Haens <sup>115</sup>	Azathioprine	Steroid-dependent, or steroid-refractory postoperative recurrence	Clinically symptomatic postoperative recurrence and induction treatment with corticosteroids, with subsequent azathioprine for steroid-dependent or steroid-refractory disease	Complete mucosal healing—complete disappearance of any pathologic findings, Near-complete mucosal healing—marked reduction of mucosal lesions with a Rutgeerts score of 1, Partial healing—significant shortening of the inflamed segment (>30% decrease in length), No healing—persistence or worsening or earlier lesions
D'Haens <sup>79</sup>	Azathioprine	Refractory disease	Refractory, clinically symptomatic disease and induction treatment with corticosteroids and azathioprine, with subsequent corticosteroid withdrawal for at least 6 months	Complete healing—disappearance of all endoscopic lesions, Near-complete healing—only aphthous ulcers (<5 mm) or erosions remain when large ulcers (>5 mm) were previously, Partial healing—large ulcers remaining with significant (>33%) reduction in size, No healing—persistence or worsening of lesions
D'Haens <sup>67</sup>	Infliximab	Moderate to severe	CDAI 220–400	Clinical response—decrease in CDAI $\geq$ 70 points, Clinical remission, CDAI < 150 Endoscopic change—based on change in the CDEIS (significant change not defined for individual patients)

### Histologic Remission

The endpoints for histologic remission that have been used in clinical trials of patients with active Crohn's disease are summarized in Table 14. The endpoints for histologic remission for individual patients have not been defined. That is, a specific "cutoff value" that defines remission in an individual patient has not been deter-

mined. Instead, studies have reported the mean or median decrease in a population of patients. This is not optimal, and ultimately, studies seeking to show histologic remission will need to a priori define and then show the occurrence of histologic remission in a significant proportion of individual patients. Because of the patchy nature of Crohn's disease, care must be taken to ade-

**Table 14.** Endpoints for Histologic Remission

Author (reference)	Drug	Disease activity	Entry criteria	Endpoint
D'Haens <sup>79</sup>	Azathioprine	Refractory disease	Refractory, clinically symptomatic disease and induction treatment with corticosteroids and azathioprine, with subsequent corticosteroid withdrawal for at least 6 months	Histologic change—based on change in the scoring system for histologic abnormalities (significant change not defined for individual patients)
D'Haens <sup>67</sup>	Infliximab	Moderate to severe	CDAI 220–400	Histologic change—based on change in the scoring system for histologic abnormalities (significant change not defined for individual patients)

quately sample the mucosa and a process to ensure adequate sampling must be defined. The clinical significance and documentation of histologic remission has not been established. The authors do not recommend that histologic remission be used as the primary endpoint for a therapeutic trial in patients with Crohn's disease until histologic remission has been defined and correlated with clinical remission and natural history.

### Quality of Life

The only endpoint for quality of life response and remission that has been used in clinical trials of patients with Crohn's disease is the IBDQ. The endpoints based on the IBDQ for quality of life response and normal quality of life (consistent with clinical remission) in individual patients are a change of 16 points and an absolute score of 170 points, respectively.<sup>56</sup> However, the clinical trials that have used the IBDQ to measure quality of life have not reported the proportions of patients who achieve these endpoints.<sup>27,28,33-35,40</sup> Instead, these studies have reported the mean or median increase in IBDQ scores in a population of patients. This is not optimal, and ultimately, studies seeking to show quality of life response or normal quality of life will need to show the occurrence of these endpoints in a significant proportion of individual patients. The authors do not recommend that a specific IBDQ value be considered indicative of normal health-related quality of life and then used as the primary endpoint for a therapeutic trial in patients with Crohn's disease until further experience is gained with using this endpoint in individual patients. However, the authors recommend that the IBDQ be routinely used as a secondary outcome measure in all prospective, randomized, controlled trials to ensure that quality of life is improved in medically treated patients with this chronic disease.

### Conclusions

Important progress in the development of measurement instruments for assessing the efficacy of medical therapies for Crohn's disease has occurred over the last 25 years. Well-accepted activity indices and endpoints currently exist for the indications of treatment and induction of remission, maintenance of medically induced remission, and prevention of postoperative recurrence in patients with inflammatory Crohn's disease not complicated by significant fistulas or intestinal obstruction. There is preliminary experience with clinical trials targeting the indications of corticosteroid sparing and closure of fistulas, but determination of the optimal endpoints for clinical trials for these indications is still in

evolution. The definition of endoscopic and histologic improvement or remission and the application of these endpoints to clinical trials have not yet been undertaken. Likewise, the application of quality of life improvement or remission has not yet been undertaken. Examination of the relevance of response measures by academic investigators, the pharmaceutical industry, and regulators is an important issue that should be examined collaboratively.

### Appendix 1. Institutional Affiliations of the Authors

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### References

1. Kitching A, Sackett D, Yusef S. Approaches to evaluating evidence. London, England: BMJ Books, 1998.

2. Smith RC, Rhodes J, Heatley RV, Hughes LE, Crosby DL, Rees BI, Jones H, Evans KT, Lawrie BW. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. *Gut* 1978;19:606–610.
3. Bergman L, Krause U. Postoperative treatment with corticosteroids and salazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. *Scand J Gastroenterol* 1976;11:651–656.
4. Anthonisen P, Barany F, Folkenborg O, Holtz A, Jarnum S, Kristensen M, Riis P, Walan A, Worning H. The clinical effect of salazosulphapyridine (Salazopyrin r) in Crohn's disease. A controlled double-blind study. *Scand J Gastroenterol* 1974;9:549–554.
5. Lennard-Jones JE. Sulphasalazine in asymptomatic Crohn's disease. A multicentre trial. *Gut* 1977;18:69–72.
6. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;2:1273–1276.
7. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. *Gastroenterology* 1974;66:916–922.
8. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;2:944–947.
9. Rosenberg JL, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. *Am J Dig Dis* 1975;20:721–726.
10. O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978;2:955–957.
11. Winship DH, Summers RW, Singleton JW, Best WR, Beckett JM, Lenk LF, Kern F Jr. National Cooperative Crohn's Disease Study: study design and conduct of the study. *Gastroenterology* 1979;77:829–842.
12. Best WR, Beckett JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439–444.
13. Best WR, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979;77:843–846.
14. de Dombal FT, Softley A. IOIBD report no 1: Observer variation in calculating indices of severity and activity in Crohn's disease. International Organisation for the Study of Inflammatory Bowel Disease. *Gut* 1987;28:474–481.
15. Cook IJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. *Gastroenterology* 1987;93:727–733.
16. Bernstein CN, Niazi N, Robert M, Mertz H, Kodner A, Munakata J, Naliboff B, Mayer EA. Rectal afferent function in patients with inflammatory and functional intestinal disorders. *Pain* 1996;66:151–156.
17. Chang L, Munakata J, Mayer EA, Schmulson MJ, Johnson TD, Bernstein CN, Saba L, Naliboff B, Anton PA, Matin K. Perceptual responses in patients with inflammatory and functional bowel disease. *Gut* 2000;47:497–550.
18. Isgar B, Harman M, Kaye MD, Whorwell PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983;24:190–192.
19. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. *Lancet* 1980;1:514.
20. Myren J, Bouchier IA, Watkinson G, Softley A, Clamp SE, de Dombal FT. The O.M.G.E. Multinational Inflammatory Bowel Disease Survey 1976-1982. A further report on 2,657 cases. *Scand J Gastroenterol Suppl* 1984;95:1–27.
21. Wright JP, Marks IN, Parfitt A. A simple clinical index of Crohn's disease activity—the Cape Town index. *S Afr Med J* 1985;68:502–503.
22. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;302:981–987.
23. van Hees PA, van Elteren PH, van Lier HJ, van Tongeren JH. An index of inflammatory activity in patients with Crohn's disease. *Gut* 1980;21:279–286.
24. Summers RW, Switz DM, Sessions JT Jr, Beckett JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847–869.
25. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (EC-CDS): results of drug treatment. *Gastroenterology* 1984;86:249–266.
26. Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, Danielsson A, Goebell H, Thomsen OO, Lorenz-Meyer H, Hodgson H, Persson T, Seidegard C. A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 1994;331:842–845.
27. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;331:836–841.
28. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996;110:45–51.
29. Lofberg R, Rutgeerts P, Malchow H, Lamers C, Danielsson A, Olaison G, Jewell D, Ostergaard Thomsen O, Lorenz-Meyer H, Goebell H, Hodgson H, Persson T, Seidegard C. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one-year study. *Gut* 1996;39:82–86.
30. Singleton JW, Hanauer SB, Gitnick GL, Peppercorn MA, Robinson MG, Wruble LD, Krawitt EL. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;104:1293–1301.
31. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;37:674–678.
32. Ewe K, Press AG, Singe CC, Stuffer M, Ueberschaer B, Hommel G, Meyer zum Buschenfelde KH. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenterology* 1993;105:367–372.
33. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M, Hanauer SB, McDonald JWD. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;332:292–297.
34. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;342:1627–1632.
35. Feagan BG, McDonald JW, Rochon J, Laupacis A, Fedorak RN, Kinnear D, Saibil F, Groll A, Archambault A, Gillies R, Volberg B, Irvine EJ. Low-dose cyclosporine for the treatment of Crohn's disease. The Canadian Crohn's Relapse Prevention Trial Investigators. *N Engl J Med* 1994;330:1846–1851.
36. Stange EF, Modigliani R, Pena AS, Wood AJ, Feutren G, Smith PR. European trial of cyclosporine in chronic active Crohn's disease: a 12-month study. The European Study Group. *Gastroenterology* 1995;109:774–782.
37. Jewell DP, Lennard-Jones JE, and the cyclosporin study group of Great Britain and Ireland. Oral cyclosporine for chronic active

- Crohn's disease: a multicentre controlled trial. *Eur J Gastroenterol Hepatol* 1995;5:499-505.
38. Sutherland L, Singleton J, Sessions J, Hanauer S, Krawitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M, Levine J, Thomson A, Alpert E, Prokipchuk E. in all categories except type of perianal dis Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991;32:1071-1075.
  39. Rutgeerts P, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;108:1617-1621.
  40. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029-1035.
  41. Sandler RS, Jordan MC, Kupper LL. Development of a Crohn's index for survey research. *J Clin Epidemiol* 1988;41:451-458.
  42. Faubion WA, Zinsmeister AR, Persson T, Persson A, Sandborn WJ. Development of a simplified patient-based Crohn's Disease Activity Index (abstr). *Gastroenterology* 2001;120:A-273.
  43. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.
  44. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. *J Clin Gastroenterol* 1995;20:27-32.
  45. Drossman DA, Leserman J, Li ZM, Mitchell CM, Zagami EA, Patrick DL. The rating form of IBD patient concerns: a new measure of health status. *Psychosom Med* 1991;53:701-712.
  46. Drossman DA, Patrick DL, Mitchell CM, Zagami EA, Appelbaum MI. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns. *Dig Dis Sci* 1989;34:1379-1386.
  47. Garrett JW, Drossman DA. Health status in inflammatory bowel disease. Biological and behavioral considerations. *Gastroenterology* 1990;99:90-96.
  48. Drossman DA, Leserman J, Mitchell CM, Li ZM, Zagami EA, Patrick DL. Health status and health care use in persons with inflammatory bowel disease. A national sample. *Dig Dis Sci* 1991;36:1746-1755.
  49. Drossman DA, Li Z, Leserman J, Patrick DL. Ulcerative colitis and Crohn's disease health status scales for research and clinical practice. *J Clin Gastroenterol* 1992;15:104-112.
  50. Drossman DA. Measuring quality of life in inflammatory bowel disease. *Pharmacoeconomics* 1994;6:578-580.
  51. Talal AH, Drossman DA. Psychosocial factors in inflammatory bowel disease. *Gastroenterol Clin North Am* 1995;24:699-716.
  52. Levenstein S, Li Z, Almer S, Barbosa A, Marquis P, Moser G, Sperber A, Toner B, Drossman DA. Cross-cultural variation in disease-related concerns among patients with inflammatory bowel disease. *Am J Gastroenterol* 2001;96:1822-1830.
  53. Mitchell A, Guyatt G, Singer J, Irvine EJ, Goodacre R, Tompkins C, Williams N, Wagner F. Quality of life in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1988;10:306-310.
  54. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96:804-810.
  55. Love JR, Irvine EJ, Fedorak RN. Quality of life in inflammatory bowel disease. *J Clin Gastroenterol* 1992;14:15-19.
  56. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. 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.
  57. Irvine EJ, Feagan BG, Wong CJ. Does self-administration of a quality of life index for inflammatory bowel disease change the results? *J Clin Epidemiol* 1996;49:1177-1185.
  58. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol* 1996;91:1571-1578.
  59. Gregor J, McDonald J, Klar N, Wall R, Atkinson K, Lamba B, Feagan BG. An evaluation of utility measurement in Crohn's disease. *Inflamm Bowel Dis* 1997;3:265-276.
  60. Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. *Gut* 1986;27:92-95.
  61. Olaison G, Sjodahl R, Tagesson C. Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. *Gut* 1990;31:325-328.
  62. Reproducibility of colonoscopic findings in Crohn's disease: a prospective multicenter study of interobserver variation. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Dig Dis Sci* 1987;32:1370-1379.
  63. 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 Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;30:983-989.
  64. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990;98:811-818.
  65. Landi B, Anh TN, Cortot A, Soule JC, Rene E, Gendre JP, Bories P, See A, Metman EH, Florent C, Lerebours E, Mary JY, Modigliani R. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1992;102:1647-1653.
  66. Cellier C, Sahnoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut* 1994;35:231-235.
  67. D'Haens G, Van Deventer S, Van Hogezaand R, Chalmers D, Kothe C, Baert F, Braakman T, Schaible T, Geboes K, Rutgeerts P. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 1999;116:1029-1034.
  68. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984;25:665-672.
  69. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;99:956-963.
  70. Hellers G, Cortot A, Jewell D, Leijonmarck CE, Lofberg R, Malchow H, Nilsson LG, Pallone F, Pena S, Persson T, Prantera C, Rutgeerts P. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology* 1999;116:294-300.
  71. Ewe K, Bottger T, Buhr HJ, Ecker KW, Otto HF. Low-dose budesonide treatment for prevention of postoperative recurrence of

- Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1999;11:277-282.
72. Caprilli R, Andreoli A, Capurso L, Corrao G, D'Albasio G, Gioieni A, Assuero Lanfranchi G, Paladini I, Pallone F, Ponti V, Rigo GP, Rossini FP, Sturniolo GC, Tonelli F, Valpiani D. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Aliment Pharmacol Ther* 1994;8:35-43.
  73. Brignola C, Cottone M, Pera A, Ardizzone S, Scribano ML, De Franchis R, D'Arienzo A, D'Albasio G, Pennestri D. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group. *Gastroenterology* 1995;108:345-349.
  74. Florent C, Cortot A, Quandale P, Sahmound T, Modigliani R, Sarfaty E, Valleur P, Dupas JL, Daurat M, Faucheron JL, Lerebours E, Michot F, Belaiche J, Jacquet N, Soule JC, Rothman N, Gendre JP, Malafosse M. Placebo-controlled clinical trial of mesalazine in the prevention of early endoscopic recurrences after resection for Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Eur J Gastroenterol Hepatol* 1996;8:229-233.
  75. Lochs H, Mayer M, Fleig WE, Mortensen PB, Bauer P, Genser D, Petritsch W, Raithel M, Hoffmann R, Gross V, Plauth M, Staun M, Nesje LB. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000;118:264-273.
  76. Korelitz B, Hanauer SB, Rutgeerts P, Present DH, Peppercorn M, Workgroup CS. Postoperative prophylaxis with 6-MP, 5-ASA or placebo in Crohn's disease: a 2 year multicenter trial (abstr). *Gastroenterology* 1998;114:A1011.
  77. Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. *J Clin Gastroenterol* 1984;6:123-127.
  78. D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology* 1998;114:262-267.
  79. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999;50:667-671.
  80. Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D, Geboes K, Rutgeerts PJ. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999;116:22-28.
  81. Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology* 1975;68:627-635.
  82. Farmer RG, Whelan G, Fazio VW. Long-term follow-up of patients with Crohn's disease. Relationship between the clinical pattern and prognosis. *Gastroenterology* 1985;88:1818-1825.
  83. Greenstein AJ, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, Aufses AH Jr. Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. *Gut* 1988;29:588-592.
  84. Sachar D, Andrews H, Farmer R, Pallone F, Pena A, Prantera C, Rutgeerts P. Proposed classification of patient subgroups in Crohn's disease. *Gastroenterology Int* 1992;5:141-154.
  85. Steinhart AH, Girgrah N, McLeod RS. Reliability of a Crohn's disease clinical classification scheme based on disease behavior. *Inflamm Bowel Dis* 1998;4:228-234.
  86. Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;6:8-15.
  87. Fredd S. Standards for approval of new drugs for IBD. *Inflamm Bowel Dis* 1995;1:284-294.
  88. European Agency for the Evaluation of Medicinal Products E. Points to consider on clinical investigation of medicinal products for the management of Crohn's disease, draft 5. EMEA website. Volume <http://www.emea.eu.int/pdfs/human/ewp/228499en.pdf>, 2000.
  89. Yaffe BH, Korelitz BI. Prognosis for nonoperative management of small-bowel obstruction in Crohn's disease. *J Clin Gastroenterol* 1983;5:211-215.
  90. Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994;35:360-362.
  91. Faubion WJ, Loftus EJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001;121:255-260.
  92. McLeod RS, Wolff BG, Steinhart AH, Carryer PW, O'Rourke K, Andrews DF, Blair JE, Cangemi JR, Cohen Z, Cullen JB, Chaytor RG, Greenberg GR, Jaffer NM, Jeejeebhoy KN, MacCarty RL, Ready RL, Weiland LH. Risk and significance of endoscopic/radiological evidence of recurrent Crohn's disease. *Gastroenterology* 1997;113:1823-1827.
  93. Vantrappen G, Rutgeerts P. Recurrence of Crohn's lesions in the neoterminal ileum after ileal resection and ileocolonic anastomosis. *Verh K Acad Geneesk Belg* 1990;52:373-382.
  94. Department of Health and Human Services. Gastrointestinal drugs advisory committee, discussion of guidance for the clinical development of drugs and biologics for Crohn's disease, volume II. <http://www.fda.gov/ohrms/dockets/ac/98/transcript/3423t2.rtf>. FDA Website, 1998.
  95. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;19:278-282.
  96. Prantera C, Cottone M, Pallone F, Annese V, Franze A, Cerutti R, Bianchi Porro G. Mesalamine in the treatment of mild to moderate active Crohn's ileitis: results of a randomized, multicenter trial. *Gastroenterology* 1999;116:521-526.
  97. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, Vatn M, Persson T, Pettersson E. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;339:370-374.
  98. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;41:209-214.
  99. Bar-Meir S, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, Reshef R, Odes S, Moshkovitz M, Bruck R, Eliakim R, Maoz E, Mittmann U. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology* 1998;115:835-840.
  100. Gross V, Andus T, Caesar I, Bischoff SC, Lochs H, Tromm A, Schulz HJ, Bar U, Weber A, Gierend M, Ewe K, Scholmerich J. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1996;8:905-909.
  101. Sutherland LR, Martin F, Bailey RJ, Fedorak RN, Poleski M, Dallaire C, Rossman R, Saibil F, Lariviere L. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1997;112:1069-1077.

102. Brignola C, Iannone P, Pasquali S, Campieri M, Gionchetti P, Belluzzi A, Basso O, Miglioli M, Barbara L. Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. *Dig Dis Sci* 1992;37:29-32.
103. Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. The Italian IBD Study Group. *Gastroenterology* 1992;103:363-368.
104. Gendre JP, Mary JY, Florent C, Modigliani R, Colombel JF, Soule JC, Galmiche JP, Lerebours E, Descos L, Viteau JM, Rene E, Metman EH, Bories P, Bremond A, Bouvry M, Lamouliatte H, Ginston JL. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Gastroenterology* 1993;104:435-439.
105. Thomson AB, Wright JP, Vatn M, Bailey RJ, Rachmilewitz D, Adler M, Wilson-Lynch KA. Mesalazine (Mesasal/Claversal) 1.5 g b.d. vs. placebo in the maintenance of remission of patients with Crohn's disease. *Aliment Pharmacol Ther* 1995;9:673-683.
106. Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezaand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;117:761-769.
107. McLeod RS, Wolff BG, Steinhart AH, Carryer PW, O'Rourke K, Andrews DF, Blair JE, Cangemi JR, Cohen Z, Cullen JB, Chaytor RG, Greenberg GR, Jaffer NM, Jeejeeboy KN, MacCarthy RL, Ready RL, Weiland LH. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995;109:404-413.
108. Modigliani R, Colombel JF, Dupas JL, Dapoigny M, Costil V, Veyrac M, Duclos B, Soule JC, Gendre JP, Galmiche JP, Danne O, Cadiot G, Lamouliatte H, Belaiche J, Mary JY. Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1996;110:688-693.
109. Cortot A, Colombel JF, Rutgeerts P, Lauritsen K, Malchow H, Hamling J, Winter T, Van Gossum A, Persson T, Pettersson E. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. *Gut* 2001;48:186-190.
110. Gross V, Caesar I, Andus T, Vogelsang H, Adler G, Malchow H, Weber A, Gierend M, Scholmerich J. Replacement of systemic steroids by oral budesonide in patients with post-active or chronic Crohn's ileocolitis - a dose finding study (abstr). *Gastroenterology* 1997;112:A987.
111. Gross V, Andus T, Ecker KW, Raedler A, Loeschke K, Plauth M, Rasenack J, Weber A, Gierend M, Ewe K, Scholmerich J. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. *Gut* 1998;42:493-496.
112. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;119:895-902.
113. Sandborn WJ, Tremaine WJ, Wolf DC, Targan SR, Sninsky CA, Sutherland LR, Hanauer SB, McDonald JW, Feagan BG, Fedorak RN, Isaacs KL, Pike MG, Mays DC, Lipsky JJ, Gordon S, Kleoudis CS, Murdock RH Jr. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. *Gastroenterology* 1999;117:527-535.
114. Feagan BG, Sandborn WJ, Baker J, Cominelli F, Sutherland LR, Elson C, Salzberg B, Archambault A, Bernstein C, Lichtenstein G, Heath PK, Hanauer SB. A randomized, double-blind, placebo-controlled, multi-center trial of the engineered human antibody to TNF (CDP571) for steroid sparing and maintenance of remission in patients with steroid-dependent Crohn's disease (abstr). *Gastroenterology* 2000;118:A655.
115. D'Haens G, Geboes K, Ponette E, Penninckx F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology* 1997;112:1475-1481.

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