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## Monitoring Crohn's disease activity: clinical, endoscopic and histological indices

### Monitorowanie aktywności choroby Crohna: skala kliniczna, endoskopowa oraz histologiczna

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#### Summary

Crohn's disease (CD) together with ulcerative colitis (UC) belong to chronic gastrointestinal condition called inflammatory bowel disease (IBD). The clinical course of both disorders is similar and is characterized by exacerbations and spontaneous or drug-induced remissions but their histopathological features are different. Moreover, the various clinical patterns are reflected in the microscopic features observed in biopsies obtained during endoscopy, which is used for monitoring of disease activity. However, endoscopic mucosal biopsies do not show all the characteristic features of CD. In the last years, many disease-specific instruments, especially complex numeric activity indices to measure activity have been created. Therefore, the review of biopsies, in combination with clinical, laboratory, radiographic and endoscopic observations, is needed for both diagnosis and monitoring of IBD, and for the differentiation CD and UC from other conditions. The aim of this article is to make a revision of available clinical, endoscopic and histopathological scales used in common practice for diagnosis and monitoring of CD.

#### Streszczenie

Choroba Crohna (ang. *Crohn's disease* – CD) razem z wrzodziejącym zapaleniem jelita grubego (ang. *ulcerative colitis* – UC) należą do grupy nieswoistych chorób zapalnych jelit (ang. *inflammatory bowel disease* – IBD). Przebieg kliniczny obydwu chorób jest podobny i charakteryzuje się okresami zaostrzeń oraz remisji, jednak ich obraz histopatologiczny różni się między sobą. Ponadto, obraz mikroskopowy odzwierciedla stopień aktywności choroby i jest wykorzystywany do monitorowania przebiegu IBD. Jednak, w przypadku CD obraz endoskopowy nie zawsze oddaje wszystkie cechy charakterystyczne choroby. W ostatnim czasie pojawiło się wiele swoistych dla CD parametrów, zwłaszcza kompleksowych numerycznych skal służących do oceny aktywności choroby. Dlatego też całościowa ocena kliniczna, endoskopowa i histologiczna są niezbędne zarówno do postawienia rozpoznania, jak i do śledzenia przebiegu IBD, a także do różnicowania CD i UC od innych jednostek chorobowych. Celem artykułu jest omówienie dostępnych skal oceny klinicznej, endoskopowej i histologicznej IBD wykorzystywanych w praktyce klinicznej.

#### INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) belong to chronic gastrointestinal condition called inflammatory bowel disease (IBD). The clinical course of both disorders is similar and their most common symptoms are abdominal pain, diarrhea, often with bloody stools and malnutrition, typical for pediatric population (1). IBD is characterized by exacerbations and spontaneous or drug-induced remissions.

However, the histopathological features are different whether CD or UC. UC primarily affects the mucosa of the large bowel, while CD is a transmural disease that can affect the whole gastrointestinal tract (2). Moreover, the various clinical patterns are reflected in the microscopic features observed in biopsies obtained during endoscopy, which is used for monitoring of disease activity. Therefore, biopsies allow assessment of disease activity but also identification of

pre-cancerous lesions and cancer, which apply rather to adult patients than pediatric population. In CD, in contrast with UC, the rectum is not always involved and lesions in this type of IBD frequently occur in a background of normal mucosa (3). Thus, it is more appropriate to take multiple endoscopic biopsies in different segments of the colon (and ileum) during both initial work-up of a patient and while monitoring treatment efficacy (4). However, endoscopic mucosal biopsies do not show all the characteristic features of CD. Therefore, the review of biopsies, in combination with clinical, laboratory, radiographic and endoscopic observations, is needed for both diagnosis and monitoring of IBD, and for the differentiation CD and UC from other conditions. In the last years, many disease-specific instruments, especially complex numeric activity indices to measure activity have been created (5). Objective measures of activity in CD are very useful not only in everyday work but also in clinical trials to enroll homogeneous groups of patients and to evaluate their response treatment. Therefore, in order to be widely used, activity indices should be simple and easily reproducible. In this article, we make a revision of available clinical, endoscopic and histopathological scales used in common practice for diagnosis and monitoring of CD.

### Clinical activity scores

There have been few activity indices proposed so far: the Simple index (or Harvey Bradshaw index) (6), the Organization Mondiale de Gastroenterologie (OMGE) index (7), the Cape Town index (8) and **Crohn's Disease Activity Index (CDAI)** (9) **with its pediatric version – PCDAI** (10). However, only the last two are widely used in clinical practice. The CDAI was developed by Best et al. from the Midwest Regional Health Center in Illinois, in 1976 (9). The index consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI and weighting factors are collected in table 1.

Remission of CD is defined as CDAI below 150. Severe disease was defined as a value of greater than 450. Most major research studies on medications in CD define response as a fall of the CDAI of greater than 70 points (12, 13). PCDAI, on the other hand, is a specific tool for assessment of CD activity in children (age 6-17 years old). It ranges from 0 to 100. Remission is defined as score < 10, moderate disease as score between 11-30, active disease as score > 30, and severe CD as score > 50. Table 2 presents components of the PCDAI.

### Endoscopic activity scores

The endoscopic pattern of CD has been characterized and it is based on a number of mucosal lesions: erythema, cobblestoning, aphthoid ulcerations and ulcers of variable size and depth, fistulas, and stenosis (14). **There are 2 endoscopic scales**

**Table 1.** The components of the CDAI and weighting factors.

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for seven days	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	x 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	x 7
Presence of complications*	x 20
Taking Lomotil or opiates for diarrhea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Hematocrit of < 0.47 in men and < 0.42 in women	x 6
Percentage deviation from standard weight	x 1

\*One point each is added for each set of complications:

- the presence of joint pains (arthralgia) or frank arthritis
- inflammation of the iris or uveitis
- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- anal fissures, fistulae or abscesses
- other fistulae
- fever during the previous week

**which have been proposed for endoscopic activity assessment: Crohn's Disease Endoscopic Index of Severity (CDEIS), and more commonly used, and Simple Endoscopic Crohn's Disease Index (SES-CD).** The CDEIS has been proposed and validated in a large multicentre trial. Since then, it has been used as marker of mucosal healing (MH) in a number of therapeutic trials (15, 16). At present it represents the gold standard for evaluation of endoscopic activity. Table 3 presents parameters and scoring system of CDEIS.

However, the correlation of CDEIS with clinical activity seems to be poor (16). Moreover, although reliable and reproducible, it is time consuming and elaboration of the score requires analogue scale transformation. That is why, this endoscopic score is rather unsuitable for everyday clinical practice. Therefore, SES-CD has been proposed recently. This simple, reproducible, and easy-to-use endoscopic scoring system for CD is based on the score of 0-3 of the following four endoscopic variables: ulcer size, ulcerated and affected surfaces, and stenosis determined in five ileocolonic segments (17). MH is defined as the complete absence of ulcers or a significant decrease in SES-CD as a sign of inflammatory lesions decrease in the presence of ulcerated surfaces, while stationary endoscopic features stood for the lack of progression or regression. It is easier and faster to score and calculate than CDEIS, and its results are reproducible and reliably correlating with the present standard.

### Histopathological activity assessment

At first, it is important to underline that, so far, there is no standardized histological scoring system for the assessment of disease activity in IBD, although many scores have been proposed. Most of

**Table 2.** The components of the PCDAI and weighting factors.

Parameter	Description	Score		
Abdominal pain	None	0		
	Mild – brief, does not interfere with activities	5		
	Mod/severe – daily, longer lasting affects activities, nocturnal	10		
Stools (per day)	Formed stools or up to 1 liquid stool, no blood	0		
	Up to 2 semi-formed with small blood, or 2-5 liquid with or without small blood	5		
	Any gross bleeding, or $\geq 6$ liquid, or nocturnal diarrhea	10		
Patient Functioning – General Well-Being	No Limitation of activities, well	0		
	Occasional difficulty in maintaining appropriate activities, below par	5		
	Frequent limitation of activity, very poor	10		
<b>Laboratory</b>				
Hematocrit %	< 10 yr > 33	11-14 (M) > 35	0	0
	28-32	30-34	2.5	2.5
	< 28	< 30	5	5
	15-19 (M) > 37	11-19 (F) > 34	0	0
	32-36	29-33	2.5	2.5
	< 32	< 29	5	5
ESR (mm/hr)	< 20		0	
	20-50		2.5	
	> 50		5	
Albumin (g/dl)	> 35		0	
	31-35		2.5	
	< 31		5	
<b>Examination</b>				
Weight	Weight gain or voluntary weight stable/loss		0	
	Involuntary weight stable, weight loss 1-9%		5	
	Weight loss $\geq 10\%$		10	
Height	< 1 channel decrease		0	
	$\geq 1$ , < 2 channel decrease		5	
	> 2 channel decrease		15	
Abdomen	No tenderness, no mass		0	
	Tenderness, or mass without tenderness		5	
	Tenderness, involuntary guarding, definite mass		10	
Perirectal disease	None, asymptomatic tags		0	
	Inflamed tags or 1-2 indolent fistula(e) or fissure(s), scant drainage, no tenderness		5	
	Active fistula, drainage, tenderness, or abscess		15	
<b>Extraintestinal Manifestations</b>				
Fever $\geq 38.5^\circ\text{C}$ for 3 days over past week, oral ulcers, definite arthritis, uveitis, erythema nodosum, pyoderma gangrenosum	None		0	
	One		5	
	$\geq$ Two		10	

them were introduced for UC (18), probably due to the more homogeneous distribution of the lesions in comparison to CD. Moreover, even recent consensus conferences on IBD have not included a formal histological score for the pathological evaluation of disease activity. This may be due to the possible impact of sampling error, on one hand, and to the limits of routine haematoxylin-eosin (HE) staining, as well as to the existence of some poorly known

variables, on the other hand. Histologically, disease activity is usually based upon the combination of the presence of neutrophils and epithelial damage. It is because neutrophils can be recognized reliably and it is known that they release molecules that are capable of damaging the tissue. The activity status of other inflammatory cells such as macrophages and lymphocytes can however not be assessed on HE-stained sections. D'Haens et al. published in

**Table 3.** The components of the Crohn's Disease Endoscopic Index of Severity (CDEIS) and weighting factors.

	Ileum	Sigmoid and left colon	Transverse	Right colon	Rectum	
Deep ulcerations (0 if non: 12 points if present)	0	0	0	0	0	Total 1+0
Superficial ulcerations (0 if non: 12 points if present)	0	0	0	0	0	Total 2+0
Surface involved by disease (cm)	20	0	0	0	0	Total 3+20
Surface involved by ulcerations (cm)	0	0	0	0	0	Total 4+0
						TOTAL A 20
Number of segments explored (1-5)						n 5
Total A/n						TOTAL B 4
If ulcerated stenosis is present anywhere add 3						C 0
If non-ulcerated stenosis is present anywhere add 3						D 0
TOTAL B + C + D = CDEIS score						4

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Gastroenterology, a Histologic Disease Activity in CD. Based upon a combination of following variables: epithelial damage, architectural changes, and different inflammatory cells infiltration (19). Table 4 presents histologic scoring system by D'Haens. How-

**Table 4.** Histologic Disease Activity in CD (21).

Histologic variable	Score
Epithelial damage	0-2
Architectural changes	0-2
Mononuclear infiltrate in LP	0-2
PMN infiltrate in LP	0-2
PMN infiltrate in epithelium	1-3
Erosion/ulcers	0-1
Granulomas	0-1
Proportion of biopsies affected	0-3

PMN – polymorphonuclear leukocytes

ever, major shortcomings of any histologic scoring system are that correlation between histological changes and clinical improvement is poor, and all these scores are not validated prospectively. Therefore, there is still a great need for proper exploratory studies on that issue. Since, it seems that histological healing should be considered as an end point in the treatment of IBD patients, additional studies looking for optimal sampling, standardizing scores and features should be performed.

**CONCLUSIONS**

The review of biopsies, in combination with clinical, laboratory, radiographic and endoscopic observations, is needed for monitoring of CD. Objective measures of activity in CD are very useful not only in everyday work but also in clinical trials. That is why, activity indices should be simple and easily reproducible. Currently, there are clinical (CDAI/PCDAI) and endoscopic (SES-CD) activity standardized scoring systems approved and widely used for CD. However, no formal histological score for the pathological evaluation of disease activity has been established so far.

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