REVIEW PAPER

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Clinical assessment of inflammatory bowel disease activity: a critical overview

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ABSTRACT

Crohn's disease (CD) and ulcerative colitis (UC), which belong to the group of inflammatory bowel diseases (IBD), are chronic inflammatory conditions of the gastrointestinal (GI) tract. Over the last eighty years the overview of IBD has evolved, along with disease symptom recognition, hypotheses on etiology and recommendations for clinical treatment. This review focuses on the clinical aspects of IBD throughout the years and discusses the most recent and future concepts in IBD diagnosis.

Keywords: disease activity index; disease classification; endoscopic and histopathological changes.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), which belong to the group of inflammatory bowel diseases (IBD), are chronic inflammatory conditions of the gastrointestinal (GI) tract. IBD affect up to 5–10% of worldwide population and currently their etiology remains unknown, although several factors, such as dysregulation of the immune and nervous system functions and changes in gut microflora have been suggested [1].

CD was first mentioned in 1903 by Leśniowski [2] and the full description of the disease was provided by Crohn in 1932 [3]. CD may reveal at any age, but most commonly its symptoms are observed in 15 to 30-year-old patients. A consecutive, small peak of CD incidence is also reported in patients between 40 and 60 years of age. The main manifestations of CD are GI lesions, which are most frequently observed in distal part of ileum, caecum and all parts of the large intestine, but not in rectum. Furthermore, upper parts of the digestive system may be affected as well. Other symptoms of CD include abdominal pain, escalating after the meal and localized in the region of umbilicus or in right iliac fossa. Fever, lasting a few days or even weeks, nausea and vomiting, diarrhea and weight loss may also occur. Moreover, there are frequent manifestations associated with CD outside the GI tract, such as arthritis, iritis, skin lesion and primary sclerosis cholangitis (PSC).

UC was first described in 1875 by Wilks and Moxon [4]. The onset of UC may reveal at any age, but most frequently it occurs in 15 to 40 year old patients, with second peak observed between 50 and 80 years of age. Contrary to CD, UC may be restricted only to rectum, or to rectum and colon. Moreover, while in CD non-inflamed parts of intestine are observed, the inflammation in UC is more continuous. The main symptoms of UC are bloody diarrhea (up to 20 stools per day), rectal urgency and rectal tenesmus. UC may also manifest by abdominal pain associated with defecation and localized in left iliac fossa. In UC, the extra-intestinal manifestations, similar to those seen in CD patients, are observed.

In this review we give a comprehensive outline of clinical, endoscopic and histological indices used in IBD classification and critically discuss by comparing their theoretical usefulness to practice. We also sug-

gest further directions in the design of IBD indices based on clinical experience with those currently used. The experimental results discussed in this review were obtained from a systematic literature search carried out by consulting electronic scientific databases, including MEDLINE, SCOPUS and Web of Science, electronic editorial networks, such as BMJ, Blackwell, Elsevier, Karger, Nature Publishing Group, Springer, and literature distributors. The scientific papers were selected according to the time span ranging principally from 2000 to present.

Disease classification throughout the years

Crohn's disease

As it was shown in numerous studies, CD is a heterogeneous entity (for review, see: [5, 6]) and thus it is usually divided into several subgroups to facilitate the work of both, a clinician and a scientist. Clinician's benefits from a multistage disease classification include simplified assessment of disease prognosis and a relatively easier choice for a successful patient therapy. In case of scientists, a multiscale classification may facilitate the research on understanding the pathomechanisms of the disease.

The Rome classification for CD, established in 1991, included anatomic location and behavior (inflammatory, fistulising, stenotic) of the disease in the GI tract, extent of lesions and operative history. As it turned out to be insufficient and had not been widely used, international Working Party met in Vienna in 1998 to adjust and to update the classification with the most recent findings [7]. New classification contained the age of onset of the disease; changes to the disease behavior and location were also made (**Table 1**).

In 2001, Louis et al. showed, using inter alia phenotype-genotype analyses that the location of lesions is the most reliable component of CD classification, while its behavior varies as the disease progresses [8]. Subsequently, in 2005 the National Working Party presented in Montreal a modified Vienna classification [9]. An overall division based on age at diagnosis, disease location and behavior remained unchanged, but several new features were introduced (**Table 1**). To begin with, the group of the youngest patients was included in the age of onset and thus the former A1 category was split into A1, which now indicated the age of onset before 16 years and A2, from 17 to 40 year old patients. As for location, the L4 modifier was introduced to allow CD in the upper GI tract coexist with disease manifestations in other parts of the digestive system. Additionally, the perianal disease modifier has been included in the behavior section.

It is well known that pediatric patients suffering from any disease need special approach and no exceptions should be made for IBD. Several weaknesses involving pediatrics patients affected by CD were found in the Montreal classification. Thus, pediatric experts met in Paris in 2011 to adjust the existing classification to be more suitable for the youngest patients without influencing the adult assessment [10], in particular as regards the age of diagnosis. The A1 category was now divided into A1a, which stands for age <10 years and A1b (10>17 years old) (**Table 1**). As regards location, the upper GI disease (L4) was rearranged to proxi-

Table 1. Current classifications of Crohn's disease

	Vienna	Montreal	Paris
Age of diagnosis	A_1, below 40 years A_2, above 40 years	A_1, below 17 years A_2, between 17 and 40 years A_3, above 40 years	A_{1a}, between 0 and 10 years A_{1b}, between 10 and 17 years A_2, between 17 and 40 years A_3, above 40 years
Location	L_1, ileal L_2, colonic L_3, ileocolonic L_4, upper GI tract	L_1, ileal L_2, colonic L_3, ileocolonic L_4, separated upper GI tract[a]	L_1, disease in 1/3 of distal ileum L_2, colonic L_3, ileocolonic L_{4a}, upper GI tract disease proximal to ligament of Treitz* L_{4b}, upper GI tract disease distal to ligament of Treitz*
Behavior	B_1, non-stricturing, non-penetrating B_2, stricturing B_3, penetrating	B_1, non-stricturing, non-penetrating B_2, stricturing B_3, penetrating p perianal disease modifier	B_1, non-stricturing, non-penetrating B_2, stricturing B_3, penetrating B_2B_3, penetrating and stricturing disease p perianal disease modifier
Growth retardation			G_0, no growth retardation G_1, growth retardation observed

**L4 modifier can be added to L1, L2, L3 if co-exists with upper GI tract disease.*

mal to the ligament of Treitz (L4a) and distal to the ligament of Treitz, above the 1/3 distal ileum (L4b). In addition, stenosing and penetrating disease could be classified concurrently as B2B3 category. However, the most important was the inclusion of growth retardation in the classification (G0 if negative, G1 if positive).

The comparison between Rome, Montreal and Paris classifications is shown in **Table 1**.

Ulcerative colitis

The UC classification was taken into consideration for the first time by Montreal Working Party and – based on the disease extent and severity – three subtypes have been proposed: ulcerative proctitis (distally to the rectosigmoid junction), left sided UC (distally to the splenic flexure) and extensive UC (proximally to the splenic flexure), known now as pancolitis, when the whole colon is involved in inflammation [9]. Five years later, during a meeting in Paris, a small – but crucial for children patients – change has been made based on the observation made by Van Limbergen et al. [11], who showed that in young patients the extensive involvement of the colon is significantly more frequent compared to the adults (82 vs. 48%, respectively). It was decided that the hepatic flexure will define whether the involvement of the colon is extensive, but not complete or whether the entire colon is affected by the disease.

Current UC classification based on the disease severity assumes the existence of four grades of the disease – remission, mild, intermediate and severe. The symptoms evaluated in UC include bowel movements, heart rate, temperature, hemoglobin level, erythrocyte sedimentation rate, CRP level and the presence of systemic illness.

Establishment of inflammatory bowel disease indices

Crohn's disease indices

Several scales have been used in IBD for the assessment of disease severity, patient's condition, treatment effects, and future clinical approach. In CD, the most common and widely used disease scale is Crohn's Disease Activity Index (CDAI), established by Best et al. in 1976 [12]. Eight parameters are characterized when calculating CDAI: number of liquid stools, presence of abdominal pain, patient's activity, occurrence of extra-intestinal manifestations, administration of antidiarrheals by patient, palpable abdominal mass, hematocrit (HTC), and body weight. Each parameter has its numerical range and – in case of first three – the numbers are summed over 7 days. The final CDAI value below 150 indicates remission, 150 – 450 means active disease and values above 450 are an indication of severe form of CD. Despite its usefulness, CDAI was criticized for a long period of time needed for its assessment, which may be complicated in contemporary practice. Therefore in 1980 Harvey and Bradshaw [13] decided to simplify the index by excluding the laboratory data and the information about the antidiarrheals.

The necessity of establishing a disease scale for young patients resulted in a creation of a pediatric version of CDAI (PCDAI) in 1990 [14]. Three sections were created, i.e. patient's history of the past 7 days, laboratory tests, and clinical examination, in which original CDAI parameters were integrated, unchanged. Additionally, erythrocyte sedimentation rate, albumin concentration, presence of perirectal disease, weight and height have been included. In 1995, Ryżko and Woynarowski [15] presented their version of PCDAI, where weight and height were substituted with Cole index and HTC with hemoglobin concentration. Similarly to CDAI, each parameter in PCDAI is scored for 0, 5 or 10 points, where maximum is 100. A lower PCDAI value indicates better prognosis.

Finally, the efforts were made to create the index for perianal manifestations of CD, which could help directing the surgical approach towards an accurate treatment of the disease. The scoring system proposed by Pikarsky and collaborators in 2002 [16] proved to correlate well with the results of the procedures in patients with perianal CD.

The comment of the clinician

The CDAI / PCDAI indexing system is widely used due to its simplicity and the easiness of collecting the data necessary to calculate the index value. Some may criticize the lack of information about the use of antidiarrhoeal, but in most cases it does not influence further treatment of the patient and therefore no improvement can be necessary.

Ulcerative colitis indices

As summarized in **Table 2**, a wide range of indices have been created for assessing the severity of UC. This was mainly triggered by the need of evaluating the effectiveness of each of the newly created drugs in clinical trials, beginning with steroids and concluding with the latest biological agents.

Table 2. A summary of ulcerative colitis indices

Variable	Index					
	Powell-Tuck	Rachmilewitz (CAI)	Lichtiger	SCCAI	Mayo	UCSS
Number of stools	< 3/24 h = 0 3–6/24 h = 1 > 6/24 h = 2	< 18/week = 0 18–35/week = 1 36–60/week = 2 > 60/week = 3	0–2/24 h = 0 3–4/24 h = 1 5–6/24 h = 2 7–9/24 h = 3 > 10/24 h = 4	1–3/24 h = 0 4–6/24 h = 1 7–9/24 h = 2 > 9/24 h = 3	normal = 0 1–2 more than normal = 1 3–4 more = 2 > 5 more = 3	Similar to Mayo
Stool consistency	normal = 0 semiformed = 1 liquid = 1					
Nocturnal diarrhea			absent = 0 present = 1	1–3 = 1 4–6 = 2		
Urgency of defecation			absent = 0 present = 1	if hurry = 1 if immediately = 2 if incontinence = 3		
Need for antidiarrheal drugs			no = 0 yes = 1			
Blood in stool	no sign = 0 trace = 1 more than a trace = 2	none = 0 little = 2 a lot = 4	none = 0 in < 50% of stools = 1 in ⩾50% of stools = 2 in 100% of stools = 3	traces = 1 occasionally = 2 usually = 3	none = 0 streaks of blood in stool visible = 1 obvious blood in stool visible = 2 blood passes alone = 3	Similar to Mayo
Abdominal pain or cramping	no abdominal pain = 0 with bowel actions = 1 more continuous = 2	none = 0 mild = 1 moderate = 2 severe = 3	none = 0 mild = 1 moderate = 2 severe = 3			
Nausea or vomiting	absent = 0 present = 1					
Abdominal tenderness	none = 0 mild = 1 marked = 2 rebound = 3		none = 0 mild, localized = 1 mild to moderate, diffused = 2 severe or rebound = 3			
Pyrexia	< 37.1 = 0 37.1–38 = 1 > 38 = 2	37–38 = 0 > 38 = 3				
Extra-intestinal manifestation	none = 0 mild on 1 site = 1 severe or mild on 2 sites = 2	if any of these appears: iritis, erythema nodosum, arthritis = 3 / each		if any of these appears: arthritis, pyoderma gangrenosum, erythema nodosum, uveitis = 1 / each		
General condition	no impairment = 0 impaired, able to continue activities = 1 activity reduced = 2 unable to work = 3		perfect = 0 very good = 1 good = 2 average = 3 poor = 4 terrible = 5	very good = 0 fair = 1 poor = 2 very poor = 3 terrible = 4	generally good = 0 fair = 1 poor = 2 terrible = 3	Similar to Mayo
Physician's global assessment		good = 0 average = 1 poor = 2 very poor = 3			from normal to severe = 0–3	from quiescent to severe = 0–3
Laboratory tests		ESR > 50 in 1st h = 1 ESR > 100 in 1st h = 2 Hemoglobin < 100g/l = 4				

ESR, erythrocyte sedimentation rate

The first clinical index for UC activity, the Truelove and Witts Severity Index, was established in 1955 [17]. The scale included six variables: amount of stools per day, blood in stools, body temperature, pulse rate, hemoglobin concentration and erythrocyte sedimentation rate (ESR). One or two stools per day without blood, normal temperature and heart rate, hemoglobin above 11 g/dl and ESR below 20 mm/h defined clinical remission. The Truelove and Witts Severity Index was principally qualitative and it distinguished mild, moderate and severe disease. Its main drawback was that the improvement in patient's condition could not reflect the improvement in index and vice versa, what shows the advantage of the quantitative over qualitative scales. Of interest, Truelove and Witts also created the first 3-point endoscopic scale. Based on a sigmoidoscopic assessment, the following scores were attributed: 1, normal or near normal mucous membrane (slight hyperemia or slight granularity is observed), 2, improved and 3, no change or worse.

The Powell-Tuck Index, named also as the St. Mark's Index, was created in 1978 [18]. Ten clinical variables were included in this scale: number of stools, stool consistency, abdominal pain, associated anorexia, nausea or vomiting, general health, extra-intestinal manifestation in eyes, joints, mouth and/or skin, abdominal tenderness, body temperature and blood in stool (**Table 2**). The Powell-Tuck Index also includes a three-point endoscopic scale (0–2 points), which was added in 1982, describing hemorrhagic intensity in the sigmoid colon. The final score in this index varies from 0 to 22 points and the remission is defined by the score of 3 points and less [19].

In 1987, Schroeder et al. [20] introduced the Disease Activity Index (also known as the Mayo Score or Mayo Clinic Score) (**Table 2**). The score ranges from 0 to 12 and consists of four features with maximum points of 3 each: stool frequency, rectal bleeding, proctosigmoidoscopy score and PGA (Physician's Global Assessment). PGA depends on three subscores and the patient's well-being assessment (which is not, however, included in Mayo Score's final score). Feagan et al. [21] further modified the scale by excluding the endoscopic score and including the patient's functional assessment to obtain the ulcerative colitis clinical score (UCCS) (**Table 2**).

In the same year, Sutherland et al. [22] developed the Ulcerative Colitis Disease Activity Index, in which four variables were included: stool frequency, rectal bleeding, mucosal appearance and physician's assessment of disease activity. Assessment of mucous membrane included friability (1 or 2 points), exudation and spontaneous hemorrhage (3 points).

In 1988, Rachmilewitz et al. [23] established a scoring system including clinical symptoms (medical history and physical examination) and endoscopic findings (colonoscopy). When establishing the Clinical Activity Index (CAI, **Table 2**), seven parameters were characterized: number of stools per week, presence of blood in stools and abdominal pain or cramp, general patient's condition, body temperature, extra-intestinal manifestation of UC and results of the laboratory tests, such as erythrocyte sedimentation rate and hemoglobin concentration. An endoscopic index, also developed by Rachmillewitz et al., was based on the assessment of granulation scattering reflected light, vascular pattern, vulnerability of mucosa and mucosal damage, which included the presence of mucus, fibrin, exudate, erosions and ulcers. The index score of 4 points or less defined remission. CAI is now widely used, especially to confirm effectiveness of new therapies in UC.

In 1992, Seo et al. [24] have made efforts to create another quantitative evaluation of the disease's severity based on Truelove and Witt's classification. Among 18 clinical, laboratory and endoscopy variables, 5 have been proven to significantly correlate with the disease severity, i.e. blood stools, bowel movements, ESR, hemoglobin and serum albumin. The index was calculated as follows: 60 × amount of bloody stools + 13 × bowel movements + 0.5 × ESR + 4 × Hb − 15 × albumin + 200 and the values <150 and >200 refer to mild and severe activity, respectively, with moderate activity located between these two. The newly developed Activity Index showed crucial advantages comparing with previously created scales: the calculations were not cumbersome, could be used for repeating the evaluations, chosen variables were not too invasive to patients and the index was shown to correlate well with endoscopic findings [25].

The Lichtiger Index, which was another modification of Truelove and Witts index, was designed by Lichtiger et al.in 1990 [26] (**Table 2**). Eight features were taken into account: frequency of bowel movements, nocturnal bowel movements, number of blood-stained stools, fecal incontinence, abdominal pain or cramping, general well-being, abdominal tenderness and patient's need for taking antidiarrheals. With the maximum score of 21, the scale is evaluated again in two consecutive days. The final score below 10 means a clinical response to the drug.

The Sigmoidoscopic Inflammation Grade Score was developed by Lémann et al. in 1995 [27]. It is

a four-point scale, in which normal mucous membrane receives 0 points, edema and/or loss of mucosal vascular pattern and granularity – 1 point, induced bleeding on examination (friability) – 2 points and spontaneous hemorrhage, visible ulcers obtained 3 points.

Walmslay and colleagues aimed at developing a scoring system that will suit for daily practice. In 1998, they adopted some features of the Powell-Tuck Index and – using additional scores (sigmoidoscopic assessment with the Baron scoring system, nocturnal defecation and urgency of defecation) and multivariable regression analysis – developed the Simple Clinical Colitis Activity Index (SCCAI) with six variables [28] (**Table 2**). Of note, instead of general health question from Powell-Tuck Index, a general well-being score from the Harvey-Bradshaw index for CD was introduced. The SCCAI scoring system does not require any of the laboratory or endoscopic assessment and therefore seems perfect for the activity assessment even by the general practitioner.

Since the need to perform repeated endoscopies, the existing scales for the assessment of UC described above were acceptable for adult, but not suitable for pediatric patients. Therefore, in 2007 Turner et al. [29] provided the Pediatric Ulcerative Colitis Activity Index (PUCAI). Six variables were chosen as representative: abdominal pain, rectal bleeding, stool consistency, number of stools per day, presence of nocturnal stools and limitation of the activity. With the maximum score of 85, the authors suggested to correlate the response to the therapy with the following changes in PUCAI: small response ⩾10 points, moderate response ⩾20 points and large response ⩾35 points.

The comment of the clinician

Unlike the CDAI, which turned to be the gold standard in assessing disease activity in CD, we lack a fully validated indexing tool in UC. The only exception is the PUCAI, which underwent rigorous evaluations by its authors and may be regarded as superior to other indices [30, 31]. In line, Turner et al. made efforts to compare the existing noninvasive disease activity indices in UC and to elect the most valid ones [32]. The study showed a significant prevalence of three indices over others: SSCAI, PUCAI and, in part, the Mayo score, as it appeared to be strong only in three of four categories chosen in study. As for the PUCAI- even if it was initially constructed with children in mind, the index can be used successfully for evaluating the disease activity in adults, as it includes none of children-specific parameters.

IBD endoscopic indices

Endoscopy is a diagnostic tool, which enables identification of lesions in the GI tract and evaluation of disease progression. It is also used to distinguish CD and UC from enterocolitis with known etiology. Another advantage of endoscopy is the possibility to obtain bioptic samples for histological examination.

Using endoscopy as an imaging tool, Maratka [33] distinguished five types of endoscopic changes in CD: 1) aphtoid stadium with erosions and slight ulcerations surrounded by normal-looking mucous membrane, 2) ulcerative stadium, in which ulcerations with irregular border are surrounded by almost normal mucosa, 3) polypoid stadium with pseudopolyps – fragments of inflamed mucous membrane located between altered, ulcerative surround, 4) cobblestoning stadium, in which surface of mucous membrane resembles cobblestone due to edematous mucosa that is separated by linear ulcerations, and 5) constrictive stadium with stenosis caused by fibrosis of intestinal wall (**Figure 1**).

In 1989, Mary and Modigliani [34] created the Crohn's Disease Endoscopic Index of Severity (CDEIS) (**Table 3**). Bowels were divided into five parts: 1) rectum, 2) sigmoid and left colon, 3) transverse colon, 4) right colon and 5) ileum. In each segment of the bowel, lesions were assessed endoscopically and scored, based on their depth, extent and ulcerative surface; the presence of stenosis with or without ulcerations was also evaluated. The total CDEIS score is a sum of parameters described above and, similarly to other indices, an increased score signified a more severe CD manifestation. However, CDEIS is nowadays regarded as time and labor-consuming and unsuitable in daily practice due to its complexity.

In 2004, Daperno et al. [35] developed a Simple Endoscopic Score for CD (SES-CD). Partition of bowels into five segments is maintained in this scoring system and lesions are given from 0 to 3 points depending on their intensity (**Table 4**).

Capsule endoscopy (CE) was invented in 2000 and was approved by the American Food and Drug Administration FDA in 2001. It became an important element of diagnosis of lesions in the small intestine over the last 10 years. Nowadays, CE is used in case of CD and tumors of small intestine suspicion, as well as a persistent GI bleeding, an ambiguous iron deficiency anemia, chronic abdominal pain and polyposis syndrome. CE allows the visualization of mucous membrane and shows small ulcerations of mucosa, that are not visible in other screening [36–38].

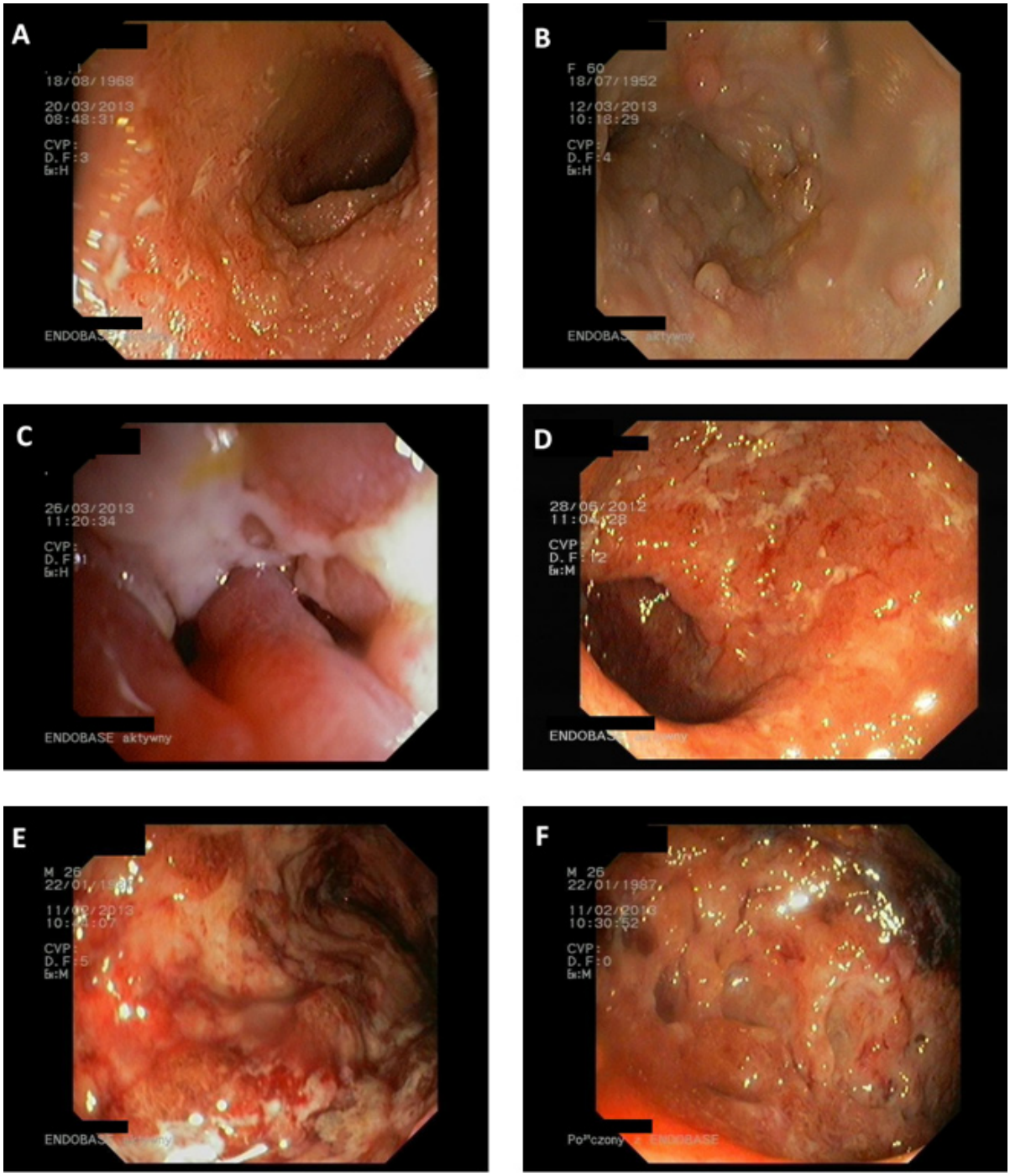

Figure 1. Endoscopic images of histopathological changes in the gastrointestinal tract in Crohn's disease (A-C) and ulcerative colitis (D-F). Crohn's disease: A. Edematous mucous membrane with slight ulceration covered by fibrin in distal part of small intestine. B. Pseudopolyps in sigmoid colon. C. Stenosis of colon at a level of splenic flexure with extensive ulceration covered by fibrin. Ulcerative colitis: D. Hemorrhagic stadium in sigmoid colon – edematous mucous membrane, redness and friability with flat erosions covered by fibrin. E. Ulcerative stadium – flat ulceration covered by fibrin. F. Polypoid stadium – several deep ulcerations covered by fibrin and pseudopolyps

Table 3. Format of calculation of the Crohn's Disease Endoscopic Index of Severity (CDEIS)

	Rectum	Sigmoid and left colon	Transverse colon	Right colon	Ileum	
Deep ulceration	0 or 12 pt	0 or 12 pt	0 or 12 pt	0 or 12 pt	0 or 12 pt	Total 1
Superficial ulceration	0 or 6 pt	0 or 6 pt	0 or 6 pt	0 or 6pt	0 or 6 pt	Total 2
Surface of CD lesions	0–10 cm	0-10 cm	0-10 cm	0-10 cm	0-10 cm	Total 3
Ulcerative surface	0–10 cm	0-10 cm	0-10 cm	0-10 cm	0-10 cm	Total 4
Total 1+Total 2+ Total 3+ Total 4 = A A/number of occupied parts (1-5)= B Presence of ulcerative stenosis: 0 or 3 pt = C Presence of non-ulcerative stenosis: 0 or 3 pt= D B+C+D=CDEIS						

Table 4. Simple endoscopic score for Crohn's disease (SES-CD)

Variable	0	1	2	3
size of ulceration	none	aphthoid ulcerations (diameter: < 0.5 cm)	large ulcerations (diameter: 0.5–2 cm)	very large ulcerations (diameter: > 2 cm)
ulcerative surface	none	< 10%	10–30%	> 30%
inflamed surface	unaffected segment	< 50%	50–75%	> 75%
presence of stenosis	none	singe, can be passed by endoscope	multiple, can be passed by endoscope	cannot be passed by endoscope

Table 5. Baron score and modified Baron Score

Score	Classic Baron Score	Modified Baron Score
0	Normal mucous membrane	Normal mucous membrane, vascular pattern visible, not friable
1	Abnormal mucous membrane, but without bleeding	Granular mucous membrane, vascular pattern not visible, not friable
2	Moderate bleeding – bleeding to light touch	1, but friable, no spontaneous bleeding seen
3	Severe bleeding – spontaneous bleeding	2, but spontaneous bleeding seen
4		3, but ulcerated, bare mucous membrane

In 2008 Gralinek et al. [38] created a capsule endoscopy scoring index, which is based on three endoscopic elements: villous edema, ulcers and stenosis, and integrates their number, range and additional descriptors. The score below 135 indicates normal mucous membrane or clinically insignificant mucosal inflammatory change. A mild condition is between 136 and 790 points and condition from moderate to severe is above 790 points.

Over the years, several indices for UC based on endoscopic imaging have also been established. In 1964 Baron et al. [39] proposed evaluating mucosal appearances in the colon and the rectum in UC by viewing the color, friability and moisture of mucous membrane, granularity, distensibility, presence of blood vessels, polyps, ulcers and blood in intestinal lumen. Based on the score, four stages of endoscopic activity were distinguished: 1) normal stadium with pale mucous membrane and visible vascular pattern, 2) inactive stadium, in which dry and granular mucous membrane is present, 3) moderately active stadium with moist, granular and friable mucosa, and 4) active stadium, in which mucous membrane is friable, moist and smooth (**Table 5**). A general endoscopic grading system, based on the stages described, has been established and has been used since with only a minor modification, introduced by Feagan et al. [21]. The Modified Baron Score (**Table 5**) allows the evaluation of whether the patient is in remission or not (score 1 or 0). While assessing lesions of colon mucosa, they distinguished a normal or inactive mucous membrane (0 points), mild changes, in which hyperemia, friability and fragmentary loss of vascular pattern occur (1 point), moderately active with massive hyperemia, erosions and completely loss of vascular pattern (2 point) and severe condition, in which spontaneous bleeding and ulceration occur (3 points). The Modified Baron Score is currently the most frequently used scale by clinicians [20] and until 2011 it has been the only validated endoscopic scale for measuring disease activity [40].

In 2012, the group of Travis et al. presented the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), which included three variables: vascular pattern, bleeding and erosions and ulcers. Each variable is divided into three to four levels of severity with a comprehensive definition. This endoscopic scale, unlike previously developed indices, excluded friability of mucosa [41]. Since the first report, UCEIS has been validated and

showed to correlate well with overall assessment of severity [42]. Furthermore, UCEIS is now also viewed as a possible indicator for an early decision to use infliximab or ciclosporin (Corte et al., unpublished results reported at ECCO 2013).

The most recent scale, the Ulcerative Colitis Colonoscopy Index of Severity (UCCIS), was established by Neumann and Neurath in 2012 [42]. In this scale four parameters (mucosal lesions) are being assessed: vascular pattern, granularity, ulceration and friability (bleeding) (**Table 6**). Additionally, the index consists of four-point (0–3 points) grading of segmental assessment of endoscopic activity (SAES – assessing endoscopic severity of each colonic segment) and global assessment of endoscopic activity (GAES – assessing endoscopic severity of all five colonic segments). GAES is further shown as the 10 cm-visual analogue scale presenting severity of UC from normal to extremely severe. In 2013, Samuel et al. validated this endoscopic assessment tool [40].

Histopathological indices in IBD

The histological examination of endoscopic biopsies is a very useful tool to distinguish CD from UC. In 2013 the European Crohn's and Colitis Organization (ECCO) and the European Society of Pathology (ESP) published a Consensus containing recommendation for histopathological diagnosis of IBD [43], underlining its importance.

The histopathological assessment can be used to establish microscopic activity scales in CD and UC. The Riley index was created in 1991 [44]. In this four-point scale (0–3 points), six parameters are assessed: polymorphonuclear cells in lamina propria, chronic inflammatory cell infiltration, presence of crypt abscesses, mucin depletion, integrity of epithelial surface and irregular crypt structure.

In 1998, D'Haens et al. [45] developed the Scoring System for Histological Abnormalities in Crohn's Disease Mucosal Biopsy Specimens. In this scale 8 parameters were considered: epithelial damage, structure changes, infiltration of mononuclear cells in lamina propria, infiltration of polymorphonuclear cells in lamina propria, polymorphonuclear cells in epithelium, presence of erosion or ulcers, presence of granulomas and number of biopsy specimens occupied (**Table 7**).

The frequently used histopathological scale in UC, Geboes index, was created in 2000 [46]. The scale has 5 grades. Any architectural changes are indicated by grade 0. Grade 1 is characterized by the increase of chronic inflammation in the lamina propria. Increased level of eosinophils in the lamina propria is represented by grade 2A and increased of neutrophils – 2B. Grade 3 describes the presence of neutrophils in the epithelium. Expansion of crypt destruction is assigned to grade 4. Grade 5 indicates erosion and ulceration.

Table 6. Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

Variable	0	1	2	3	4
vascular pattern	normal vascular pattern	partially visible vascular pattern	complete loss of vascular pattern	–	–
granularity	normal, smooth and glistening	fine	leathery	–	–
ulceration	normal mucosa, lack of erosion or ulcer	presence of erosion or pinpoint ulcerations	presence of numerous, superficial ulcers covered by mucous	presence of deep, excavated ulcerations	widespread ulceration with >30% involvement
friability/bleeding	normal mucosa, no friability, no bleeding	friable, bleeding to light touch	spontaneous bleeding	–	–
grading of SAES and GAES	normal: visible vascular pattern and lack of bleeding, erosions, ulcers or friability	mild: presence of fine granularity and erythema, decreased or loss of vascular pattern, lack of mucous friability or spontaneous bleeding	moderate: presence of mucous friability and bleeding to light touch, coarse granularity, erosion or pinpoint ulceration	severe: presence of spontaneous bleeding or gross ulcers	–
GAES VAS 10cm scale	| - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | - - - - - | Normal Extremely severe				

Table 7. The overview of the Scoring System for Histological Abnormalities in Crohn's Disease Mucosal Biopsy Specimens

Epithelial damage	0 – normal 1 – focal damage 2 – extensive damage
Architectural changes	0 – normal 1 – moderate lesions (< 50%) 2 – severe lesions (> 50%)
Infiltration of mononuclear cells in the lamina propria	0 – normal 1 – moderate infiltration (up to 2x the normal number of cells) 2 – severe infiltration (> 2x the normal number of cells)
Infiltration of polimorphonuclear cells in the lamina propria	0 – normal 1 – moderate infiltration (up to 2x the normal number of cells) 2 – severe infiltration (> 2x the normal number of cells)
Polimorphonuclear 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
Number of biopsy specimens occupied	0 – none (0 of 6) 1 – ⩽ 33% (1–2 of 6) 2 – 33–66% (3–4 of 6) 3 – > 66% (5–6 of 6)

Conclusion and future perspectives

It has been more than a century since the very first descriptions of the CD and UC were reported and the research on IBD began. Currently, the numbers of IBD incidents are still increasing, not only due to higher morbidity, but also better diagnostic tools available. Following the progress in endoscopic and histopathological techniques, numerous indices and disease activity scales have been established for IBD. However, we still do not possess a perfect diagnostic tool or a disease marker or symptom, which would precede the development of the inflammation process for years and serve for disease indexing and facilitating IBD treatment. The indices nowadays are mainly used in clinical conditions to assess the response to drugs.

Clearly, the major problem nowadays is the lack of a single, internationally accepted and consistently used disease activity index for UC. Although numerous indices have been established, none is being used widely and/or properly; even the Mayo index, which is used in multiple clinical trials, exists in different forms, where the cutoff scores defining remission and response differ significantly. The use of several indices in different versions in clinical trials is only troubling the research processes and makes the data often hard to compare.

The index for clinical practice needs to be straightforward and easy to use. Ideally, one quantitative scale, with a short explanation of a score, would possibly facilitate the communication between physicians from completely different specialties. Another desired feature in clinical index is noninvasiveness, as repeated endoscopy can discourage potential clinical trial participants and is prone to inter-observer variation.

Importantly, none of the indices discussed above shows a significant prognostic value. Possibility to predict the clinical course of the disease over time comes with biological markers (for review see: [47]). The proposed number of potential markers is increasing, but we still lack the best. Ideally, the marker level should coincide with the process of mucosal healing, the latest target in IBD treatment. Of several possible disease markers, perinuclear antineutrophil cytoplasmic (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) seem to have the highest potential in being used on a larger scale. pANCA and ASCA have low sensitivity, but both were shown to distinguish UC from CD [48]. Fecal calprotectin (FC) and lactoferrin are also promising. FC with higher sensitivity and specificity than lactoferrin [49;50] appeared as a recommended marker used in clinical practice. The question whether these and other markers or symptoms will be widely used for IBD diagnosis and whether new disease indices are to be developed remains unanswered, but the need for an efficient IBD treatment requires prompt actions in this field.

New scanning techniques for IBD diagnosis and progress are emerging. Apart from refinement of endoscopy, which leads to procedures that are more efficient and safer for patient, methods like magnetic resonance enterography have been evaluated and initially approved to be used in clinical conditions, e.g. for patient inclusion to therapeutic trials (Higgins et al., unpublished results).

A better understanding of IBD causes, standardization of definitions and validation of new disease indices, evaluation of long-term effectiveness of drug therapies and many more may now be assured – among others – by two groups established in the early 1980's, International Organization For the Study of Inflammatory Bowel Disease (IOIBD) and Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID). The initial aim of IOIBD was to agree on an international index for CD activity, which further led to splitting the discussion into for topics: the clinical features of severity, a morphological index based on radiological/endoscopic features, an index based on laboratory parameters of inflammation and a nutritional index and assigning task forces related to epidemiology, clinical trials or surgery. Recent activity of IOIBD continues to address the initial goals like validation of endoscopic activity scores [52], but has expanded to finding new IBD biomarkers [53] or long-term therapeutic and side-effects of anti-IBD drugs [54]. The ongoing projects of GETAID include, inter alia, the FER study, which seeks for effective treatment of CD patients suffering from anemia, TAILORIX, which evaluates the benefits of the anti- IBD treatment with infliximab, or MICA, whose aim is to characterize the effect of adalimumab in IBD patients with intra-abdominal or pelvic abscess. They are mostly multi-center studies, involving large patient cohorts and with both, clinical and educational aspects.

To conclude, it has been more than a century since the first case of IBD was reported. However, a massive progress in the studies on the disease was made recently, which warrants many new exciting developments in the field of epidemiology, therapy and healthcare organization with regard to IBD in the very near future. They will shape the view of the clinical aspects of the disease and are expected to facilitate its better diagnosis and treatment.

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Conflict of interest statement

The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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