

Assessment of disease activity in inflammatory bowel disease; relevance for clinical trials

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ABSTRACT

In patients with inflammatory bowel disease, assessment of disease activity is important in order to monitor and adjust therapy. In individual patients, disease evaluation is largely based on subjective symptoms. However, for disease evaluation in clinical trials, an objective and reproducible disease activity index is needed. At present, a number of activity indices are available for Crohn's disease and for ulcerative colitis. These indices may be distinguished in more subjective clinical indices, more objective endoscopic and histological indices, and in indices with combinations of both subjective and objective parameters. In the design of a new clinical trial, an appropriate disease activity index should be selected which is based on the patient selection criteria and the aims of the study.

INTRODUCTION

In clinical practice, the subjective assessment of disease activity is relevant for the treatment of individual patients with inflammatory bowel disease (IBD). For disease evaluation in clinical trials, this subjective assessment of disease activity should be translated into an objective disease activity index. Preferably, the index should consist of as few variables as possible, which are easily obtainable in any hospital and applicable in a majority of the patients. Furthermore, the index should be validated, objective, reproducible and accepted by physicians and investigators. Such an instrument is necessary to define the characteristics of patients taking part in therapeutic trials, and to compare the results of treatment. It may be expressed in discrete classes or as a continuous numerical scale. Because of the

differences in objectives of the studies and the variability in patient characteristics, no single disease activity scoring system can be applied for both ulcerative colitis and Crohn's disease. In the 1950s and 1960s the first disease activity indices were introduced.^{1,2} For disease activity in ulcerative colitis, Truelove and Witts introduced a three-grade scale of absent, mild, moderate and severe disease (*table 1*). For Crohn's disease, Best *et al.* developed the Crohn's disease activity index (CDAI), which has been used on a large scale in clinical trials. After multivariable regression analysis eight out of 18 variables were included in the CDAI (*table 2*).^{3,4} The recent introduction of (potential) new drugs in the treatment of inflammatory bowel diseases has revived interest in the assessment of disease activity. In the design of a new clinical trial, it is essential to select the appropriate index to

Table 1

Severity categories of ulcerative colitis (Truelove-Witts)²

MILD

Diarrhoea <4 times/day, non-bloody
No fever
Pulse rate <90 beats/min
ESR <30 mm/h

MODERATE

Intermediate between mild and severe

SEVERE

Diarrhoea >4 times/day, bloody
Haemoglobin 75% or below
Evening temperature >37.5°C
Pulse rate >90 beats/min
ESR >30 mm/h

ESR = erythrocyte sedimentation rate.

Table 2
Crohn's disease activity index (CDAI)^{3,4}

	SUM OF 7 DAYS	FACTOR	SUBTOTAL
Number of liquid or soft stools	---	2	---
Abdominal pain ¹	---	5	---
General well-being ²	---	7	---
Number of complications (presence or absence):			
Arthritis or arthralgia			
Iritis or uveitis			
Anal fissure, fistula or abscess	---	20	---
Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis			
Other fistula			
Fever over 37.8°C			
Loperamide or diphenoxylate for diarrhoea (none = 0, yes = 1)	---	30	---
Abdominal mass (none = 0, questionable = 2, definite = 5)	---	10	---
Haematocrit (males 47- Ht (%), females 42- Ht (%))	---	6	---
Body weight: (1- Body weight/standard weight) x 100 =	---	1	---
			CDAI total ---

¹ Pain score per day: 0 = none, 1 = mild, 2 = moderate, 3 = severe. ² General well-being score per day: 0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible. ³ Total number of complications from the list that are present.

Table 3
Factors influencing the choice for a disease index in inflammatory bowel disease

AIMS OF THE STUDY

Inflammatory activity
Symptoms of disease activity noticed by the patient: clinical activity
Quality of life
Endoscopic score or histological score

DISEASE VARIABLES

Crohn's disease or ulcerative colitis
Active disease, disease in remission, chronic active disease or refractory disease
Period of disease free interval
Effects on drug treatments
Location of the disease activity
Extraintestinal localisations: arthritis
Patient with a stoma or without
Adults or children, age at onset or diagnosis
Fistula: site, entero-cutaneous, postoperative
Perforating or nonperforating disease
Structuring or nonstructuring disease
Number of surgical resection
Extraintestinal symptoms

answer the aims of the study. In *table 3*, the main factors influencing the choice for a disease index are summarised. Recently, an international group of experts has published a consensus on endpoints for clinical trials in Crohn's disease.⁵

INDICES IN CROHN'S DISEASE

The most frequently used index for the assessment of disease activity in Crohn's disease is the CDAI (*table 2*). The outcome of the CDAI varies between 0 and 600 points. A score below 150 is associated with clinical remission, 150 to 219 with mildly active disease, 220 to 450 with moderately active disease and above 450 with very severe disease. This index is used in trials to select groups of patients based on the severity of the disease activity and to evaluate the effect of treatments. In most studies complete remission is defined by a value of less than 150 points, and clinical response is characterised by a decrease in CDAI of more than 70 to 100 points. The CDAI is also used to monitor patients for worsening of the disease during a trial. Relapse or reactivation of disease is defined as an increase in CDAI by more than 150 points or a score above 150 together with an increase by more than 50 to 100 points (not well defined). An increase in the index by more than 60 to 100 points or a disease activity of more than 200 at the end of the treatment period indicates treatment failure. Although it is broadly applied in clinical trials, substantial criticism has been raised. The inter-observer variability can be substantial because of differences in interpretation in variables that are part of the CDAI.⁶ This is due to the subjective variables that are included in the index. For instance, the patient scores important variables like 'Abdominal pain' and 'General well-being'. Also the number of liquid or soft stools is an important variable, more or less subjective, and influenced by the presence or absence of the ileum. Overflow of bile acids in the colon due to

resection of the ileum and the subsequent interruption of the entero-hepatic cycle may be the cause of diarrhoea without any inflammatory activity. Although it is a relevant score for improvement or worsening of the patient's symptoms, it is not representative for disease activity in the intestinal wall. The CDAI is a complex index and is difficult to calculate in daily clinical practice. A more suitable index has now been developed, which is known as the Harvey-Bradshaw index or Simple index.⁷ It includes five of the main variables of the CDAI and is easier to calculate, but has the same disadvantages. Other indices have also been developed such as the Therapeutic Goals Score,⁸ the Cape Town index⁹ and the index of the Organisation Mondiale de Gastro-Entérologie (OMGE)¹⁰ of which the Therapeutic Goals Score is not validated. These indices correlate quite well and are appropriate for assessment of improvement in the patient's symptoms in clinical trials.

For assessment of the quality of life in IBD patients, the Inflammatory Bowel Disease Questionnaire (IBDQ) has been introduced.¹¹⁻¹⁴ At present, this questionnaire is not frequently used in clinical trials.¹⁵

Because of the disadvantages of scoring systems based mainly on the complaints of the patient, an index mainly based on objective variables has been developed. This Van Hees index or Dutch index is partly based on the patient's symptoms but also on laboratory data and physical examination (*table 4*).¹⁶ The Van Hees index does not correlate well with the indices mentioned above; it is probably more appropriate for trials in which disease activity should be assessed and correlated with the inflammatory parameters such as cytokines.

In fistulising Crohn's disease, the CDAI is not the most suitable index because the presence or absence of fistulae is only one of a number of listed complications in the index. In 1980, the first attempt was made for an index evaluating fistula closure, but this index was not validated.⁸ Irvine proposed the Perianal Disease Activity Index with five categories and five grades for each category.¹⁷ However, not all the fistulae are perianal and no consensus has been reached about the criteria on activity of the fistulae, the period of inactivation of fistulae or the percentage of the number of fistulae that should be inactive. Recently, a simple and easily reproducible fistula drainage assessment score was described by Present *et al.* (*table 5*).¹⁸ This index is promising but should be validated in additional prospective trials.

The frequently applied indices to evaluate Crohn's disease are summarised in *table 6* and for the separate indices, all contributing variables are indicated.

Besides these clinical indices, there are other methods that can be used for assessment of disease activity. Radiological methods such as x-rays of the small bowel and colon are widely used. More recently, also sonography, computer tomography and magnetic resonance imaging techniques have been applied. For external fistulae photography may be useful. Disease activity may also be estab-

Table 4
*Van Hees index (VHI)*¹⁶

Serum albumin g/l	- x -5.48	---
ESR mm/h	- x 0.29	---
Quetelet Weight Height ² =	- x -0.22	---
Abdominal mass	- x 7.83	---
1 = 0 2 = questionable 3 = <6 cm 4 = 6-12 cm 5 = >12 cm		
Gender	- x -12.3	---
1 = male 2 = female		
Temperature °C	- x 16.4	---
Consistency of the stools	- x 8.46	---
1 = normal 2 = soft 3 = liquid		
Resection	- x -9.17	---
1 = none 2 = yes		
Extraintestinal manifestations	- x 10.7	---
1 = none 2 = yes		
	Total	---
Subtract		-209
	VHI	---

ESR = erythrocyte sedimentation rate.

Table 5
*Fistula drainage assessment*⁸

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% on at least two consecutive visits (i.e. at least four 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 on at least two consecutive visits (i.e. at least four weeks).

lished by the nuclear scintigraphy such as the ¹¹¹In-labelled leucocyte scan. Furthermore, scoring systems have been developed for the endoscopic disease activity assessment. Most frequently applied and also well validated is the Crohn's Disease Endoscopic Index of Severity (CDEIS).¹⁹ Rutgeerts *et al.* have described an endoscopic score for activity of Crohn's disease after surgical resection of the ileum.^{20,21} Korelitz and Sommers²² and D'Haens *et al.*²³

Table 6
Disease activity indices in Crohn's disease

	CDAI	HARVEY-BRADSHAW	VHI	OXFORD INDEX	CAPE TOWN INDEX
Abdominal pain	X	X		X	X
Bowel habits	X	X	X	X	X
Perianal complications				X	X
Other complications	X	X	X	X	X
Palpable mass	X	X	X	X	X
Body weight	X			X	X
Haemoglobin level	X			X	X
Well-being	X	X			X
Anti-diarrhoeal drugs	X				
Quetelet index			X		
Temperature			X	X	X
Serum albumen			X		
ESR			X		
Sex			X		
Bowel resections			X		
Tenderness				X	X
Fistula				X	

CDAI = Crohn's disease activity index, VHI = Van Hees index, ESR = erythrocyte sedimentation rate.

have proposed histological scores to evaluate the effect of medical treatment. The clinical relevance of these indices is a matter of debate because clinical symptoms will not only be influenced by the focal signs of the severity of the inflammatory process but also by the location and extent. However, these indices may be relevant in studies aiming at the effect of interventions on the inflammatory process in the intestinal mucosa.

INDICES FOR ULCERATIVE COLITIS

In ulcerative colitis, the intestinal inflammation is confined to the colon mucosa. In active disease, this results in specific symptomatology with frequent diarrhoea and blood loss. The first index to quantify disease activity in IBD patients was based on these symptoms and developed for ulcerative colitis specifically.^{1,2} This Truelove-Witts score was mainly used to characterise a severe relapse (*table 1*) and was frequently applied in clinical trials. The disadvantage of the index is the difficulty in classifying a number of patients to the appropriate disease category and changes in disease activity over time are difficult to quantify. Other activity indices have been proposed by various authors.²⁴⁻³⁰ The index by Talsted and Gjone²⁴ consists of 15 variables and is not applicable due to its complexity. Also the Powell-Tuck index,²⁵ consisting of ten items, has a low feasibility. Endoscopic assessment of disease activity is important,

because the complaints of a patients do not always represent the severity and extent of the disease. Severe proctitis of 10 cm, or less, may provoke more complaints than a moderate colitis over more than half the colon. Another advantage of endoscopy is the opportunity to obtain biopsies. Histology obtained in a remission period may demonstrate features of acute inflammation, which increases the risk on a relapse.³¹ Furthermore, dysplasia and malignant tumours may be established by endoscopy.³² Based on endoscopic findings, Dick *et al.* introduced a five-scale endoscopic index³³ and Rachmilewitz developed an endoscopic index, scoring for granularity, vascular pattern, vulnerability and mucosal damage. The Rachmilewitz score is numerical and has been used in clinical trials.²⁹ The Baron scale, distinguishing three grades of activity, is the most commonly used score to evaluate the degree of activity endoscopically.³⁴ To combine the advantages of the clinical Truelove score^{1,2} and the endoscopic Baron scale,³⁴ the Mayo score was developed.³⁰ Currently, the Mayo score is favourite in clinical studies. In *table 7* indices for the activity of ulcerative colitis are summarised, with the contributing variables.

CONCLUSIONS

For the evaluation of IBD in clinical trials, a variety of disease activity indices are available. The patient selection criteria and aims of the study are major determinants to select

Table 7
Most frequently used indices in ulcerative colitis

	INDEX			
	POWELL-TUCK	SUTHERLAND	RACHMILEWITZ	MAYO
Bowel frequency	X	X	X	X
Blood in stools	X	X	X	X
Well-being	X	X		
Abdominal pain	X		X	
Stool consistency	X			
Nausea	X			
Weight loss	X			
Extraintestinal signs	X		X	
Fever	X			
ESR			X	
Physician's global assessment				X
Sigmoidoscopy	X	X	X	X

ESR = erythrocyte sedimentation rate.

the activity index of choice. In Crohn's disease patients, the Van Hees index as an overall index seems suitable to evaluate inflammatory disease activity. For local mucosal monitoring, endoscopic and histological indices are preferable. For the quality of life evaluation, the IBDQ is preferred. To evaluate the clinical effect of treatment in a group of patients the CDAI is suitable. Furthermore, CDAI was most widely used in previous trials which enables comparisons with previous results. For evaluation of fistulising disease, specific indices are suggested. For ulcerative colitis, classification of the extent of the inflammation is essential. This can be performed by endoscopy or X-ray examination of the bowel. For the assessment of disease activity, clinical scoring lists are available. The activity index of choice contains endoscopic as well as clinical variables.

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