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Assessing Severity of Disease in Patients with Ulcerative Colitis

Baldeep Singh Pabla, MD, MSCI*, David Allen Schwartz, MD

KEYWORDS

• Truelove and Witts • Mayo score • UCEIS • PRO • CRP • *Clostridium difficile*

KEY POINTS

- The Truelove-Witts classification of disease severity has been the basis of severity index scoring in ulcerative colitis (UC).
- The Ulcerative Colitis Endoscopic Index of Severity is a validated endoscopic scoring tool that may improve standardization of endoscopic disease scoring in UC.
- Acute severe (fulminant) UC is a major source of morbidity for patients with UC. Several disease scoring systems, such as the Oxford (Travis) index and the Ho index, exist for predicting the need for colectomy. Rapid, evidence-based care remains vital to ensuring good outcomes in these patients.
- Overall disease severity scoring and treat-to-target strategies are important concepts in disease severity. Further prospective studies supporting treat-to-target strategies will be important in helping the widespread adoption of this approach.

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease that can present at various stages of disease activity and severity. Depending on disease activity at any moment and the overall severity of disease, treatment approaches vary considerably, from the use of topical mesalamine preparations to systemic immunosuppression. Accurately assessing these disease states as well as thoroughly understanding the role of concomitant noninflammatory causes of symptoms is vital to choosing the optimal management strategy for patients with this disease. This article reviews the history of disease severity scoring in UC and discusses the standard of care in assessing disease severity.

Department of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Suite 220, 1211 21st Avenue South, Nashville, TN 37232-5280, USA
* Corresponding author.
E-mail address: baldeep.pabla@vumc.org
Twitter: @BaldeepPablaMD (B.S.P.); @ibddoc09 (D.A.S.)

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Early Scales for Disease Assessment

Early instruments for measuring disease severity relied on symptoms and basic clinical and laboratory tests assessed at a single moment. In 1955, Truelove and Witts[1] described a severity score composed of 6 variables during their study of the effect of treatment with cortisone in patients with UC. The variables in this scoring system included number of stools per day, blood in the stools, temperature, pulse, hemoglobin, and erythrocyte sedimentation rate (ESR). Remission was defined as (1) 1 to 2 stools a day without blood, (2) no fever, (3) no tachycardia, (4) hemoglobin level normal or returning toward normal, (5) ESR normal or returning toward normal, (6) patient gaining weight. Disease activity was divided into 3 categories (mild, moderately severe, or severe) based on these criteria. Mild disease was defined as 4 or fewer bowel motions a day with no more than small amounts of macroscopic blood in stools; no fever; no tachycardia; anemia not severe; and ESR not increased more than 30 mm in 1 hour. Severe disease was defined as 6 or more motions a day with macroscopic blood in stools; fever (mean evening temperature more than 37.5°C [99.5° F], or a temperature of 37.8°C [100° F] or more on at least 2 days out of 4); tachycardia (mean pulse rate more than 90 beats/min); anemia (hemoglobin 75% or less; allowance made for recent transfusion); and ESR much increased (>30 mm in 1 hour). Moderately severe was defined as intermediate between severe and mild. Truelove and Witts[1] also included descriptions of sigmoidoscopic assessment, indicating whether patients were (1) normal or near normal (near normal was slight hyperemia or slight granularity as the only abnormal finding); (2) improved; (3) no change or worse. These criteria helped clinicians characterize their patients with UC and served as the foundation for all severity grading for decades to come. However, the Truelove and Witts scoring system has several limitations. Chief among these limitations is the ambiguous definitions of improvement and worsening, as well as the lack of a severity score that can be tracked over time.

Overview of Commonly Used Scoring Tools

Since the Truelove and Witts[1] study in 1955, several severity scores have been developed using several variables, including clinical symptoms, laboratory studies, and endoscopic assessment. Before delving into the plethora of scores that have been developed to describe disease severity, it is important to understand that no formally validated definitions of mild, moderate, or severe UC exist. Also, the terms disease activity and severity have often been used interchangeably in the literature, but these terms represent different, albeit overlapping, concepts.

Disease activity refers to a cross-sectional, moment-in-time assessment of inflammation, whereas disease severity may include more longitudinal and historical factors. In UC, longitudinal factors that are relevant include prior biologic failure, history of maximum disease extent, and health care use metrics such as hospitalization and disability scoring tools. Practicing clinicians should note that each of the tools discussed allows a systematic approach to assess how to best to treat the patient in the moment as well as in the long term to avoid acute and chronic disease complications.

Peyrin-Biroulet and colleagues[2] described 3 main domains relevant to the evaluation of disease severity in inflammatory bowel disease (IBD): (1) impact of disease on the patient (clinical symptoms, patient-reported outcomes [PROs], quality of life, and disability); (2) inflammatory burden (extent, location, and severity of bowel involvement at a given time); (3) disease course, including structural damage.

Traditionally, severity assessment has incorporated overlapping elements of these 3 domains with a focus on real-time clinical symptoms, PROs (which are often the

clinical symptoms that comprise the scoring tools), and inflammatory burden. A detailed review of activity indices and efficacy end points in 2007[3] listed the following scores: the Baron (endoscopic) score in 1964,[4] the Powell-Tuck Index/Powell-Tuck sigmoidoscopic assessment in 1978,[5] the Mayo Score (also called the Mayo Clinic Score and the Disease Activity Index)/Mayo Score Flexible Proctosigmoidoscopy Assessment in 1987,[6] the Sutherland Index (also called the Disease Activity Index or UC Disease Activity Index)/the Sutherland Mucosal Appearance Assessment in 1987,[7] Clinical Activity Index (Rachmilewitz Index)/Endoscopic Index in 1988,[8] the Activity Index (Seo Index) in 1992,[9] Lichtiger Index (Modified Trulove and Witts Severity Index) in 1990,[10] the Physician Global Assessment/Sigmoidoscopic Index in 1993,[11] the Investigators Global Evaluation/Sigmoidoscopic Inflammation Grade Score in 1998,[12] Simple Clinical Colitis Activity Index in 1998,[13] Improvement Based on Individual Symptom Scores in 2002,[14] Ulcerative Colitis Clinical Score/Modified Baron Score in 2005,[15] and patient-defined remission in 2005.[16]

Of these, one of the most popular and commonly used scores in clinical practice has been the Mayo Score (**Table 1**). The endoscopic scoring tools listed earlier, including the Mayo Score, involve several variables that have been reported to have significant interobserver variability (namely mucosal friability). In 2012, in an effort to develop an endoscopic scoring tool with lower interobserver variability, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was developed.[17] The study showed that just 3 descriptors (vascular pattern, bleeding, and erosions and ulcers) were sufficient to create a model accounting for 90% of the overall assessment of endoscopic severity associated with UC (**Table 2**).

Table 1
Scoring system for assessment of ulcerative colitis activity

Stool frequency	0 = Normal number of stools for this patient 1 = 1–2 stools more than normal 2 = 3–4 stools more than normal 3 = 5 or more stools more than normal
Rectal bleeding[a]	0 = No blood seen 1 = Streaks of blood with stool less than half of the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed
Findings of flexible sigmoidoscopy	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment[b]	0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease

[a] This score represented the most severe bleeding of the day.
[b] The physician's global assessment acknowledged other criteria including the patient's daily abdominal discomfort, general sense of well-being, performance status, and physical findings.

From Schroeder KW, Tremaine WJ, Ilstrup DM. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. *N Engl J Med*. 1987;317(26):1625-1629. https://doi.org/10.1056/NEJM198712243172603.

Table 2
Ulcerative colitis endoscopic index of severity descriptors and definitions

Descriptor (Score Most Severe Lesions)	Likert Scale Anchor Points	Definition
Vascular pattern	Normal (1)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny ($\leq$5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge

Additional files indicating the levels of the UCEIS are available online only.

From Travis SPL, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut*. 2012;61(4):535-542. https://doi.org/10.1136/gutjnl-2011-300486.

Role of Biomarkers

Several biomarkers have been studied with a focus on the degree of correlation with endoscopic disease in UC. The most commonly used biomarkers include ESR, C-reactive protein (CRP), fecal calprotectin (FC), and fecal lactoferrin (FL). Although ESR and CRP can be helpful in differentiating inflammatory from noninfectious causes of diarrhea, these are both nonspecific markers that can be increased in various other disease states.[18] ESR especially is nonspecific and does not change as rapidly as CRP does, further limiting its utility.[18,19] Importantly, historical studies have shown that up to 50% of patients with active disease may not have increased levels of CRP.[20,21] Cutoffs of less than 5 to 6 mg/L have been proposed for CRP, with the main limitation of this test being its decreased sensitivity and negative predictive value; that is, a large proportion of patients with mild disease may have normal CRP levels.[22,23] CRP does have an important role in predicting the need for colectomy. Patients with severe acute UC with persistently increased levels greater than 45 mg/L in patients having 3 to 8 bowel movements a day despite greater than 3 days of treatment with high-dose intravenous corticosteroids (IVCS) are at increased risk for colectomy.[24]

FC and FL are more specific for intestinal inflammation, and, in general, correlate more closely with colonic disease.[25,26] Levels between 50 and 250 μg/g have been

shown to have sensitivities varying from 71% to 93% when different endoscopic disease threshold are used, with lower negative predictive values when less severe disease cutoffs are used.[22,27,28] FL levels of 7.25 to 10 μg/g have similar operating characteristics.[29–32]

Our practice is to check inflammatory markers with ESR and CRP in addition to regular maintenance laboratory tests at baseline and biannually with patients on mesalamine and more frequently with patients on biologics. It is important to correlate these values with clinical symptoms and endoscopic findings to individualize interpretation of these results. Because of inconsistent patient billing patterns, we do not routinely check FC but use this test when endoscopy is not feasible (eg, patient not able to travel; cost concerns; or increased risk of the procedure, such as during the severe acute respiratory syndrome-coronavirus-2 epidemic).

Newer Concepts in Disease Severity: Quality of Life, Histologic Assessment, Imaging

Quality-of-life metrics have increasingly become important to assess in patients with IBD, driven both by governmental oversight and patient advocacy groups. Specifically, the US Food and Drug Administration (FDA) has mandated a move toward using PROs as coprimary end points, which has led to increased research in this area. Of the 20 PROs in IBD analyzed in a recent systemic review, none met all of the FDA's criteria for development, with only 2 of these indices involving patients directly in the development of these measures (1 in UC, the Simple Clinical Colitis Activity Index).[33] Efforts to develop validated PROs in IBD with extensive patient partnerships are underway.[34,35] However, the PROs that have been included in disease activity scoring for decades are not fully informative by themselves. Several studies have shown that, especially in mild to moderate UC, PROs of rectal bleeding and stool frequency have variable positive and negative predictive values, with time on therapy affecting the accuracy of these measures, emphasizing the importance of an objective assessment before consideration of any therapy change.[36,37] Alternative causes of symptoms should be considered, including but not limited to concomitant irritable bowel syndrome, small intestinal bacterial overgrowth, and psychiatric disease.

At our institution, the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and the Patient Health Questionnaire-8 (PHQ-8) are collected and used to help guide treatment decisions.[38,39] We also use a multidisciplinary approach to manage the comorbid psychiatric illness that often develops as a result of chronic illness.

Histologic assessment for disease activity has also become increasingly important, driven by the idea that deep remission, as defined by normal endoscopic and histologic findings, may lead to improved outcomes.[40,41] As early as 1966, rectal biopsies were used to assess disease activity in UC.[42] What defines histologic remission, when there is also no corresponding endoscopic activity, has been a source of debate because there are several histologic scoring systems that have been developed for scoring UC disease activity, as well as several definitions of histologic activity that have been used in clinical trials evaluating efficacy of medications for the treatment of UC. However, active disease is generally defined by degeneration of the surface and crypt epithelium with associated neutrophilic infiltrate in the lamina propria and in the crypt regions, the latter termed cryptitis.[43]

There have been at least 30 histologic scoring systems developed in UC, with 11 of these systems having some form of validation.[44] The validated scores include the Truelove and Richards Index,[45] Gomes Index,[46] Riley Score,[47] Geboes Score,[48] Harpaz/Mount Sinai Index,[49] Modified Riley Score,[15] the Chicago/Rubin/Histologic inflammation Activity Scale,[50] Modified Harpaz Index,[51] the Simplified Geboes

Score,[52] Nancy Index,[53] and the Robarts Histopathology Score.[54] However, none of these scores has been fully validated. As an example of how histologic outcomes are being assessed in clinical trial data, the UNIFI study group, which recently reported the results of the use of ustekinumab in UC, reported on a combined histologic and endoscopic outcome that defined mucosal healing as having the following characteristics: (1) neutrophilic infiltration less than 5% of crypts; (2) no crypt destruction; and (3) no erosions, ulcerations, or granulation tissue with endoscopic improvement.[55] Histologic remission has been shown to correlate with endoscopic improvement, higher rates of sustained steroid free remission, and decreased rates of clinical recurrence and hospitalizations.[56–59]

Several imaging modalities have been studied to assess for disease activity in UC. Bowel ultrasonography has been studied both with endoscopic ultrasonography probes and with transabdominal approaches.[60–63] Although the former has been shown to be highly accurate, the utility of endoscopic ultrasonography is limited because a bowel preparation needs to be performed and the examination remains invasive. The transabdominal approach has been shown to correlate well with Mayo 2 endoscopic disease and remains an active area of research and interest. MRI has also been studied,[64,65] with some protocols having the advantage of not requiring a bowel preparation coupled with fast image acquisition, and has been shown to correlate well with endoscopic findings.[64] Despite these findings, uptake of these imaging modalities both for the assessment of Crohn disease (CD) and UC in the United States has been slow.

Treat to Target and Overall Severity Scoring

In an effort to move from a reactive, disease activity–driven approach to a proactive treatment approach to improve patient outcomes, 2 major concepts have recently been promoted: (1) treat to target, and (2) overall disease severity scoring.

In 2015, the Selective Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) guidelines were published with the goal of summarizing the current evidence behind various targets and making consensus recommendations on which targets should be prioritized in clinical practice. The investigators concluded that, in UC, disease activity should be assessed by both the resolution of clinical symptoms, including rectal bleeding and diarrhea, and with objective measures of inflammation, assessed by endoscopy with the Mayo endoscopic scoring system with a goal of a subscore of 0 to 1.[66] Noting the paucity of direct evidence linking histologic remission, biomarkers, and imaging studies to improved outcomes, the committee indicated that these measures were useful as adjunctive, but not primary, targets of treatment. In addition, this committee emphasized the need to include individual patients' goals in targets of therapy and made recommendations on the intervals for assessment in patients with active disease or ongoing symptoms. Importantly, despite making the stated goals of treatment to include an endoscopic assessment, the committee noted that there was a lack of direct evidence linking the achievement of endoscopic targets in UC to improved outcomes, with most of the evidence coming from epidemiologic studies or being inferred from clinical trial data with heterogeneous end points.[67–70] Since then, mounting evidence points to the superior predictive ability of the UCEIS scoring system compared with the Mayo endoscopic subscore. In addition, several barriers to the adoption of a treat-to-target strategy continue to limit its widespread adoption.[71] These barriers include the ongoing lack of direct evidence of improved outcomes and the increased cost of care associated with more testing. However, despite the lack of robust, direct evidence of benefit, several studies and existing clinical trial data suggest improved outcomes with endoscopic improvement, with ongoing histologic

activity also predicting an increased likelihood of disease complications (discussed earlier in relation to histologic assessment). It is our practice to target endoscopic and histologic improvement without necessarily targeting histologic remission. We recently worked with our gastrointestinal pathologists to include a Robarts score for the most affected colonic segment to better quantify the degree of histologic activity, with the intent that this score may in the future further guide treatment changes. However, although we may advocate for lifestyle, dietary, and functional medicine–based changes in the management of ongoing histologic inflammation, at present we do not routinely change drug class or dosing if the patient is otherwise doing well.

In 2018, a group of IBD specialists convened to develop an overall severity index for both CD and UC using a modified RAND panel with an adaptive choice-based conjoint (ACBD) processes.[72] These methods helped the panelists to identify key variables of IBD disease severity, break these variables into categorical levels, rank them relative to each other, and assign relative point values to each variable.

For UC, mucosal lesions as assessed by endoscopy, impact on daily activity, and CRP levels had the highest weight in the overall severity score (**Table 3**). Among several longitudinal factors included in this severity index, disease extent was dichotomized into distal colitis amenable to treatment with enemas versus extensive colitis. The Montreal classification has previously been used to classify disease extent, with 3 subtypes of UC noted: (1) ulcerative proctitis, (2) left-sided UC (distal UC), and (3) extensive UC (pancolitis) (**Table 4**).[73] Both systems of assessing disease extent allow for the recognition that patients with extensive UC (pancolitis) have an increased risk of developing colorectal cancer and requiring colectomy.[74–80] By incorporating this variable into a severity index, Siegel and colleagues allowed for this variable to be dynamically captured, as 41% to 54% of patients with proctitis will have extensive disease after 10 years.[81] Although these severity indices for UC and CD promise to allow a more comprehensive assessment of disease severity, they have yet to be prospectively validated and did not involve patients in their derivation.

Assessing for Concomitant Infections

When evaluating a patient for causes of worsening disease activity, all guidelines recommend an infectious work-up, specifically to rule out bacterial infections such as *Clostridium difficile*, with multistep testing now being the standard of care at many institutions.[82–84] However, given the challenge of differentiating colonization and active *C difficile* infection in patients with UC, a positive polymerase chain reaction for DNA of the toxin, which may simply represent colonization, is often treated with the plan to continue treatment if the patient has an improvement in symptoms and to escalate UC therapy if there is not an improvement.[85,86] Care should also be taken to inquire about other factors that may be contributing to disease activity, such as the use of nonsteroidal antiinflammatory drugs (NSAIDs) and recent smoking cessation. Additional nonbacterial infectious causes are important to consider because they may mimic disease activity, especially in patients on biologic therapy. In particular, there is a significantly increased risk of fungal infections in patients on anti–tumor necrosis factor alpha agents. These infectious agents are covered in detail in an earlier article in this issue and include atypical mycobacterial infections such as tuberculosis, fungal infections such as histoplasmosis, and viral infections such cytomegalovirus (CMV).[87–89]

Grading

Although overall disease severity scoring has gained interest in recent years, the original Truelove-Witts criteria remain the basis on which guidelines throughout the world

Table 3
Ulcerative colitis overall disease severity index

Attribute	Level	Score
Mucosal lesions	No active erosions or ulcers	0
	Active erosions confirmed by endoscopy	14
	Active ulcers confirmed by endoscopy	18
Daily activity impact	Disease does not significantly affect daily activities	0
	Disease significantly affects daily activities	14
CRP level	Normal CRP levels (1—3 mg/L)	0
	Slightly increased CRP levels (3–5 mg/L)	4
	Increased CRP levels (>5 mg/L)	11
Biologics use	Has never used biologics/ immunomodulators	0
	Has experienced some symptom improvement with the use of biologics/ immunomodulators	4
	Has not experienced symptom improvement with the use of biologics/ immunomodulators	10
Recent hospitalization	No disease-related hospitalization within last 12 mo	0
	Has disease-related hospitalization within last 12 mo	8
Steroid use	No steroid use within the past year	0
	Has steroid use within the past year	8
Anemia	Not anemic (according to WHO criteria)	0
	Anemic (according to WHO criteria)	5
Frequency of loose stools	No change in frequency of loose stools compared with baseline	0
	Increase in frequency of loose stools by 1 per day compared with baseline	4
	Increase in frequency of loose stools of at least 2 per day compared with baseline	5
Albumin level	Normal albumin level (>3.5–5.0 g/dL)	0
	Low albumin level (<3.5 g/dL)	5
Disease extent	Distal colitis (inflammation potentially treatable using enemas)	0
	Extensive colitis (inflammation extending beyond the reach of enemas)	5
Nocturnal bowel movements	Does not have nocturnal bowel movements	0
	Has nocturnal bowel movements	4
Anorectal symptoms	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	0
	At least 1 of the following: anorectal pain, bowel urgency, incontinence, discharge, Tenesmus	4
Rectal bleeding	No rectal bleeding	0
	Has rectal bleeding	3

Abbreviation: WHO, World Health Organization.

From Siegel CA, Whitman CB, Spiegel BMR, et al. Development of an index to define overall disease severity in IBD. *Gut*. 2018;67(2):244-254. https://doi.org/10.1136/gutjnl-2016-312648.

Table 4
Montreal classification of extent of ulcerative colitis

Extent	Condition	Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left-sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

From Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. *Gut*. 2006;55(6):749-753. https://doi.org/10.1136/gut.2005.082909.

grade UC. The American College of Gastroenterology (ACG) released new guidelines in 2019 that update the last practice guideline released by this organization in 2010. The update makes several changes, including reclassifying the categories of remission, mild, moderate, severe, and fulminant to remission, mild, moderate-severe, and fulminant.[83,90] The investigators also add FC, Mayo subscore, and UCEIS to these categories, in line with the UC disease severity index from Siegel and colleagues,[72] noting the importance of endoscopic findings as well as biomarkers showing an increased inflammatory burden (**Table 5**). They suggest a cutoff in FC of 150 to 200 μg/g to differentiate remission from active disease based on a meta-analysis of optimal cutoffs, but acknowledge the variation in the literature regarding an optimal threshold.[91]

Guidelines from the European Crohn's and Colitis Organization (ECCO) published in 2017 add CRP and endoscopic findings to the original Truelove-Witts criteria, and

Table 5
Proposed American College of Gastroenterology ulcerative colitis activity index

	Remission	Mild	Moderate to Severe	Fulminant
Stools/d (n)	Formed stools	<4	>6	>10
Blood in Stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Increased	Increased	Increased
FC (μg/g)	<150–200	>150–200	>150–200	>150–200
Endoscopy (Mayo Subscore)	0–1	1	2–3	3
UCEIS	0–1	2–4	5–8	7–8

From Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol*. 2019;114(3):1. https://doi.org/10.14309/ajg.0000000000000152.

reference the Montreal Classification Working Party descriptions of severity classification of remission, mild, moderate, and severe UC.[73,84] They note than any increase in CRP level greater than 30 mg/L along with bloody stools greater than or equal to 6 in a day should be considered severe disease, and note that patients in remission should have no mucosal lesions on endoscopy. In previous ECCO guidelines, they note that the use of the term fulminant UC is dated and not applicable to the modern era, because this term was initially used to describe patients who presented with a single exacerbation or initial presentation that resulted in death within 1 year.[92,93] Treatment has now progressed to the point where mortality is a rare complication of such presentations.

Inpatient Severe Disease Considerations

In patients admitted to the hospital with severe UC (fulminant disease), additional work-up should be undertaken to assess for toxic megacolon and CMV.[83,94] Severe colitis requiring hospital admission remains a major source of morbidity, with up to 25% of patients with UC requiring hospitalization for severe disease, and ultimately requiring colectomy in 40% of cases.[95] Colonic dilatation greater than 5.5 to 6 cm on imaging in combination with systemic toxicity are consistent with the diagnosis of toxic megacolon; however, the epidemiology of toxic megacolon has shifted to mainly infectious causes in the past few decades with advances in the care of UC and increase of infectious agents such as *C difficile*.[96] Cross-sectional imaging should be reserved for patients in whom there is a clinical concern for complication such as a bowel perforation, which may present in a more subtle fashion in patients on high-dose steroids. An endoscopic evaluation should be pursued, with an early evaluation if there is a high clinical suspicion for an infectious cause. A flexible sigmoidoscopy is sufficient given the concern for an increased rate of perforation with a full colonoscopy in severe disease, and biopsies to assess for CMV should be obtained.[83,94,97] Rescue therapy with infliximab, cyclosporine, tacrolimus, and possibly tofacitinib can then be considered as alternatives to surgery if pursued early in the disease course (day 3 of admission). The strategies regarding rescue therapy are discussed in another article in this issue.

There are several disease scores used to determine the risk of requiring rescue therapy or colectomy in patients with severe colitis. Recent studies have shown a potential advantage of using the UCEIS scoring system, with 1 study showing improved accuracy of the UCEIS score in predicting the need for colectomy compared with the Mayo Score, with score greater than 7 showing a sensitivity of 60.3% with a specificity of 85.5%.[98] Another study showed that a UCEIS score of 5 or more was associated with a 50% chance of requiring rescue therapy and 33% rate of colectomy compared with 27% and 9% for those with a score of less than or equal to 4. As mentioned previously, the commonly used Oxford (or Travis) index, developed in 1996, predicted the need for colectomy to be 85% in patients with a CRP level greater than 45 mg/L and 3 to 8 bowel movements a day after 3 days of IVCS treatment.[24] Another score, developed in 1998 by Lindgren and colleagues[99] using these same variables of bowel movements and CRP on day 3 after IVCS, showed favorable test characteristics for predicting the need for colectomy. The Ho index has also been used to risk stratify patients into low, intermediate, or high risk for colectomy.[100] This index was derived from a cohort of patients from 1995 to 2002 and found aggregate scores of 0 to 1, 2 to 3, and greater than or equal to 4 from 3 variables (mean stool frequency, averaged over the first 3 days; colonic dilatation, defined as >5.5 cm in the transverse colon within the first 3 days of admission; and serum albumin level on admission less than 3 g/L) correlated with a risk of progression to colectomy of 11%, 45%, and 85% respectively (**Table 6**).

Table 6
Integer score attributes to each category derived from the coefficients of the logistic regression equation

Variables	Score
Mean stool frequency:	
<4	0
4 ≤ 6	1
6 ≤ 9	2
>9	4
Colonic dilatation	4
Hypoalbuminemia	
<30 g/L	1

Overall risk core = [score attributable to mean stool frequency (0, 1, 2 or 4)] + [presence of colonic dilatation (0 or 4)] + [presence of hypoalbuminemia (0 or 1)]. Minimum score = 0, maximum score = 9.

From Ho GT, Mowat C, Goddard CJR, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther.* 2004;19(10):1079-1087. https://doi.org/10.1111/j.1365-2036.2004.01945.

SUMMARY

Although there has been a tremendous advance in the therapy for UC over the last several decades, guideline-based recommendations for disease severity scoring remain largely the same. New concepts of overall disease severity in UC hold the promise of improving access to care in patients with high-risk historical attributes but relatively quiescent disease activity, although these tools require further validation. Treat-to-target strategies offer hope for improved patient outcomes, although prospective data showing improved outcomes are scant. Practicing clinicians should use a combination of patient-reported variables, obtained both through a routine history and through a validated tool such as the SIBDQ, in combination with objective markers of inflammation such as endoscopy and biochemical testing, to determine disease severity. The management of acute severe UC remains a crucial area of ongoing research and has ample room for clinical improvement. Optimal treatment depends on the accurate assessment of disease severity and response to treatment with high-dose IVCS.

CLINICAL CARE POINTS

- There remain no formally validated definitions of mild, moderate, or severe UC. Instead, modern scoring systems are based on historical definitions that have been shown to be useful in distinguishing patients into categories of disease likely to respond to various treatments. A new overall severity scoring system in UC may provide a crucial link between point-in-time disease activity scoring systems and longitudinal high-risk attributes of disease.
- There are no IBD-specific PRO measures that meet FDA guidelines. PRO measures as they currently exist do not always correlate with endoscopic findings of disease activity.
- In assessing disease severity, several non-UC factors need to be considered, and include concomitant infection (especially *C difficile*), NSAID use, recent smoking cessation, and comorbid psychiatric illness.

- Acute severe (fulminant) UC remains a major source of morbidity. Care must be taken to adequately diagnose and assess response to treatment in these patients.
- Treat-to-target strategies offer the promise of improved patient outcome, although prospective studies showing their superiority are scant.

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