Journal of Crohn's and Colitis Advance Access published August 29, 2016

Manuscript Doi : 10.1093/ecco-jcc/jjw154

A SIMPLIFIED GEBOES SCORE FOR ULCERATIVE COLITIS

Aranzazu Jauregui-Amezaga[1*], Auke Geerits[2], Yannick Das[2], Bart Lemmens[2], Xavier Sagaert[2], Talat Bessissow[3], Triana Lobatón[4], Marc Ferrante[1*], Gert Van Assche[1*], Raf Bisschops[1], Karel Geboes[2], Gert De Hertogh[2], Séverine Vermeire[1*].

[1] *University Hospitals Leuven, Department of Gastroenterology, KU Leuven, Leuven, Belgium*

* Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium

[2] *University Hospitals Leuven, Department of Pathology, KU Leuven, Leuven, Belgium*

[3] *Mc Gill University Health Center, Department of Gastroenterology, Montreal, Canada*

[4] *Hospital Universitari Germans Trias i Pujol, Department of Gastroenterology, Badalona, Spain*

Corresponding author:

Aranzazu Jauregui Amezaga

Department of Gastroenterology
University hospitals Leuven
Herestraat 49 – 3000 Leuven BELGIUM
Tel: +32 16344218; Fax: +32 16 34 44 19
Mail: aran.jauregui@gmail.com

Word count: 3,413

Manuscript Doi : 10.1093/ecco-jcc/jjw154

ABSTRACT:

Background & Aims: The original Geboes Score (OGS) is the most commonly used histological score in ulcerative colitis (UC), but rather complicated to use in daily clinical practice. The aim of this study was to develop a Simplified Geboes Score (SGS) and to compare it with the OGS in patients newly diagnosed with UC.

Methods: All patients diagnosed with UC at a tertiary referral center between 2005 and 2010 who had serial colonoscopies with biopsies were retrospectively included. The 5-year endoscopic/histological evolution after diagnosis was recorded. Histological activity was scored by an experienced IBD pathologist and 3 trained readers using the OGS and the new SGS, that only includes variables linked to active inflammatory disease. The correlation between endoscopic and histologic activity and the histological inter-observer agreement were measured.

Results: A total of 528 slides from 339 colonoscopies of 103 UC patients were reviewed. Forty (12%) colonoscopies presented Mayo 0, 74 (22%) Mayo 1, 107 (31%) Mayo 2, and 118 (35%) Mayo 3. Active microscopic disease (≥ 3.1 in both scores) was described in 10/40 (25%) patients who were in complete endoscopic remission (Mayo 0) and 62/74 (84%) with mild endoscopic lesions (Mayo 1). The correlation analysis between endoscopy and OGS/SGS did not show significant differences between the histological scores. The inter-observer agreement was moderate for all the grades of the SGS.

Conclusions: The assessment of histological activity based on the OGS and the SGS was comparable in newly diagnosed active UC patients. Further prospective validation should now be done to replace the OGS with the SGS.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

KEYWORDS:

Histology, ulcerative colitis, activity.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

INTRODUCTION:

The introduction of powerful biologic drugs such as anti-TNF and anti-leucocyte trafficking agents for the treatment of ulcerative colitis (UC) has pushed the endpoints of medical management towards mucosal healing. However, endoscopy is not a good predictor of histological healing and the presence of histological activity in patients with both clinical and endoscopic quiescent UC has been associated with a higher risk of relapse or development of cancer. [1–4] Therefore histological evaluation remains important also after diagnosis of UC.

Numerous histological scores have been proposed for UC but none have been validated. Nevertheless the Geboes Score (see Table 1) has been the most used in clinical trials. The complexity of the score however limits its applicability in clinical practice.[5] It is divided in 6 grades: architectural changes (grade 0), chronic inflammatory infiltrate (grade 1), lamina propria neutrophils and eosinophils (grade 2), neutrophils in epithelium (grade 3), crypt destruction (grade 4), and erosions or ulcerations (grade 5), and each grade of the score is divided in 4 subcategories.

The aim of the current study was to develop a Simplified Geboes Score (SGS) (see Table 2 and Figure 1) and to compare its performance with the original Geboes Score (OGS) by correlating both scores with endoscopic activity in patients recently diagnosed with UC.

MATERIALS & METHODS:

Design:

All consecutive adult patients who were newly diagnosed with UC between 2005 and 2010 and had serial endoscopies with biopsies performed at the Endoscopy Department of the University Hospitals Leuven (Belgium), were retrospectively included. The 5-year histological evolution after diagnosis was recorded.

All patients had a minimum of one or several (range 2-6) colonoscopies over the study period. During the colonoscopy, biopsies were put in recipients containing a predefined volume of Carnoy's solution or 4% neutral buffered formalin. Biopsies in a single recipient were representative either for the complete colon or for a segment of the colon (biopsies from inflamed areas in the cases of active disease, or standard biopsies from the rectosigmoid in case no active disease was observed endoscopically). For every recipient received in the pathology lab, a paraffin block was made and a corresponding 5-µm haematoxylin-eosin stained slide was prepared according to routine diagnostic procedures.

Demographic data (gender, age) and UC characteristics (age at diagnosis, UC extension based on Montreal classification, smoking habit, IBD family history, and biomarkers) were recorded at inclusion. Endoscopic activity was based on the Mayo Endoscopic Subscore.[6] Histological inflammatory activity was scored by an experienced gastrointestinal pathologist (GDH) and three trained readers (AJ, AG, YD), using the original OGS (Table 1) and the SGS (Table 2).[5] The three trained readers had no previous experience in GI histopathology prior to the study. These readers were trained in UC histopathology by

two experienced gastrointestinal pathologists (GDH and KG). The training set consisted of 200 slides from non-related UC endoscopy procedures. Cases were reviewed and scored by the trainees, and thoroughly discussed with the experts using a multi-headed microscope. The slides of the present study were read by at least 2 observers, the expert and one trained reader, both of whom were blinded to the endoscopic results.

The primary objective of the study was to develop a SGS and to compare it with the OGS with regard to the accuracy of the microscopic descriptions of the endoscopic findings in patients newly diagnosed with UC and followed up over 5 years. Secondary objective included inter-observer agreement.

Simplified Geboes Score:

A simplified histological score based on the previous OGS was developed (see Figure 1).[5] The SGS describes histological features which are called grades. In contrast to the OGS, there are now 5 such grades. Variables linked to active inflammation were taken from the OGS: neutrophils in the lamina propria, neutrophils in the epithelium, and epithelial injury in the crypts and at the mucosal surface, because neutrophils are highly increased in number in active UC. Eosinophils in lamina propria were also included because, although they can be present in both active and quiescent disease, the severity of eosinophils infiltration in lamina propria has been associated with UC relapse and non-response to medical therapy.[7,8] In addition, basal plasmacytosis was included as a scoring variable, as it has been previously identified as a predictor of relapse.[2,9]

Grade 0 of the SGS comprises grade 0 and 1 of the OGS and has been included in the SGS to allow scoring of biopsies which show no active inflammation, but where signs of previous disease are still present. This refers to both architectural changes (e.g. branching crypts, crypt atrophy or loss) and the presence of an increased mononuclear cell infiltrate.

We limited grade 1 to a single component of the chronic inflammatory infiltrate, namely basal plasmacytosis (BP), as it seems to be the stronger predictor for clinical relapse.[2,9,10] BP is defined as the presence of plasma cells around or below the crypts (deep fifth of the lamina propria), alongside or penetrating the muscularis mucosae.[7] The BP can be focal (presence of BP in a single position in a single tissue fragment), multifocal (presence of BP in multiple fragments in single or multiple slides) or diffuse (presence of a band-like infiltrate of basal plasma cells in all the fragments and all the slides). For the purpose of the study, the subgrades were recorded as: 1.0-None, 1.1-Mild (focal), and 1.2-Marked (multifocal).

The grade 2, eosinophils and neutrophils in lamina propria, was maintained as in the previous score, but divided in only 3 subgrades instead of 4. The eosinophils in lamina propria (grade 2A) were subdivided in: 2A.0 – No increase (eosinophils are normally present ni lamina propria), 2A.1 - Mild increase (a compact group of eosinophils in lamina propria), and 2A.2 – Marked increase (several of such groups or a diffuse presence of eosinophils in lamina propria). Neutrophils in lamina propria (grade 2B) presented these subcategories: 2B.0 – No increase (no neutrophils), 2B.1 – Mild increase (neutrophils only visible at high magnification [objective 40x]), 2B.2 – Marked increase (neutrophils can be seen at lower magnification). Before 2010, biopsies were fixed in Carnoy's solution, an alcoholic product

that washes away the content of eosinophil granules so that these cells could not be observed (grade 2A in both scores). Only 116 (34%) of the biopsies were taken after 2010 and fixed with formalin and not Carnoy's solution, so we decided not to include the eosinophils in the score in this study.

Infiltration with neutrophils in epithelium characterized the grade 3. In the SGS, this grade was subdivided in: 3.0 – No neutrophils in crypts, 3.1 - Mild (<50% crypts involved), and 3.2 - Marked (>50% crypt involved).

The presence of epithelial injury in association with neutrophils is also a marker of increased disease activity. Epithelial injury in the OGS was separated in 2 independent grades: grade 4 represented the damage to crypt epithelium and grade 5, the damage to surface epithelium. It should be mentioned that this score was created in the context of a trial on budesonide, so the investigators estimated that a division of epithelial damage in crypt and surface injury was needed to test the effects of oral and topical treatment on histology.[5] In the new classification, the grade 4 comprised both grades 4 and 5 of the OGS, as they represent the epithelial injury at crypts and in the surface and was subdivided in 5 subgrades: 4.0 - no crypt or surface epithelium destruction, 4.1 - marked attenuation, 4.2 - probable crypt destruction/erosions, 4.3 - unequivocal crypt destruction/erosions, and 4.4 - presence of ulcers or granulation tissue.

The findings were summarized for each endoscopy by selecting as the final score the highest obtained subgrade in the slide showing the most disease activity. The presence of neutrophils in the epithelium is required for the histological diagnosis of active disease. For

the purpose of the study we defined histologically active disease as a total score ≥3.1 in both histological scores.

Correlation between the histological scores and the Mayo Endoscopic Subscore:

A validated endoscopic score was chosen in order to perform the correlation of both histological scores (OGS and SGS) Among the existing endoscopic scores for UC, the Mayo Endoscopic Subscore is used in routine clinical practice in our center. [6]

In order to make correlations between the Mayo Endoscopic Subscore and both histological scores, it was necessary to create conversions of the histological scores. The OGS is divided in 6 grades, the SGS in 5 and the Mayo Endoscopic Subscore in 4. Therefore, both histological scores were converted to a 4-tiered grading system to allow us to do comparisons with the endoscopic score: grade 0 was created for defining normal bowel tissue or inactive colitis, grade 1 corresponded to mild disease, grade 2 with moderate disease, and grade 3 with severe disease. Many conversions are possible depending on which subgrades are combined.

Two different conversions from the OGS were constructed based on the results of a previous study. [11] In this study by Lemmens et al, 9 different conversions were tested, using various upper and lower limits of grade 2 and 3. Biopsies without neutrophils were scored as grade 0. If neutrophils were present, the biopsies were at least categorized as grade 1. When or ulcerations were found, biopsies were scored as grade 3. Between these extremes, the classification depended on the density and localization of neutrophils and the degree of

epithelial damage. Conversions 3 and 9 showed the best results in this previous study, so they have been applied in the present one.

Three possible conversions were tested for the SGS, combining grade 1 and 2 (conversion 1), grade 2 and 3 (conversion 2), and grade 3 and 4 (conversion 3) of SGS. See the conversions in Figure 2.

Inter-observer agreement:

All slides were separately analysed to measure the inter-observer agreement. Histological inflammatory activity was scored by an experienced gastrointestinal pathologist (GDH) and 3 trained readers (AJ, AG, YD) blinded to endoscopic results. All parameters of the original GS and the SGS were separately analysed (intra-grade differences), as well as the end-score results (final grade differences). Comparison between the results of the experienced and trained readers was performed.

Evaluation of basal plasmacytosis as histological parameter:

The association between active microscopic disease and the presence of BP was assessed. For the comparison of BP, that is divided in 3 subcategories, with the Mayo Endoscopic Subscore that is divided in 4, we recombined the Mayo Endoscopic Subscore in 3 subcategories: inactive endoscopic disease (Mayo 0), mildly active disease (Mayo 1), and moderate-severely disease (Mayo 2 and 3).

Statistical analysis:

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Categorical variables were described in proportions and continuous variables as mean (standard deviation). Categorical data were compared using a chi-squared test. Correlation between endoscopic and histological findings was analyzed by the Kendall rank correlation coefficient, a non-parametric test that measures the strength of dependence between two categorical variables. Kappa coefficient was used to measure inter-observer agreement for qualitative items when codes are ordered. It ranges from 0 to 1: a perfect agreement would equate to a kappa of 1, excellent agreement 0.81-0.99, good agreement 0.61-0.80, moderate agreement 0.41-0.60, low agreement 0.21-0.40, and very low agreement <0.20.[12] Statistical analysis was performed using the statistical package SPSS 18 for Windows (SPSS Inc, Chicago, IL).

Manuscript Doi : 10.1093/ecco-jcc/jjw154

RESULTS

Patients

We analysed 528 slides from 339 colonoscopies obtained from 103 patients who underwent colonoscopy at the Endoscopy Department of University Hospitals Leuven. Fifty-two patients were women (51%) and the mean age of patients was 38 years (SD 18). Thirty-three (35%) were ex-smokers and 5 (5%) active smokers. UC extension was proctitis in 29 (28%) patients, left-sided colitis in 46 (45%), and extensive colitis in 28 (27%). Four (4%) patients had associated primary sclerosing cholangitis. Baseline demographic characteristics are available in Table 3.

Forty colonoscopies presented with Mayo 0 (12%), 74 with Mayo 1 (22%), 107 with Mayo 2 (31%), and 118 with Mayo 3 (35%). A straightforward comparison of endoscopic and both histological total scores of the 339 colonoscopies was performed (see Figure 2).

Correlation between endoscopy and the histology scores

The comparison of the endoscopic and histological scores is presented in Figure 2. The correlation analysis between the Mayo Endoscopic Subscore and both the OGS and the SGS assessed by Kendall rank correlation coefficient did not show significant differences between both histological scores: GS-conversion 3 (Kendall τ=0.51, $p<0.001$), GS-conversion 9 (Kendall τ=0.51, $p<0.001$), SGS-conversion 1 (Kendall τ=0.47, $p<0.001$), SGS-conversion 2 (Kendall τ=0.47, $p<0.001$), and SGS-conversion 3 (Kendall τ=0.47, $p<0.001$). The correlations between the conversions of OGS/SGS and the Mayo Endoscopic Subscore are represented in

Supplementary Table 1. The association of the different subgrades of the OGS and SGS with the Mayo Endoscopic Subscore is represented in Figure 3.

Inter-observer agreement

The results of the scoring of all separate grades in the OGS and the SGS made by any of the 3 trained readers were compared to those obtained by the experienced gastrointestinal pathologist using kappa coefficients. The agreement was moderate (kappa 0.41-0.60) for all the grades of the SGS and for all grades except for grade 2B of the OGS, where it was low (kappa 0.39). The analysis of the final scores showed a moderate agreement (kappa 0.4 for the OGS and kappa 0.56 for the SGS). The agreement for the detection of active microscopic disease was good (kappa 0.69 for the OGS and 0.7 for the SGS). Results are summarized in Table 4.

Evaluation of histological parameters:

Basal plasmacytosis

Basal plasmacytosis (grade 1 of the SGS) was observed in the biopsies of 222/339 (65%) colonoscopies. In 90 (26%) cases the BP was focal and in 132 (39%) was multifocal.

The analysis of association between the presence of BP and the Mayo Endoscopic Subscore showed that BP was present in only 3/40 (8%) cases of inactive disease (Mayo 0), in 35/74 (47%) cases of mildly active disease (Mayo 1) and in 184/225 (82%) cases of

moderate-severely active disease (Mayo 2 and 3). Two of the 3 cases with Mayo 0 and presence of BP presented an endoscopic relapse during the following 12 months. Among the patients with Mayo 1 and presence of BP, relapse was documented in 13/35 (37%), while patients with Mayo 1 without BP relapsed in 9/39 cases (23%) (p=0.19). See results of correlation in Table 5 (correlation coefficient Kendall τ: 0.4, p value <0.001).

The presence of BP also showed an association with active microscopic disease. BP was absent (0/45 patients) in those cases with no neutrophils in crypts or none epithelial damage (grade <3.1) whereas was present in 222/294 patients (76%) when severe inflammation was observed (grade ≥3.1) (p<0.001).

Neutrophils and epithelial injury

Neutrophils in lamina propria were observed in 294/339 cases (86.7%), neutrophils in epithelium in 292/339 (86.1%) and epithelial injury in 285/339 (84.1%).

Endoscopic activity and active microscopic disease

Active microscopic disease was considered when a patient presented ≥ Grade 3.1 in any of the histological scores.

As expected, patients with endoscopically active UC, it means Mayo 2 and 3, had active microscopic disease in almost all the cases (104/107 cases of Mayo 2 [97%] and 117/118 cases with Mayo 3 [99%]). But also patients in endoscopic remission (Mayo 0) presented with active microscopic disease in 10/40 (23%) cases, and those with mild endoscopic lesions (Mayo 1) in 62/74 (84%) cases.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

DISCUSSION

To date, 20 different histological scoring systems for UC have been published, but only two of them have been recently validated, the Nancy Score and the Robarts Histopathology Index.[13–15] The Nancy score comprises three histological items that define five grades of histological activity: absence of significant histological disease, chronic inflammatory infiltrate with no acute inflammatory infiltrate, mildly active disease, moderately active disease and severely active disease.[14] The Robarts histopathology index, includes 4 grades: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium and erosions or ulcerations.[15] Although they are simpler to use than the OGS, they do not include the presence of basal plasmacytosis or eosinophils in lamina propria.[15] The absence of eosinophils in these scores is acceptable because the function of these cells in IBD remains incompletely understood. The exclusion of basal plasmacytosis is less clear. Most probably this item is included in the "chronic inflammatory infiltrate". This is however defined in the Robarts study as "round cells in the lamina propria" and in the Nancy index as the quantity of lymphocytes and plasma cells in the biopsy specimen. These definitions do not take into account the basal location of these cells as it occurs in UC and the importance of the distribution pattern both for diagnosis and relation with disease activity. In our opinion, the absence of these two parameters limits the value of the scores, because both, especially basal plasmacytosis, have been identified in multiple studies now as predictors of UC evolution as relapse or non-response to medication. [2,7–9]

We therefore developed a simplified histological score for UC, the SGS, derived from the OGS. The new score comprised those variables associated with inflammatory activity

and/or prediction of relapse. The number of subcategories in the SGS was also reduced compared to the OGS and as stated above, we added basal plasmacytosis.[2,9] Neutrophils and epithelial damage were kept in the SGS as markers of microscopic activity of UC. Eosinophils in lamina propria were also included, because they are clearly increased in active disease and have also been associated with relapse or lack of response to medication in previous studies, although they may also be active in quiescent disease. [7,8]

In a first step we assessed the correlation of both histological scores (OGS and SGS) with a validated endoscopic score, the Mayo Endoscopic Subscore. An endoscopic score is considered more reliable than clinical symptoms or biomarkers in the assessment of activity in UC.[6] Among the existing endoscopic scores for UC, the Mayo Endoscopic Subscore is used in routine clinical practice in our center. The correlation of both histological scores with the endoscopic score was comparable in this cohort of newly diagnosed UC patients.

Next, we investigated the inter-observer agreement between an experienced gastrointestinal pathologist and the trained readers. Overall, a moderate agreement was reached for both the different grades and the final score of the SGS, being in this last case higher for SGS (kappa 0.56) than for the original GS (0.4). The detection of histological activity reached a good agreement (kappa 0.7) for the SGS. We consider these as good results, especially when keeping in mind that recently trained readers were involved, and that these agreement coefficients do not differ from those obtained in other studies.[5,16] Consequently, we therefore think that this simplified score could be easily taught to pathologists or gastroenterologists without a large experience in reading IBD biopsies,

thereby possibly facilitating the development of clinical trials in IBD that comprise histological assessment.

Similarly to previous studies, microscopic active disease based on the presence of neutrophils in the epithelium or epithelial injury was observed in a significant proportion of patients in endoscopic remission. Histological grade ≥3.1 was detected in 25% of patients with complete endoscopic remission (Mayo Endoscopic Subscore 0) but increased to 84% when mild endoscopic disease (Mayo Endoscopic Subscore 1) was identified. We feel it is important that randomized trials in UC with novel compounds also take into account histology in order to study the ability of new drugs to induce histological healing. This is important as persistent histological activity has been associated with higher relapse rates.

The inclusion of BP in the SGS (grade 1), defined as the presence of plasma cells in the deepest part of the lamina propria or below the crypts, alongside or penetrating the muscularis mucosae, represents the main change between the original and the proposed score. In previous studies, BP has been associated with a higher risk of relapse in UC patients in endoscopic remission.[2,9] In the present study, the presence of BP was also significantly associated with a higher degree of endoscopic activity and the presence of microscopically active disease.

The main limitation of this study is its retrospective nature. Besides, as the role of the eosinophils in lamina propria (grade 2A in both scores) could not be evaluated, the importance of eosinophils in the evolution of the UC or their relation with IBD medications is still not clear and will have to be determined in further studies.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Further validation of the SGS will be necessary in a prospective trial. We believe that a validated SGS has the potential to be implemented in clinical trials and routine practice to assess histological healing in UC. Prospective trials will provide evidence if histological healing beyond mucosal healing favorably impacts on the evolution of the disease.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

CONFLICT OF INTEREST:

A. Jauregui-Amezaga, A. Geerits, Y. Das, B. Lemmens, X. Sagaert, T. Lobaton and K. Geboes have no conflict of interest. T. Bessissow has research support from Abbvie, receives lecture fees from Abbvie, Ferring and Shire and consulting fees from Janssen, Abbvie, Actavis and Takeda..M. Ferrante has a research grant from Takeda, receives speakers fees from MSD, Janssen, Abbvie, Boehringer-Ingelheim, Ferring, Chiesi, Tillotts, Zeria, Mitsubishi Tanabe and is consultant for MSD, Janssen, Abbvie, Boehringer-Ingelheim, Ferring. G. Van Assche receives researchl support from Abbvie and MSD, lecture fees from Abbvie, Ferring, MSD, Janssen, Takeda and is consultant for Abbvie, MSD, Takeda. R. Bisschops receives lecture fees from PentaxEurope, Ipsen , Ferring. Gert De Hertogh is consultant for Galapagos, Centocor and Genentech. S. Vermeire receives grant support from Abbvie, MSD, Centocor, lecture fees from Abbie, MSD, Takeda, Ferring and is consultant for Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos

Manuscript Doi : 10.1093/ecco-jcc/jjw154

FUNDING:

No specific funding has been received.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

ACKNOWLEDGEMENTS:

Specific author contribution: A. Jauregui-Amezaga, G. De Hertogh, and S. Vermeire designed the study; S. Vermeire, G. Van Assche, M. Ferrante, and R. Bisschops performed the endoscopies and took the biopsies; X. Sagaert helped with the selection of the biopsies and the initial diagnostic evaluation; A. Jauregui-Amezaga, A. Geerits, Y. Das and G. De Hertogh read the slides of the study, worked on the acquisition of data and performed the statistical analysis and interpretation of data; All authors contributed to critical revision of the manuscript.

REFERENCES:

1. Riley SA., Mani V., Goodman MJ., Dutt S., Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;**32**(2):174–8.

2. Bitton A., Peppercorn MA., Antonioli DA., Niles JL., Shah S., Bousvaros A., et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001;**120**(1):13–20.

3. Rutter M., Saunders B., Wilkinson K., Rumbles S., Schofield G., Kamm M., et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;**126**(2):451–9.

4. Gupta RB., Harpaz N., Itzkowitz S., Hossain S., Matula S., Kornbluth A., et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;**133**(4):1091–9.

5. Geboes K., Riddell R., Ost A., Jensfelt B., Persson T., Lofberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000;**47**(3):404–9.

6. Schroeder KW., Tremaine WJ., Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**(26):1625–9.

7. Magro F., Langner C., Driessen Aa., Ensari A., Geboes K., Mantzaris GJ., et al. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013;**7**(10):827–51.

8. Zezos P, Patsiaoura K, Nakos A, Mpoumponaris A, Vassiliadis T, Giouleme O, et al. Severe eosinophilic infiltration in colonic biopsies predicts patients with ulcerative colitis not responding to medical therapy. *Color Dis* 2014;**16**(12):O420–30.

9. Bessissow T., Lemmens B., Ferrante M., Bisschops R., Van Steen K., Geboes K., et al. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. *Am J Gastroenterol* 2012;**107**(11):1684–92.

10. Villanacci V., Antonelli E., Reboldi G., Salemme M., Casella G., Bassotti G.Endoscopic biopsy samples of naïve “colitides” patients: Role of basal plasmacytosis. *J Crohn’s*

Colitis 2014;**8**(11):1438–43.

11. Lemmens B., Arijs I., Van Assche G., Sagaert X., Geboes K., Ferrante M., et al. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:1194–201.

12. Landis JR., Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**(1):159–74.

13. Mosli MH., Feagan BG., Sandborn WJ., D'haens G., Behling C., Kaplan K., et al. Histologic evaluation of ulcerative colitis: a systematic review of disease activity indices. *Inflamm Bowel Dis* 2014;**20**(3):564–75.

14. Marchal-Bressenot A., Salleron J., Boulagnon-Rombi C., Bastien C., Cahn V., Cadiot G., et al. Development and validation of the Nancy histological index for UC. *Gut* 2015 Oct 13. Doi: 10.1136/gutjnl-2015-310187.

15. Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, et al. Development and validation of a histological index for UC. *Gut* 2015;**Oct 16**. Doi: 10.1136/gutjnl-2015-310393.

16. Mosli MH., Feagan BG., Zou G., Sandborn WJ., D'Haens G., Khanna R., et al. Reproducibility of histological assessments of disease activity in UC. Gut. 2015 Nov;64(11):1765-73.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

TABLES:

Table 1: The original Geboes Score.

Grade 0: Architectural changes	0.0 No abnormality 0.1 Mild abnormality 0.2 Mild/moderate diffuse or multifocal abnormalities 0.3 Severe diffuse or multifocal abnormalities
Grade 1: Chronic inflammatory infiltrate	1.0 No increase 1.1 Mild but unequivocal increase 1.2 Moderate increase 1.3 Marked increase
Grade 2A: Eosinophils in lamina propria	2A.0 No increase 2A.1 Mild but unequivocal increase 2A.2 Moderate increase 2A.3 Marked increase
Grade 2B: Neutrophils in lamina propria	2B.0 No increase 2B.1 Mild but unequivocal increase 2B.2 Moderate increase 2B.3 Marked increase

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Grade 3: Neutrophils in epithelium	3.0 None 3.1 <5% crypts involved 3.2 <50% crypts involved 3.3 >50% crypts involved
Grade 4: Crypt destruction	4.0 None 4.1 Probable–Local excess of neutrophils in part of the crypts 4.2 Probable–Marked attenuation 4.3 Unequivocal crypt destruction
Grade 5: Erosions and ulcerations	5.0 No erosion, ulceration or granulation tissue 5.1 Recovering epithelium + adjacent inflammation 5.2 Probable erosion – focally stripped 5.3 Unequivocal erosion 5.4 Ulcer or granulation tissue

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Table 2: The proposed Simplified Geboes Score.

Grade 0: No inflammatory activity	0.0 No abnormalities 0.1 Presence of architectural changes 0.2 Presence of architectural changes and chronic mononuclear cell infiltrate
Grade 1: Basal plasma cells	1.0 No increase 1.1 Mild increase 1.2 Marked increase
Grade 2A: Eosinophils in lamina propria	2A.0 No increase 2A.1 Mild increase 2A.2 Marked increase
Grade 2B: Neutrophils in lamina propria	2B.0 No increase 2B.1 Mild increase 2B.2 Marked increase
Grade 3: Neutrophils in epithelium	3.0 None 3.1 <50% crypts involved 3.2 >50% crypts involved
Grade 4: Epithelial injury	4.0 None 4.1 Marked attenuation

Manuscript Doi : 10.1093/ecco-jcc/jjw154

(in crypt and surface epithelium)	4.2 Probable crypt destruction – Probable erosions 4.3 Unequivocal crypt destruction – Unequivocal erosion 4.4 Ulcer or granulation tissue

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Table 3 : Baseline demographic characteristics.

Patients, no.	103
N of colonoscopies.	339
Female, no. (%)	52 (51%)
Age at diagnosis, mean (SD)	38 (18)
Extension of UC, no. (%)	
E1 Proctitis	29 (28%)
E2 Left-sided colitis	46 (45%)
E3 Extensive colitis	28 (27%)
Smoking habit, no. (%)	
Non smokers	57 (60%)
Ex smokers	33 (35%)
Active smokers	5 (5%)
IBD family history, no. (%)	16 (17%)
Primary sclerosing colangitis, no. (%)	4 (4%)

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Table 4: Inter-observer agreement measured by Kappa Coefficient.

Kappa Coefficient of Original Geboes Score		Kappa Coefficient of Simplified Geboes Score	
Grade 0	0.51 (moderate)	**Grade 0**	
Grade 1	0.43 (moderate)	**Grade 1**	0.41 (moderate)
Grade 2A		**Grade 2A**	
Grade 2B	0.39 (low)	**Grade 2B**	0.42 (moderate)
Grade 3	0.49 (moderate)	**Grade 3**	0.54 (moderate)
Grade 4	0.58 (moderate)	**Grade 4**	0.56 (moderate)
Grade 5	0.47 (moderate)		
End Score	0.4 (moderate)	**End Score**	0.56 (moderate)

Table 5: Correlation between the presence of basal plasmacytosis (none, focal or multifocal) and the Mayo Endoscopic Subscore.

Presence of basal plasmacytosis (BP)	Mayo 0	Mayo 1	Mayo 2+3	Total
No BP	37 (93%)	39 (53%)	41 (18%)	117
Focal BP	1 (2%)	12 (16%)	77 (34%)	90
Multifocal BP	2 (5%)	23 (31%)	107 (48%)	132
Total	40 (100%)	74 (100%)	225 (100%)	339

Kendall τ: 0.4, p value <0.001

Manuscript Doi : 10.1093/ecco-jcc/jjw154

FIGURES - LEGENDS:

Figure 1: Simplified Geboes Score.

Figure 2: Comparison of endoscopic and both histological scores.

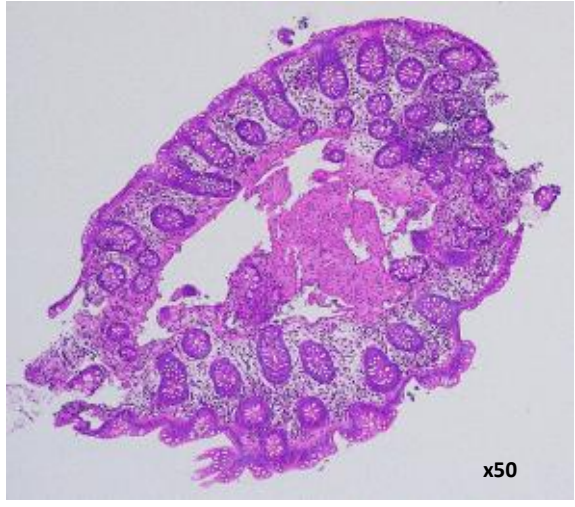
In order to perform comparisons between the Mayo Endoscopic Subscore and both histological scores, it was necessary to create conversions of both histological scores. They were converted to a 4-tiered grading system: grade 0 was created for defining normal bowel tissue or inactive colitis, grade 1 corresponded to mild disease, grade 2 with moderate disease, and grade 3 with severe disease.

At the left of the table, the performed conversions are represented in 4 different colours. Two different conversions from the original Geboes Score were constructed based on the results of a previous study (conversions 3 and 9 showed the best results in this study).[11] Three possible conversions were tested for the Simplified Geboes Score, combining grade 1 and 2 (conversion 1), grade 2 and 3 (conversion 2), and grade 3 and 4 (conversion 3) of SGS.

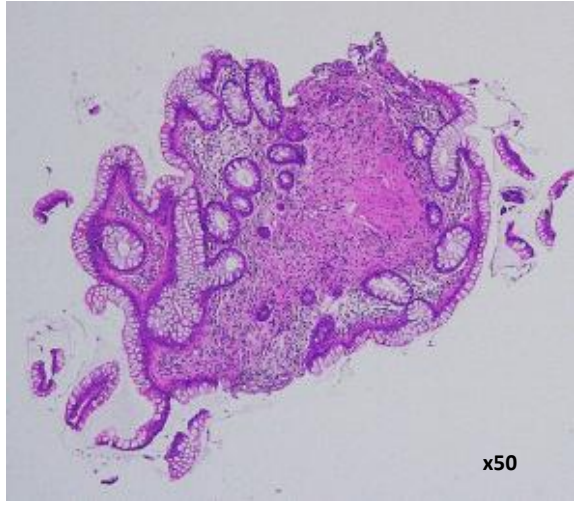
At the right of the table, a straightforward comparison between both histological scores and the Mayo Endoscopic Subscore is represented.

Manuscript Doi : 10.1093/ecco-jcc/jjw154

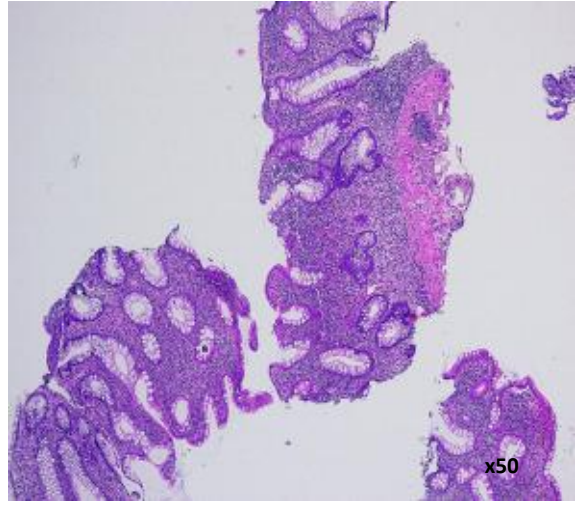
Figure 3: Association of the different subgrades of the original Geboes Score and Simplified Geboes Score with the Mayo Endoscopic Subscore.



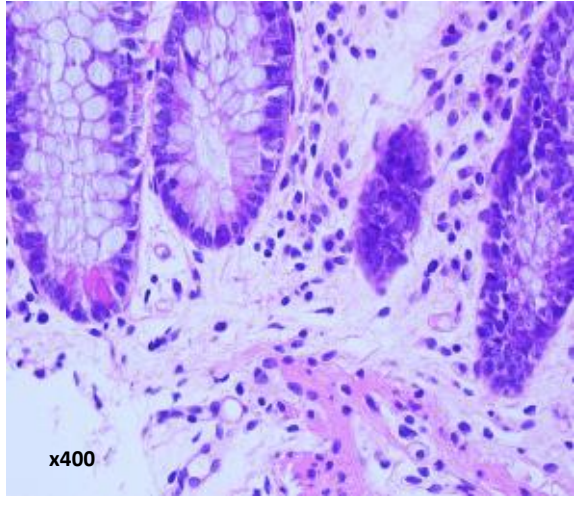
Grade 0.0. No abnormalities.



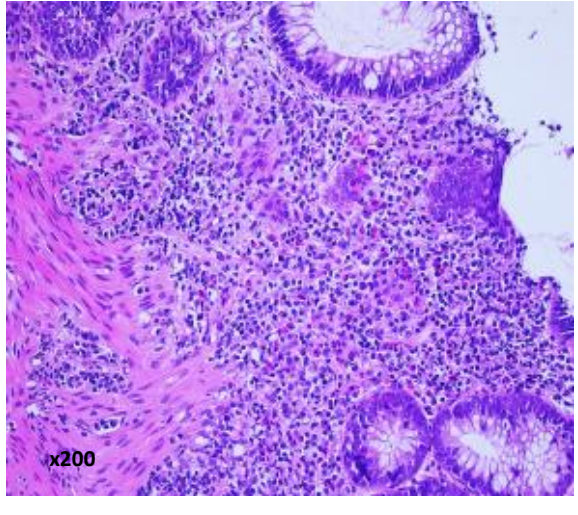
Grade 0.1. Architectural abnormalities.



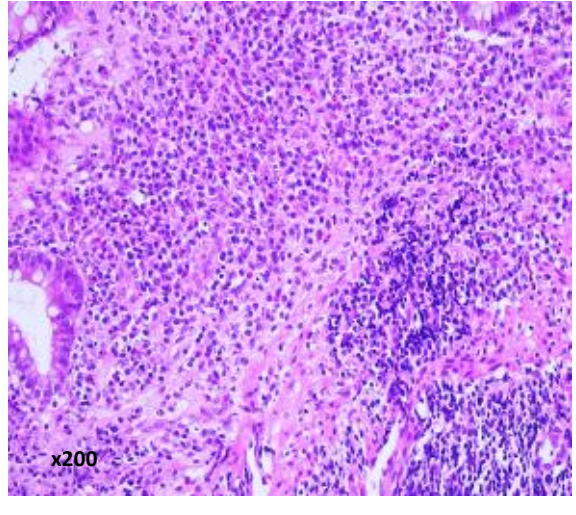
Grade 0.2. Architectural abnormalities and chronic mononuclear cell infiltrate.



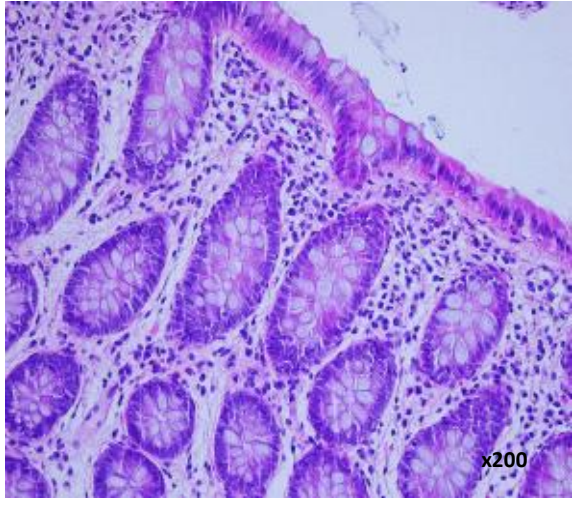
Grade 1.0. No presence of plasma cells around or below the crypts.



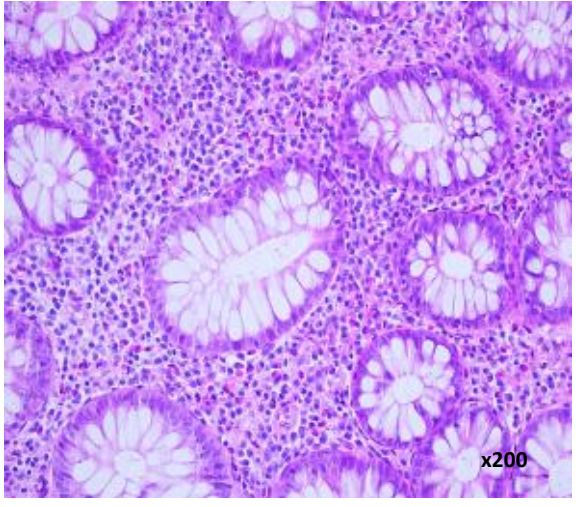
Grade 1.1. Basal plasmacytosis in a single position in a single tissue fragment (focal).



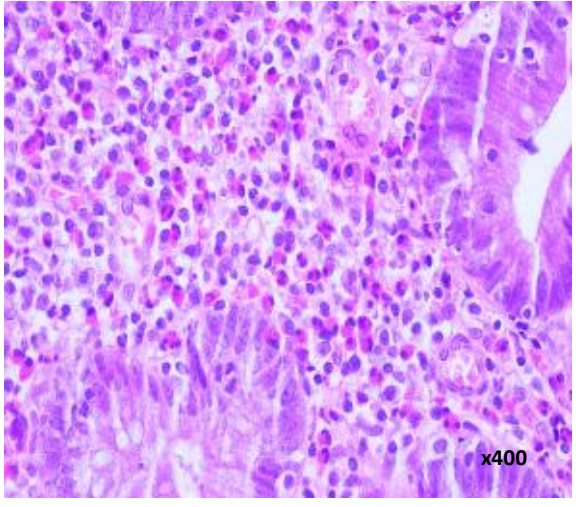
Grade 1.2. Basal plasmacytosis in multiple fragments in single or multiple slides (multifocal).



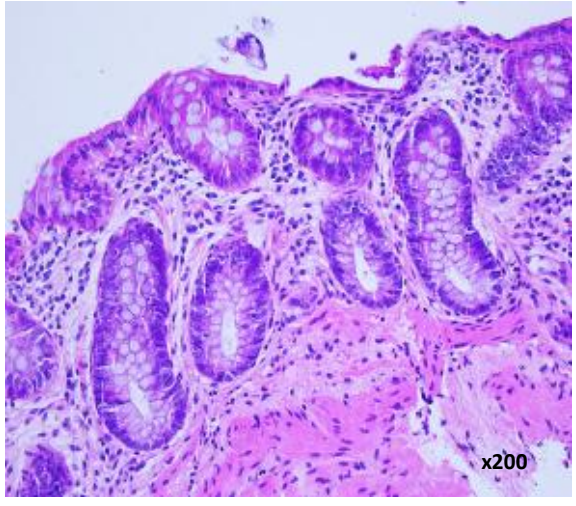
Grade 2A.0. No increase in the number of eosinophils in lamina propria.



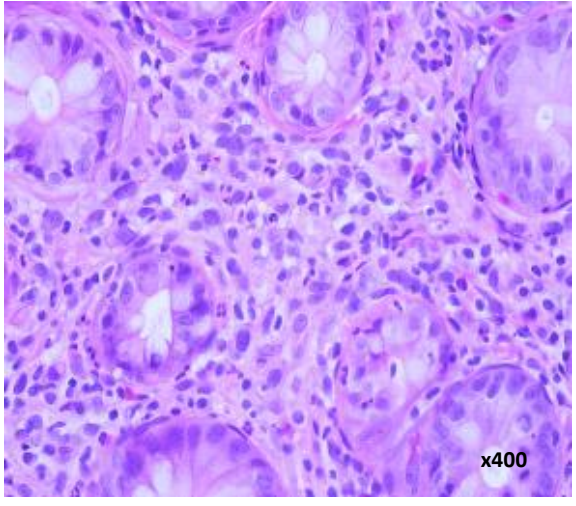
Grade 2A.1. Mild increase of eosinophils: a compact group of eosinophils in lamina propria.



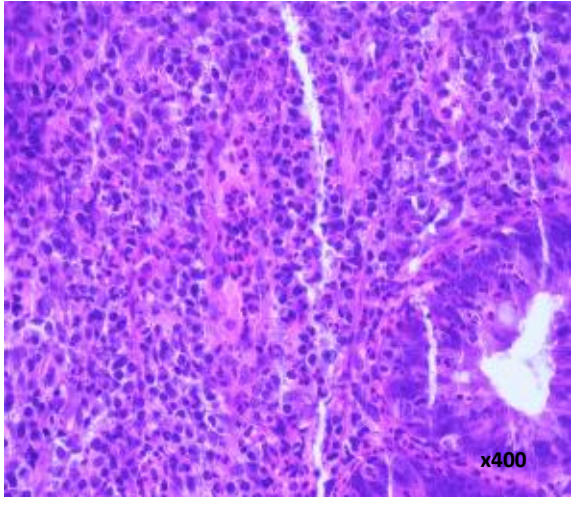
Grade 2A.2. Marked increase of eosinophils: diffuse presence of eosinophils in lamina propria.



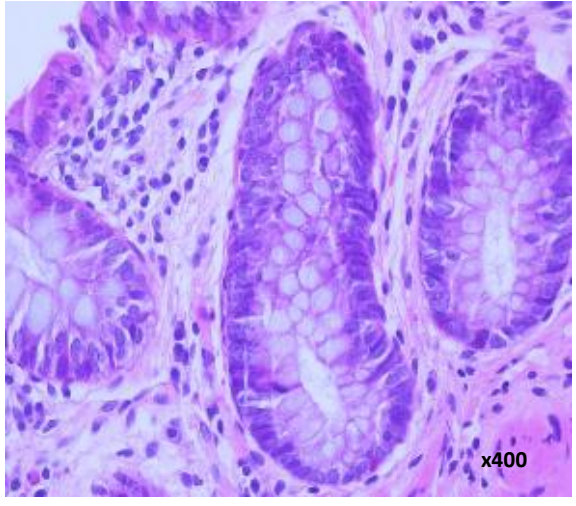
Grade 2B.0. No neutrophils in lamina propria.



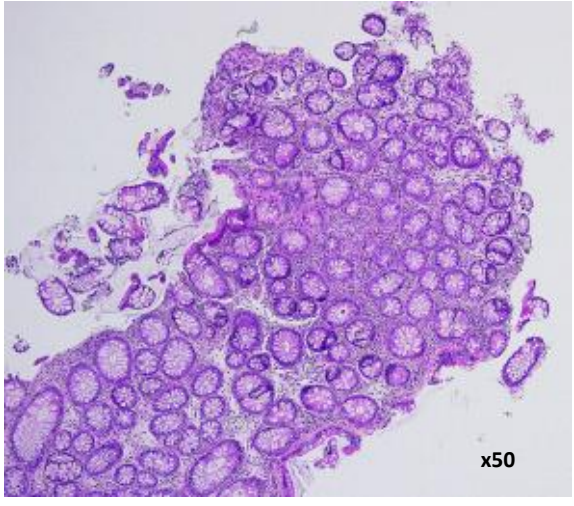
Grade 2B.1. Mild increase of neutrophils in lamina propria, only visible at high magnification.



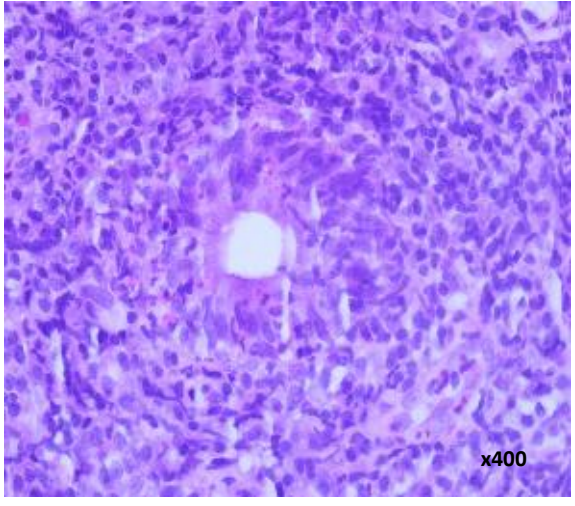
Grade 2B.2. Marked increase of neutrophils in lamina propria, visible at lower magnification.



Grade 3.0. No presence of neutrophils in the crypts.

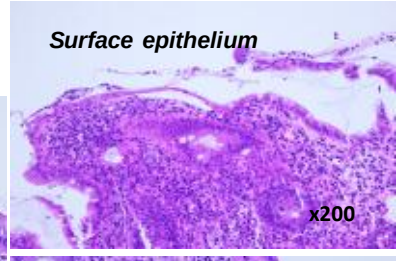


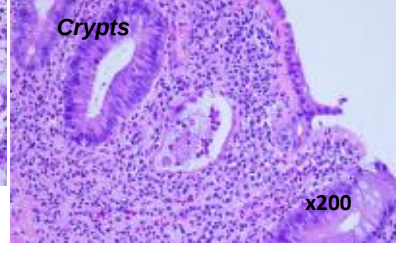
Grade 3.1. Mild presence of neutrophils in epithelium: <50% of crypts involved.



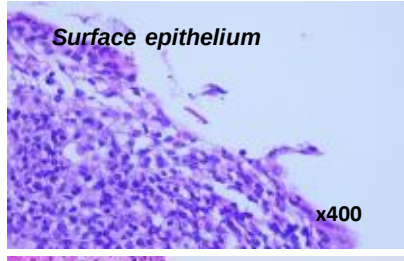
Grade 3.2. Marked presence of neutrophils in epithelium: >50% of crypts involved.

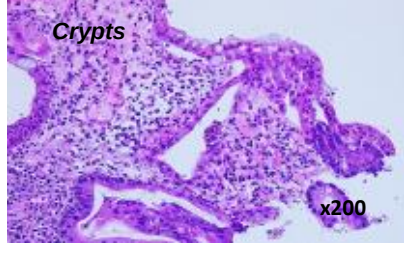
Grade 4.0. No crypt/surface epithelium destruction.



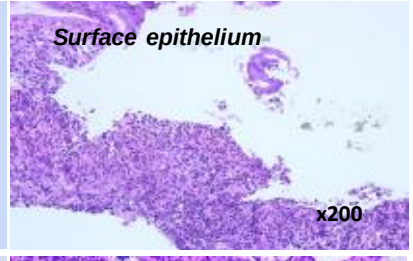


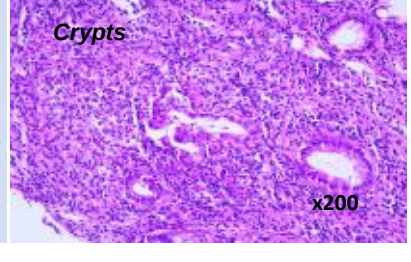
Grade 4.1. Marked attenuation of epithelium.



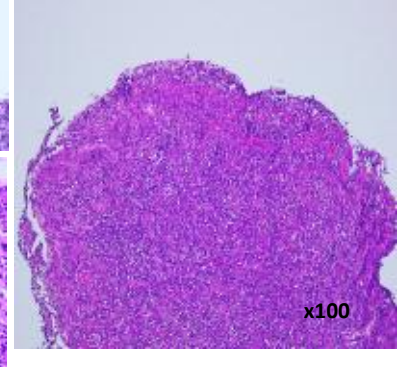


Grade 4.2. Probable crypt destruction / erosions.





Grade 4.3 Unequivocal crypt destruction / erosions



Grade 4.4. Ulcers or granulation tissue.

Figure 2

Conversions		ORIGINAL GEBOES SCORE / MAYO ENDOSCOPIC SUBSCORE						
3	9			Mayo 0	Mayo 1	Mayo 2	Mayo 3	Total
		Grade 0: Arquitectural changes	0.0: no abnormality	9	3	0	0	12
			0.1: mild abnormality	12	3	0	0	15
			0.2: mild/moderate diffuse/multifocal abnormalities	0	0	0	0	0
			0.3: severe diffuse or multifocal abnormalities	0	0	0	0	0
		Grade 1: Chronic inflammation infiltrate	1.1: mild but unequivocal increase	9	6	2	1	18
			1.2: moderate increase	0	0	0	0	0
			1.3: marked increase	0	0	0	0	0
		Grade 2B: Neutrophils in lamina propria	2B.1: mild but unequivocal increase	1	0	1	0	2
			2B.2: moderate increase	0	0	0	0	0
			2B.3: marked increase	0	0	0	0	0
		Grade 3: Neutrophils in epithelium	3.1: <5% crypts involved	2	1	3	1	7
			3.2: <50% crypts involved	0	0	0	0	0
			3.3: >50% crypts involved	0	0	0	0	0
		Grade 4: Crypt destruction	4.1: probable-local excess of neutrophils in part of crypts	0	1	1	0	2
			4.2: probable-marked attenuation	0	0	1	0	1
			4.3: unequivocal crypt destruction	0	1	1	0	2
		Grade 5: Erosions and ulcerations	5.1: recovering epithelium + adjacent inflammation	5	25	33	21	84
			5.2: probable erosion – focally stripped	1	23	34	28	86
			5.3: unequivocal erosions	0	10	30	46	86
			5.4: ulcer or granulation tissue	1	1	1	21	24

Conversions			SIMPLIFIED GEBOES SCORE / MAYO ENDOSCOPIC SUBSCORE					
1	2	3			Mayo 0	Mayo 1	Mayo 2	Mayo 3	Total
			Grade 0	Includes Grade 0&1 from Geboes Score without basal plasmacytosis	30	12	2	1	45
			Grade 1: Basal plasmacytosis	1.1: mild increase	0	0	0	0	0
				1.2: marked increase	0	0	0	0	0
			Grade 2: Neutrophils in lamina propria	2B.1: mild increase	1	0	1	0	2
				2B.2: moderate increase	0	0	0	0	0
			Grade 3: Neutrophils in epithelium	3.1: <50% crypts involved	2	1	3	1	7
				3.2: >50% crypts involved	0	0	0	0	0
			Grade 4: Epithelial injury	4.1: marked attenuation	0	1	2	0	3
				4.2: probable erosions	3	19	24	22	68
				4.3: unequivocal crypt destruction – unequivocal erosions	3	40	74	73	190
				4.4: ulcer or granulation tissue	1	1	1	21	24
				Total	40	74	107	118	339

Manuscript Doi : 10.1093/ecco-jcc/jjw154

Figure 3