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Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study

GROUPE D'ETUDES THÉRAPEUTIQUES DES AFFECTIONS INFLAMMATOIRES DU TUBE DIGESTIF (GETAID) PRESENTED BY J Y MARY AND R MODIGLIANI

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SUMMARY **The aim of this study was to develop and validate an endoscopic index for assessing the severity of Crohn's disease. Endoscopic findings were prospectively collected by a multicentre group in 75 patients with Crohn's colitis according to a previously validated procedure. The presence of nine preselected lesions was recorded in the following segments (1) rectum, (2) sigmoid and left colon, (3) transverse colon, (4) right colon, and (5) ileum. In addition the extent of the diseased and ulcerated areas were estimated in each segment. These segmental data were recorded on a standard form, together with the endoscopist's global estimate of lesion severity. A stepwise multiple regression was used to derive an index which was correlated with the endoscopist's global evaluation of lesion severity. Four mucosal lesions: deep and superficial ulcerations, ulcerated and non-ulcerated stenosis, and both estimates of extent involved were selected and weighted to obtain a Crohn's Disease Endoscopic Index of Severity which correlated with the endoscopist's global appraisal of lesion severity (r=0·83). This index was then prospectively shown to be valid in a further series of 113 colonoscopies (r=0·81). The index was calculated in 54 patients with active Crohn's disease, before and at the end of a course of corticosteroids: index variations correctly reflected changes in colitis severity as evaluated by the endoscopists (r=0·72). For endoscopists familiar with the data collection procedure, this Crohn's Disease Endoscopic Index of Severity should be of value in the follow up of patients, especially in clinical trials.**

Several indices[1–3] have been proposed to measure the activity (and/or severity) of Crohn's disease (CD) and used to evaluate drug efficacy in therapeutic trials.[4,5] All these indices are based only on clinical and/or biological data. Endoscopy is considered as essential for evaluation of new drugs in most digestive diseases; it is also routinely used in the management of patients with CD; yet endoscopic findings have never been taken into account in therapeutic trials in CD.

In a previous paper,[6] we showed that it was feasible for a cooperative multicentre group to collect, in a standardised way, reproducible endoscopic data in Crohn's colitis. The aim of the present study was to elaborate and validate a Crohn's Disease Endoscopic Index of Severity (CDEIS), reflecting endoscopists' global appraisals of lesion severity.

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Table 1 *List of the nine mucosal lesions recorded*

Lesions	*Definitions or specifications*
1 Pseudopolyp	–
2 Healed ulceration	Whitish area with a 'ground glass' appearance
3 Frank erythema (plaques, bands or diffuse)	Slight or moderate erythema should be neglected
4 Frankly swollen mucosa	Slight or moderate mucosal swelling should be neglected
5 Aphthoid ulceration	Defined as a tiny (2–3 mm), raised or flat red lesion with a white centre
6 Superficial or shallow ulceration	Defined as any ulceration which was neither aphthoid nor deep
7 Deep ulceration	Only frankly deep ulcerations should be recorded under this heading
8 Non ulcerated stenosis	Should be impossible or difficult to pass with an adult endoscope
9 Ulcerated stenosis	Should be impossible or difficult to pass with an adult endoscope

Methods

PROTOCOL

The study was conducted over a two year period by a group of gastroenterologists and endoscopists from 13 university medical centres.

PATIENTS

All patients with colonic or ileocolonic CD were included, provided they had not undergone previous proctocolectomy or total colectomy with ileorectal anastomosis. Crohn's disease was diagnosed on the basis of a previously published[7] and validated diagnostic scoring system. Clinical severity of CD was judged by the Crohn's Disease Activity Index[1] or CDAI.

DATA COLLECTION

A standardised form was used to report endoscopic findings which included segmental data and a global estimate of lesion severity.

Segmental data

The intestine was divided into five segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum, and the following data collected for each segment: (a) The presence of mucosal lesions was recorded by ticking a list of nine items (Table 1); (b) The percentage of the segmental surfaces, involved by the disease (SSD) – taking into account only these nine lesions – and by ulcerations (SSU) only were recorded, by positioning a cross on two 10 cm linear analogue scales, between 0 (no lesion or no ulceration at all) and 10 (lesions or ulcerations involving 100% of the segmental surface). For colonic segments only partially explored and for ileum, the 10 cm scale represented the area actually seen.

Global data

The endoscopists indicated a global evaluation of lesion severity (GELS) by positioning a cross on a 10 cm linear analogue scale.

LEARNING SET SAMPLE AND REPRODUCIBILITY ASSESSMENT

The learning set included 75 endoscopies carried out on 75 patients (Table 2). Each of these colonoscopies was done simultaneously by two endoscopists following a protocol previously described[6]: one handled the instrument while the other inspected through the teaching tube. Both physicians then recorded their findings independently on standardised forms. They were not allowed to exchange any information until the procedure was finished and the forms completed. One endoscopist of each pair was selected randomly through a permutation table of size 2 and his findings used for the construction of CDEIS. Data recorded by both members of the pair were used to test CDEIS reproducibility.

TEST SET SAMPLE

The test set, as shown in Table 2, was a sample of 103 further colonoscopies done on different CD patients. In order to check the ability of CDEIS to evaluate visit-to-visit changes in lesion severity, a colonoscopy was performed on 54 patients with clinically active CD (CDAI>150) and repeated after a three to five weeks' course of oral prednisone (1 mg/kg bw/day).

STATISTICAL ANALYSIS

Statistical procedures were designed to derive from independent variables, describing lesion nature and surfaces, an endoscopic index highly correlated with the dependent variable, the GELS.

Independent variables

Data concerning each segmental item were available for each segment explored – that is, usually five for each endoscopy. In order to achieve a single figure by endoscopy for each item, the following calculations were carried out: (1) The average segmental surfaces involved by the disease (ASSD) was calculated by dividing the sum of SSD by the number of segments explored at each endoscopy. An identical calculation was performed with SSU to obtain the average segmental surfaces involved by ulcerations only (ASSU). (2) For each mucosal lesion, two variables were derived: (a) the first (PRES) was either 0 if the lesion was not seen at all or 1 if it was seen at least once at a given endoscopy; (b) the second – the

Table 2 *Number of colonoscopies (patients) and of endoscopist pairs per centre in the learning set, and number of colonoscopies and of endoscopists per centre in the test set and in the visit-to-visit change sample*

	Learning set		*Test set*		*Visit-to-visit changes*	
Centres	*Patients*	*Endoscopist pairs*	*Patients*	*Endoscopists*	*Patients*	*Endoscopists*
Bichat Hospital (Paris)	10	1	9	3	5	3
Mondor Hospital (Paris)	5	1	4	3	3	2
Rothschild Hospital (Paris)	5	1	10	2	4	3
St Lazare Hospital (Paris)	5	1	39	3	25	3
	10	1				
	10	1				
	5	1				
St Antoine Hospital (Paris)			2	1	2	1
Regional Hospital (Pontoise)			2	1	1	1
University Hospital (Paris)			5	3		
St André Hospital (Bordeaux)	5	1	2	2		
Nicolle Hospital (Rouen)	5	1	6	2	1	1
St Eloi Hospital (Montpellier)	5	1	3	2	1	1
Lyon-Sud Hospital (Lyon)	5	1	1	1		
Regional Hospital (Lille)	5	1	14	3	12	3
Regional Hospital (Tours)			6	3		
Total	75	12	103	29	54	18

individual segmental rectocolonic frequency (ISRCF) – was calculated by dividing the number of segments in which a lesion was seen by the number of segments examined. Thus ISRCF could take a series of values from 0 (lesion not seen in any of the segments explored) to 1 (lesion seen in all segments explored).

Dependent variable

The dependent variable was the GELS.

Table 3 *Frequency (percentage) of each lesion detection per segment explored in the learning and test sets, mean and standard deviation of surface (expressed in cm on a 10 cm linear analogue scale) involved by the disease and by ulcerations only per segment explored*

	Learning set 75 colonoscopies 314 segments	*Test set 103 colonoscopies 405 segments*
Frequency of lesion detection (%)		
Pseudopolyp	105 (33·4)	117 (28·9)
Healed ulceration*	28 (8·9)	63 (15·6)
Frank erythema	76 (24·2)	96 (23·7)
Frankly swollen mucosa	62 (19·7)	66 (16·3)
Aphthoid ulceration	55 (17·5)	56 (13·8)
Superficial or shallow ulceration	146 (46·5)	190 (46·9)
Deep ulceration	68 (21·6)	87 (21·5)
Non ulcerated stenosis	7 (2·2)	4 (1·0)
Ulcerated stenosis	11 (3·5)	10 (2·5)
Mean [SD] (cm)		
SSD	2·4 [1·9]	2·4 [1·9]
SSU	1·1 [1·1]	1·1 [1·2]

*Significative difference in healed ulceration frequencies between learning and test sets ($p<0·05$).

INDEX CONSTRUCTION

Relationships between the dependent and independent variables were assessed through the classical correlation coefficient for the lesion ISRCF and surfaces and by Student's *t* test for the lesion PRES.[8]

Multiple linear regression methods were used to define the linear combination of independent variables which had the highest correlation value with the dependent variable. In order to simplify the calculation of the index, independent variables were selected successively by a stepwise regression method, using the classical F test at each step.[9] The BMDP package was used for this purpose.[10] Applicability of the method was assessed by examining residuals against predicted values.[11]

Initially only mucosal lesions (ISRCF and PRES) were included as independent variables in the stepwise multiple linear regression. Subsequently tests were made taking into account the surface variables (ASSU and ASSD) to determine whether an improved prediction could be obtained.

INDEX VALIDATION

The reproducibility of CDEIS and GELS were assessed by the intraclass correlation coefficient[12] using results obtained from the paired endoscopists in the learning set sample.

Crohn's Disease Endoscopic Index of Severity validation was first carried out by estimating the correlation between the calculated index and GELS in the test set. Changes in GELS were then correlated with the corresponding changes in CDEIS when two successive endoscopies, before and after treatment, were carried out on the same patient.

Table 4 *Correlation between GELS (global evaluation of lesion severity) and independent variables*

	Correlation coefficient (p)	
Lesion	*ISRCF**	*PRES**
Pseudopolyp	·072 (NS)	·017 (NS)
Healed ulceration	−·246 (·05)	−·120 (NS)
Frank erythema	·118 (NS)	·121 (NS)
Frankly swollen mucosa	·427 (·001)	·391 (·001)
Aphthoid ulceration	−·025 (NS)	·071 (NS)
Superficial ulceration	·372 (·001)	·248 (·05)
Deep ulceration	·626 (·001)	·560 (·001)
Non ulcerated stenosis	·103 (NS)	·046 (NS)
Ulcerated stenosis	·225 (·05)	·196 (NS)
Surface		
ASSD†	·687 (·001)	
ASSU†	·717 (·001)	

*ISRCF: number of segments exhibiting the lesion divided by the number of explored segments.
PRES is taken to be 1 if the lesion is seen at least once at a given endoscopy and 0 otherwise.
†ASSD: Average surface involved by the disease.
ASSU: Average surface involved by ulcerations only.

Results

PATIENT DESCRIPTION

Among the 75 colonoscopies of the learning set, 75 reached the splenic flexure, 73 the right flexure, 65 the caecum, and 26 the ileum. In the test set of 103 colonoscopies, the corresponding figures were 101, 89, 74, and 39. No complication occurred in these patients.

Clinical severity of CD evaluated by CDAI was determined in 73 and 99 subjects in the two samples respectively. Sixty six and 62% of patients of the learning and test sets respectively had active disease (CDAI>150).

Table 3 shows the segmental frequency of each detected lesion in the learning and test sets respectively. The only difference between the two groups of patients was a higher incidence of healed ulcerations in the test set ($p<0·05$).

INDEX CONSTRUCTION AND CALCULATION

Table 4 gives the correlation coefficients between GELS and each independent variable.

Table 5 indicates the variables successively selected by the stepwise multiple linear regression method with their corresponding coefficients.

Coefficients were standardised by dividing by the smallest coefficient and rounded to allow straightforward calculation of CDEIS. The final formula for CDEI calculation is as follows:

Table 5 *Variables selected by the multiple linear regression method: selection rank and corresponding coefficients*

	Rank	Coefficient
ISRCF (deep ulceration)	1	56·6
ISRCF (superficial ulceration)	2	24·6
PRES (ulcerated stenosis)	3	12·9
PRES (non-ulcerated stenosis)	4	14·5
ASSD	5	4·0
ASSU	6	3·7

CDEIS = 12×ISRCF (deep ulcerations)
+6×ISRCF (superficial ulcerations)
+ ASSD
+ ASSU
+3×PRES (non ulcerated stenosis)
+3×PRES (ulcerated stenosis)

One example is given in Table 6. The correlation coefficient between CDEIS and GELS was 0·83 ($p<0·001$) in the learning set. The Figure shows the scatterplot of GELS *versus* CDEIS.

INDEX VALIDATION

The reproducibility of CDEIS and GELS, as assessed with the learning set of data recorded by two endoscopists having performed the colonoscopy simultaneously, was excellent: the intraclass correlation values were 0·96 and 0·86 respectively ($p<0·001$).

In the test set (n=103), the correlation coefficient between CDEIS and GELS was still high (0·81, $p<0·001$). In the 54 patients, who underwent colonoscopy twice (the first one while the disease was clinically active and the second after a three to five weeks' course of oral prednisone), the visit-to-visit change in CDEIS was highly correlated with the corresponding change in GELS ($r=0·72$, $p<0·001$).

Discussion

Since its introduction in gastroenterology, fibreoptic endoscopy has been a routine procedure not only for diagnosis but also for evaluation of therapy both in individual patients and in therapeutic trials. Nowadays no one would imagine a therapeutic trial in – for example, reflux oesophagitis, peptic ulcer, or ulcerative colitis which completely ignored endoscopic healing rates. Yet, this is the way in which therapeutic trials in CD have been carried out so far, all the indices of activity and severity being purely clinicobiological.[1-3] An attempt has been made to evaluate morphological changes by barium *x*-ray examination in the National Cooperative Crohn's Disease Study,[13] but the results were disappointing, showing that radiological changes did not correlate with clinical response and hence were not valuable in assessing response to therapy.

Table 6 *Format for calculation of the Crohn's Disease Endoscopic Index of Severity (CDEIS) shown with an example*

	Rectum		Sigmoid and left colon		Transverse colon		Right colon		Ileum			
Deep ulceration quote 12 if present in the segment 0 if absent	0	+	0	+	12	+	0	+	/	=	12	Total 1
Superficial ulceration quote 6 if present in the segment 0 if absent	0	+	0	+	6	+	6	+	/	=	12	Total 2
Surface involved by the disease measured in cm*	0·0	+	2·0	+	8·0	+	6·0	+	/	=	16·0	Total 3
Ulcerated surface measured in cm*	0·0	+	0·0	+	6·0	+	1·5	+	/	=	07·5	Total 4
Total 1 + Total 2 + Total 3 + Total 4 =										=	47·5	Total A
Number (n) of segments totally or partially explored (1-5)										=	4	n
Total A divided by n										=	11·9	Total B
Quote 3 if ulcerated stenosis anywhere, 0 if not										+	0	C
Quote 3 if non ulcerated stenosis anywhere, 0 if not										+	3	D
Total B + C + D										=	14·9	CDEIS

+ for partially explored segments and for the ileum, the 10cm linear scale represents the surface effectively explored

*For partially explored segments and for the ileum, the 10 cm linear scale represents the surface effectively explored.
The findings at this colonoscopy are as follows:
(a) normal rectum;
(b) presence of non-ulcerative lesions involving 20% of the sigmoid and left colon area;
(c) 80% of the transverse colon area was diseased including superficial and deep ulcerations; the ulcerations represent 60% of the segment surface;
(d) the right colon was incompletely explored, due to a non ulcerated stenosis, 60% of the explored right colon was diseased, 15% being accounted for by superficial ulcerations;
(e) ileum was not reached.
No ulcerated stenosis was seen anywhere.

Although colonoscopy is superior to barium studies in assessing the extent and severity of CD,[14-17] the complexity and unpredictable topography of CD mucosal lesions have probably hampered the use of colonoscopic data in therapeutic trials so far. Thus we felt it useful to test whether it was possible to elaborate, on a multicentric basis, an endoscopic index capable of assessing the severity of mucosal lesions in colonic or ileocolonic CD, using a method inspired from that used by Best *et al*[1] to construct CDAI.

The method used in the present work to collect endoscopic data in CD has been validated in a previous study,[6] which assessed interobserver variation for each endoscopic finding. Interobserver agreement was good to excellent for the following items: pseudopolyps, superficial and deep ulcerations, ulcerated and non-ulcerated stenosis, SSD, SSU, and GELS.

The aim of the present work was (a) to derive from the previously mentioned descriptive items an endoscopic index reliably predicting GELS; (b) to validate this index.

The first step in CDEIS construction was to choose how to express in a single value, the endoscopic features available for each segment explored (usually five times per ileocolonoscopy). Segmental lesion and ulceration surfaces were scored between 0 and 10. The most straightforward procedure was to average the values obtained for each segment. For each of the nine elementary mucosal lesions, two different variables were tested, PRES and ISRCF. The former could take only the values 0 or 1 (lesion not seen at all or lesion seen once or more at a given

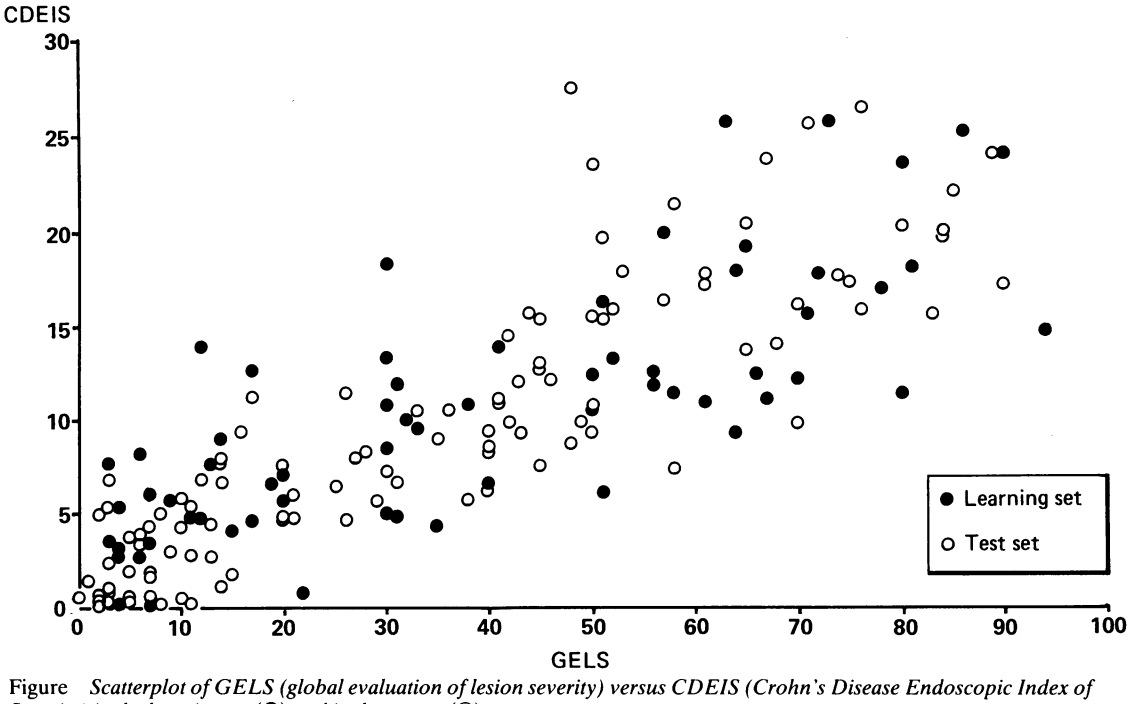

Figure *Scatterplot of GELS (global evaluation of lesion severity) versus CDEIS (Crohn's Disease Endoscopic Index of Severity) in the learning set* (●) *and in the test set* (○).

endoscopy, respectively). The latter variable (ISRCF) was the ratio of the number of segments exhibiting the lesion to the number of segments examined. The rationale for using this procedure was that we anticipated the predictive value of some lesions – that is, their contribution to GELS, to depend mainly on their presence anywhere, regardless of the number of segments involved, while for other lesions the mono versus plurisegmental location would also influence the endoscopist's judgment.

In a second step all recorded endoscopic items were tested regardless of their level of reproducibility found in the previous interobserver study.[6] As shown on Table 4, the correlations between GELS and endoscopic items were extremely variable: (1) Frank erythema, stenosis (whether ulcerated or not), pseudopolyps and aphthoid ulcerations showed no or borderline correlation with GELS, suggesting that their presence does not influence the endoscopist's judgment on the overall severity of colitis. Several factors, however, may have contributed to this finding. Frank erythema was shown in the previous reproducibility study[6] to exhibit large interobserver variation and this may have blurred a weak correlation. On the other hand, stenoses of both types were reproducible and their lack of correlation with GELS is obviously accounted for by their low incidence. Consistent with this view is the fact that they were selected by the regression procedure. Finally, pseudopolyps and aphthoid ulcers were frequent and reproducible, but their presence does not seem to influence the endoscopist's global evaluation of colitis severity; (2) Despite the previously observed large interobserver variation,[6] mucosal oedema ('swollen mucosa') was significantly correlated with GELS; yet it was not selected by the regression procedure which means that it was closely linked with at least one of the variables shown in Table 5. Indeed, when deep ulcerations were introduced in the stepwise linear regression, the relationship between GELS and swollen mucosa disappeared; (3) Finally superficial and deep ulcerations, ASSU and ASSD were, as expected, strongly correlated with GELS.

It is both interesting and reassuring that the lesions selected by the regression procedure were among those for which the highest reproducibility had been shown in our previous paper.[6] This really makes sense, indicating that endoscopists reliably recognised the endoscopic items they felt to be important indicators of severity.

Crohn's Disease Endoscopic Index of Severity was

then validated on a test sample of patients entirely different from those from which it had been constructed, as should be done with any index of this type. The quality of the prediction remains quite good in the test set. Furthermore, CDEIS also reflected quite satisfactorily the visit-to-visit changes in endoscopic severity.

None of the clinicobiological indices of CD activity of CD activity had their reproducibility tested, when first published. A recent study has in fact shown large interobserver variation for most of them.[18] In our study, CDEIS reproducibility was tested by the endoscopist pair method and shown to be excellent (intraclass correlation value of 0·96). This low interobserver variation probably reflects the long cooperative phase which preceded the reproducibility study.[6]

In conclusion, the final CDEIS illustrated by an example in Table 6 meets the following requirements: (1) it is well correlated with the endoscopist's judgment of the overall severity of the lesions; (2) the quality of the prediction is stable when evaluated on a set of patients different from that used for its elaboration; (3) it shows quite well visit-to-visit changes consistent with the modifications perceived by the endoscopists; (4) it incorporates items intuitively considered as important by experienced endoscopists; (5) it includes only items previously shown to be reproducibly collected, and is itself highly reproducible; (6) it is simple to calculate. Crohn's Disease Endoscopic Index of Severity should prove useful in conjunction with clinicobiological indices to elaborate better therapeutic trials in CD. Crohn's Disease Endoscopic Index of Severity is not, however, immediately applicable everywhere, because it relies entirely on a precise and specific data recording procedure which must be learnt beforehand: for an experienced endoscopist the training period should probably include five ileocolonoscopies done with a colleague already familiar with the method. This requirement which may limit the use of CDEIS is in fact a reflection of the complexity of CD endoscopic picture, and as such, thus seems difficult to circumvent.

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