Histopathological diagnosis and scoring of IBD

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PART 1
HISTOPATHOLOGICAL DIAGNOSIS OF IBD

Overview

- Introduction
- Procedures needed for the diagnosis of IBD
- Ulcerative colitis – microscopic features
- Crohn’s disease – microscopic features
- IBD unclassified
- How accurate are we on endoscopic biopsies ?

INTRODUCTION

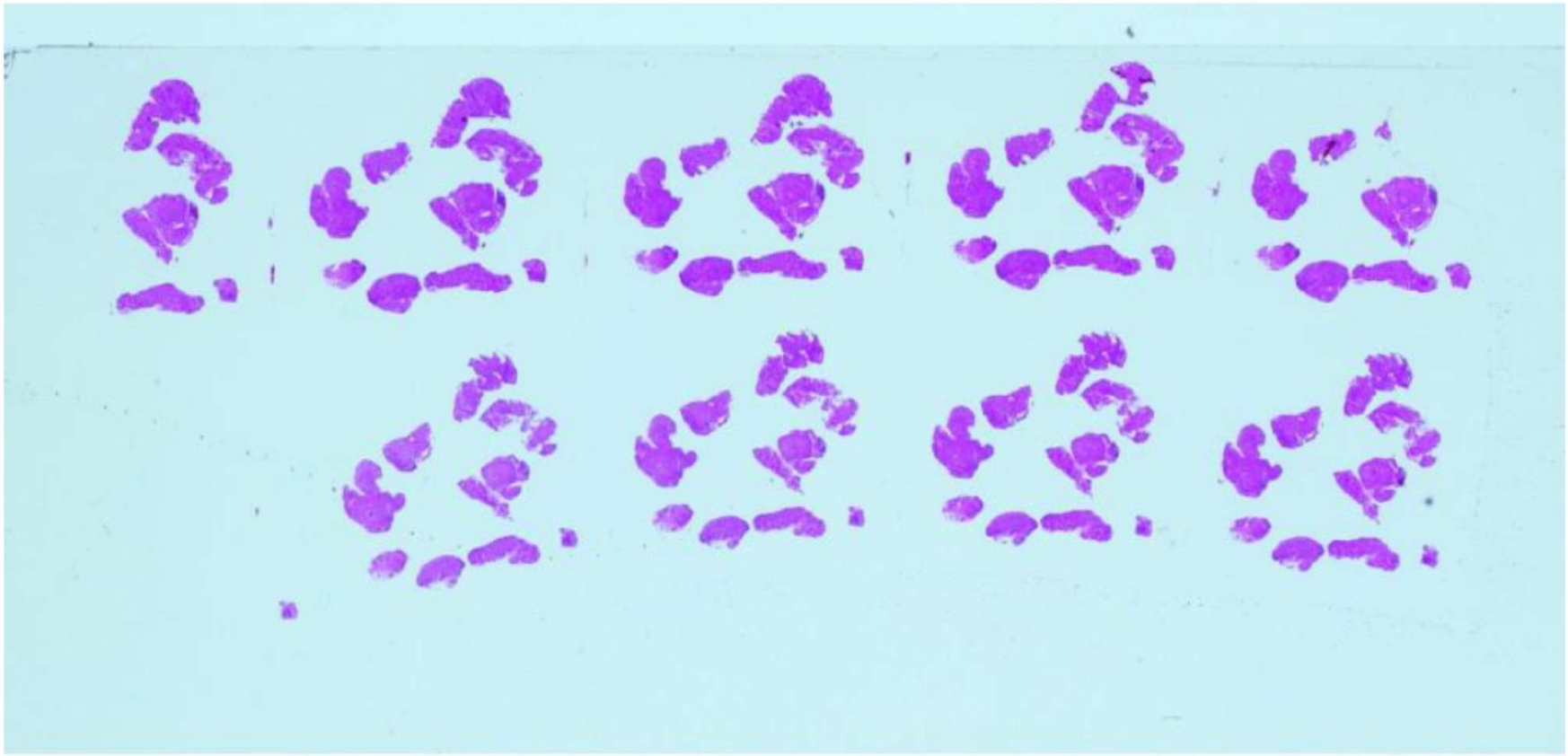
- Colonoscopy increasingly used in patients with diarrhea
- Endoscopy alone may be non-specific or misleading
  - Mucosal biopsies often needed
- Range of findings:
  - Normal, acute self-limited colitis, microscopic colitis, other
  - Chronic colitis (IBD)
    - Ulcerative colitis, Crohn's disease
- Problems for IBD:
  - Morphologic overlap UC / CD in endoscopic biopsies
  - Unusual patterns of presentation
  - Mimickers

Table 1. Entities Causing Difficulty in the Diagnosis and Classification of Inflammatory Bowel Disease

Ulcerative colitis with Crohn's disease like features
Discontinuous disease
Superficial fissuring ulcers
Aphthous ulcers
Ileal involvement
Involvement of the upper gastrointestinal tract
Granulomas
Crohn's disease with ulcerative colitis-like features
Pancolitis
Superficial colitis
Inflammatory bowel disease complicated by infections
Pseudomembranous colitis
Cytomegalovirus
Other
Chronic recurrent (refractory) pouchitis
Unusual pathologic manifestations of other forms of colitis
Ischemia
Radiation
Microscopic colitis with features of IBD
Diverticular disease associated colitis
Diversion colitis
NSAID-induced colitis mimicking IBD
Acute self-limited colitis
Other
Polyposis disorders that mimic inflammatory bowel disease
Solitary rectal ulcer syndrome
Inflammatory "cap" polyposis
Juvenile polyposis

PROCEDURES NEEDED FOR IBD DIAGNOSIS

- Multidisciplinary approach
- Ileocolonoscopy > rectoscopy
- 2 biopsies from at least 5 sites incl ileum (accuracy ↑)
  - Fulminant colitis
  - Separate vials
  - Immediately fixed (buffered formalin)
- Relevant clinical info
  - Endoscopic findings, age, disease duration, R/, travel history
- For every vial : HEs (serial sections at 2 levels)



Geboes K et al

http://dx.doi.org/10.5772/52739

ULCERATIVE COLITIS : microscopy, active

- Widespread crypt architectural distortion
  - More frequent than in CD
- Diffuse transmucosal infiltrate …
  - Diffuse without skip lesions
- … with basal plasmocytosis
  - DD infectious colitis, but not CD
- Active component (cryptitis, crypt abscesses)
- (Mucin depletion)

- NOTE : if uncertain : repeat biopsies after ≥ 6 wks

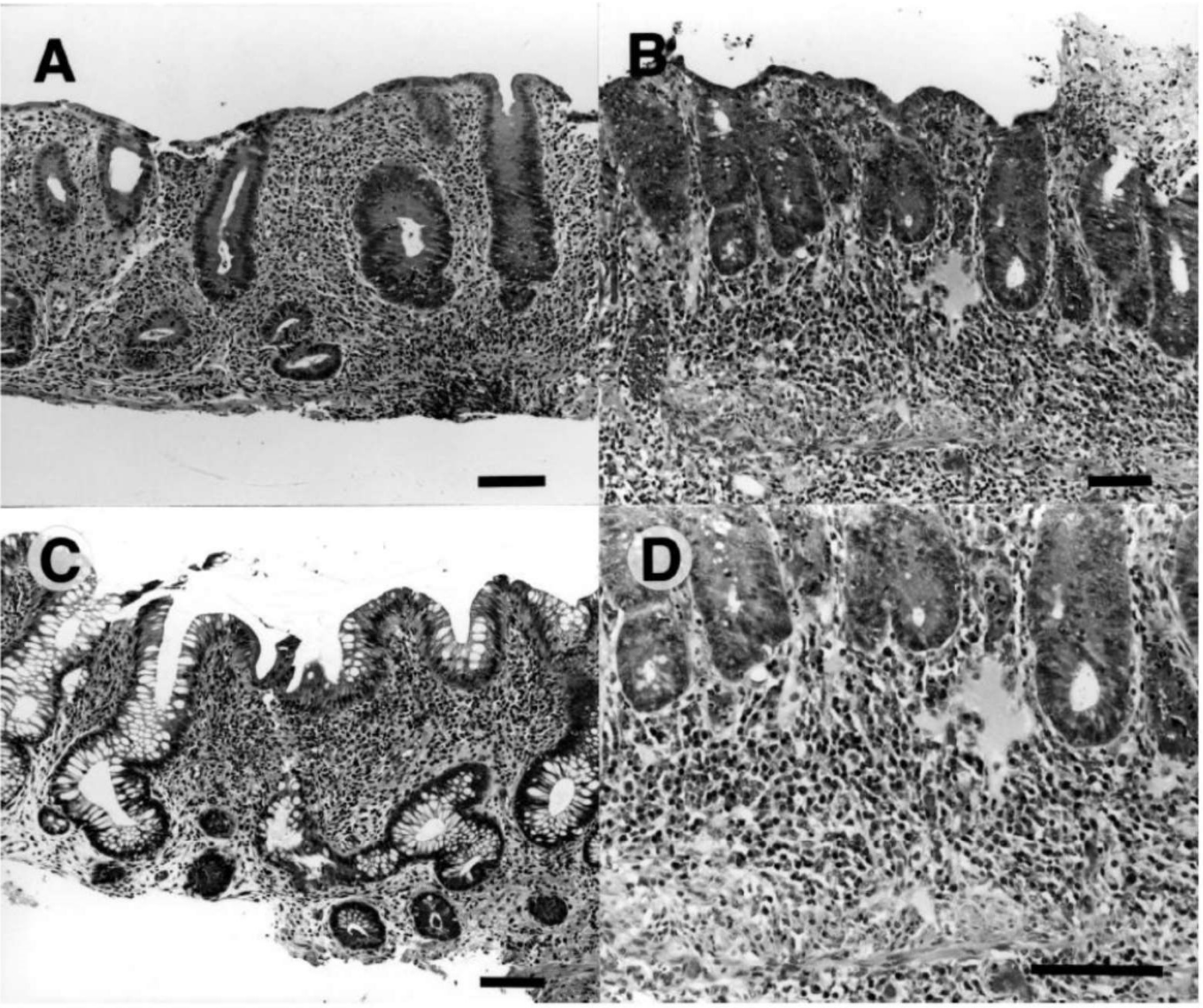
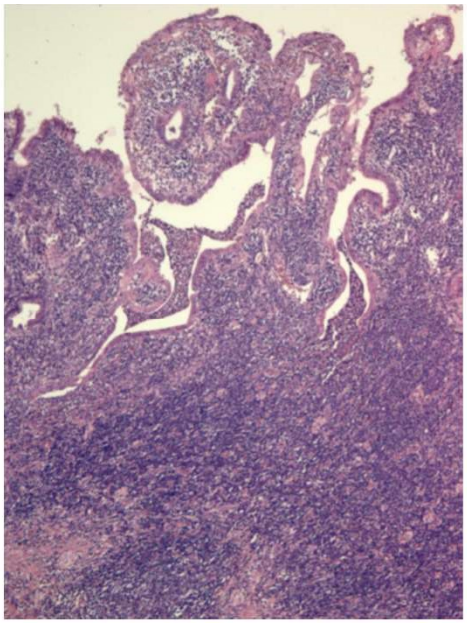
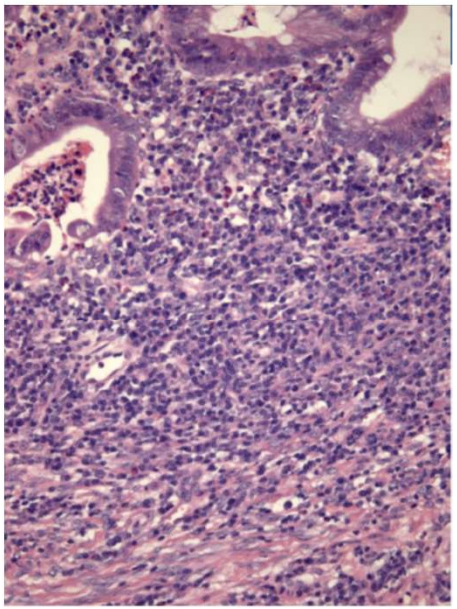


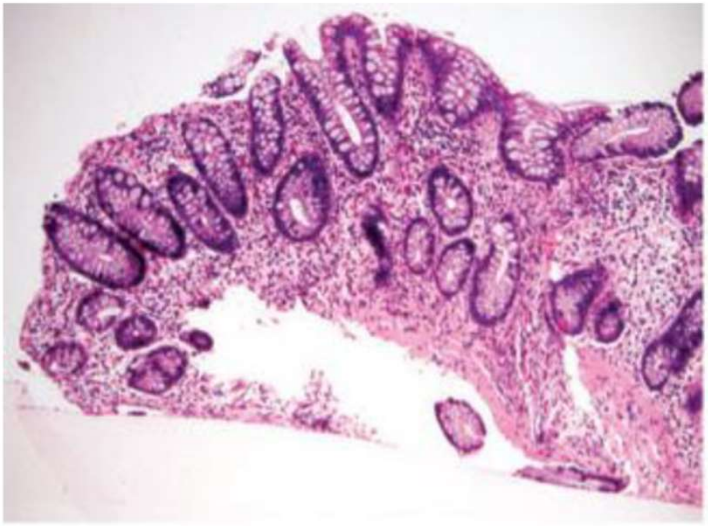
Fig. 1. Crypt architectural abnormalities and basal plasmacytosis. 1A and B. Typical figures judged as 'presence' of crypt atrophy which was recognized by generally increased distance of more than one crypt diameter between crypts (A), or a general increase in the distance between crypts and the muscularis mucosae (B). 1C. Typical figure judged as 'presence' of crypt distortion, which was recognized by branched crypts with non-parallelism. 1D. Typical basal plasmacytosis (Hematoxylin and eosin; bar = 100 μm.)

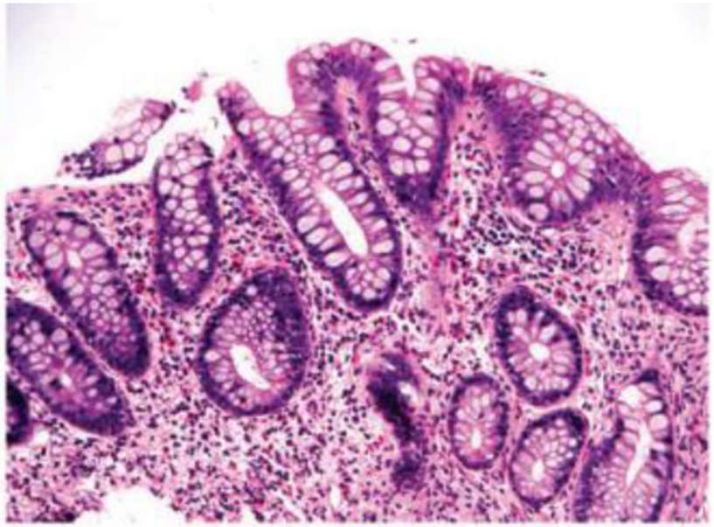




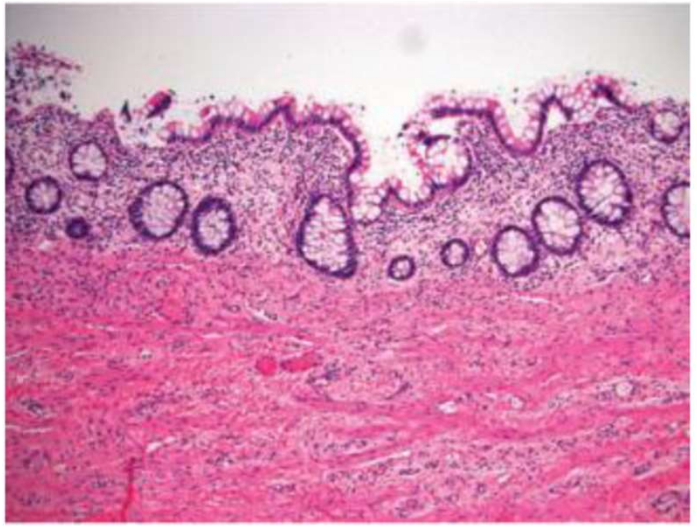
ULCERATIVE COLITIS : microscopy, inactive

- Long-standing disease: ↓ involvement
  - Rectal sparing
  - Discontinuous disease
  - Disappearance of basal plasmocytosis
  - Absence of active inflammation
- Predictive of clinical relapse:
  - Persistence of LP cellularity
  - (basal plasmocytosis, high numbers of eosinophils)
  - Presence of neutrophils
  - Epithelial damage
- Influence of treatment !

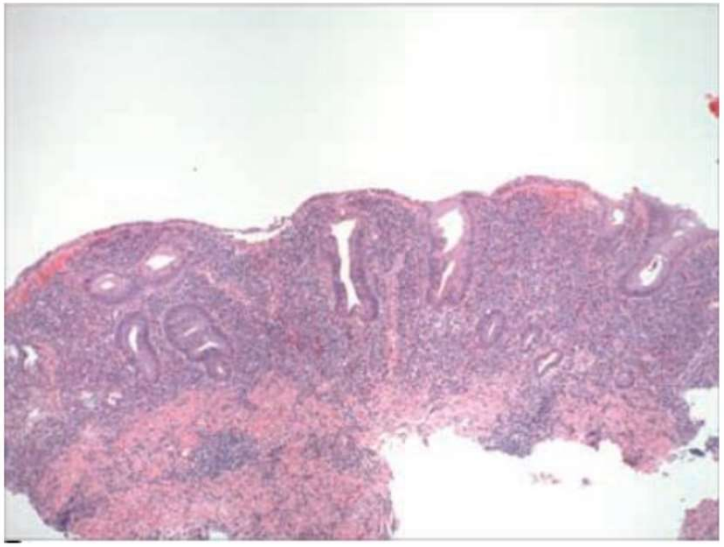




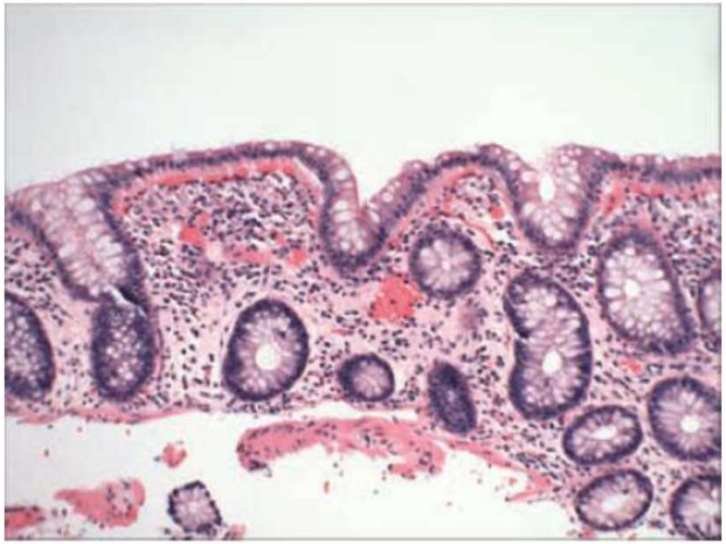
resolving phase of ulcerative colitis



quiescent colitis



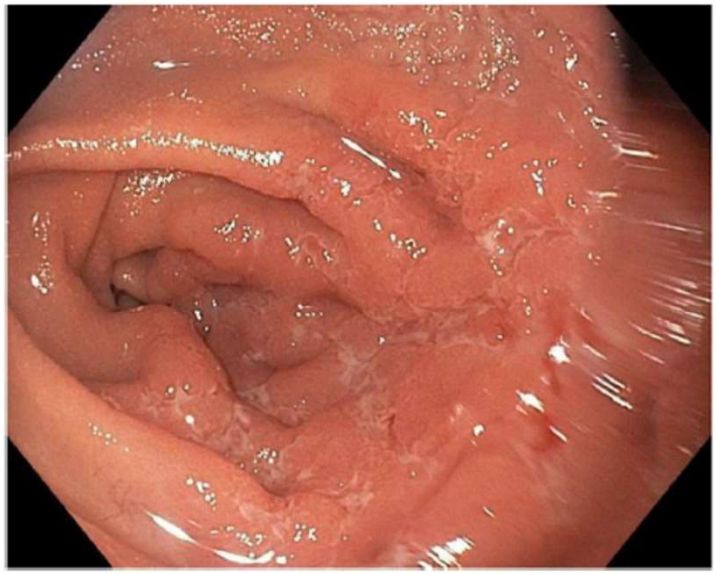
Before R/

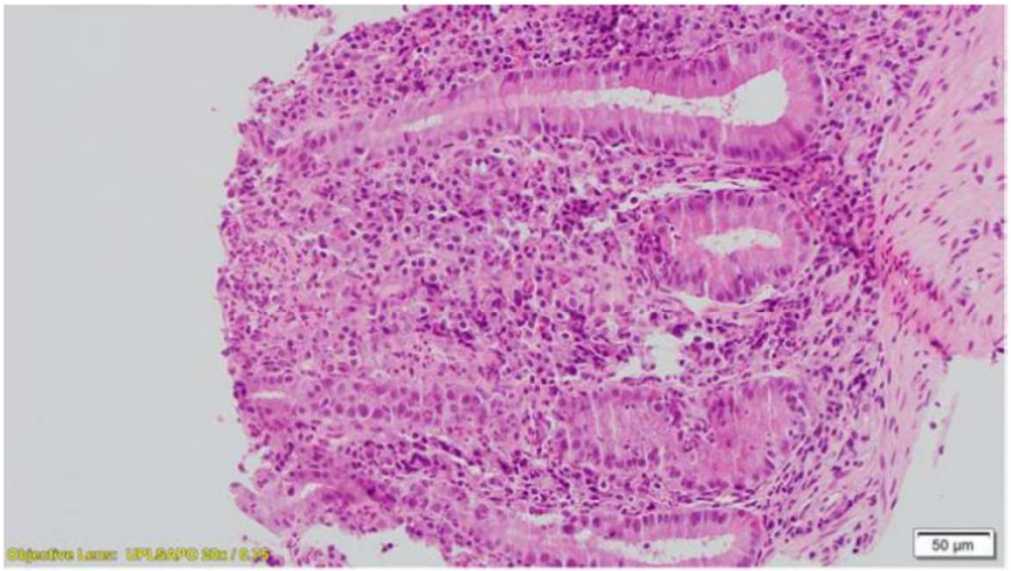


After R/

ULCERATIVE COLITIS : children

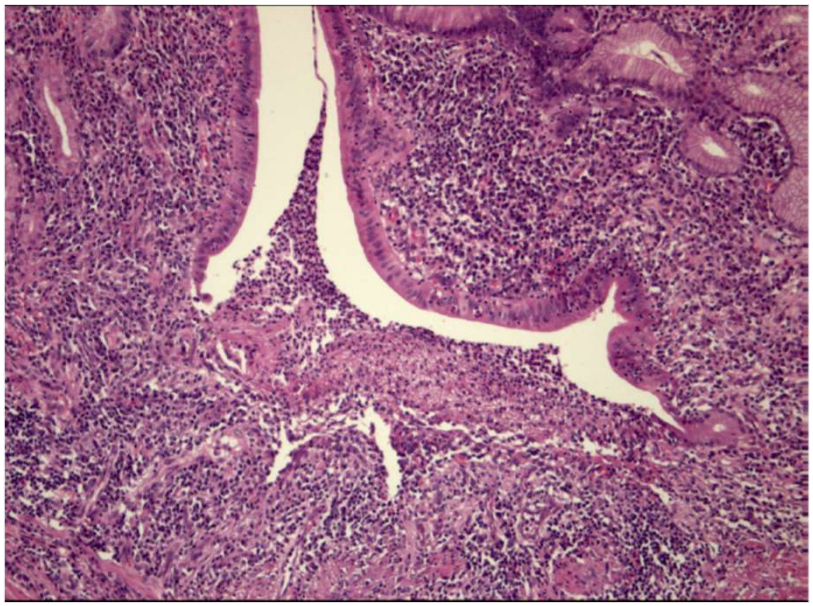
- Compared with adults:
  - More subtotal / extensive colitis
  - Less severe & less diffuse architectural abnormalities
  - When < 10 yrs of age : commonly relative rectal sparing
  - Duodenitis not uncommon

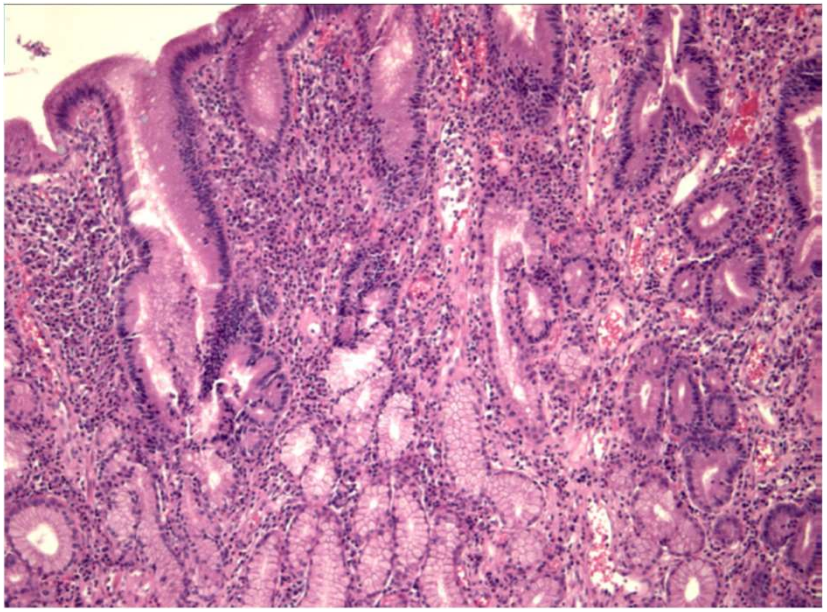


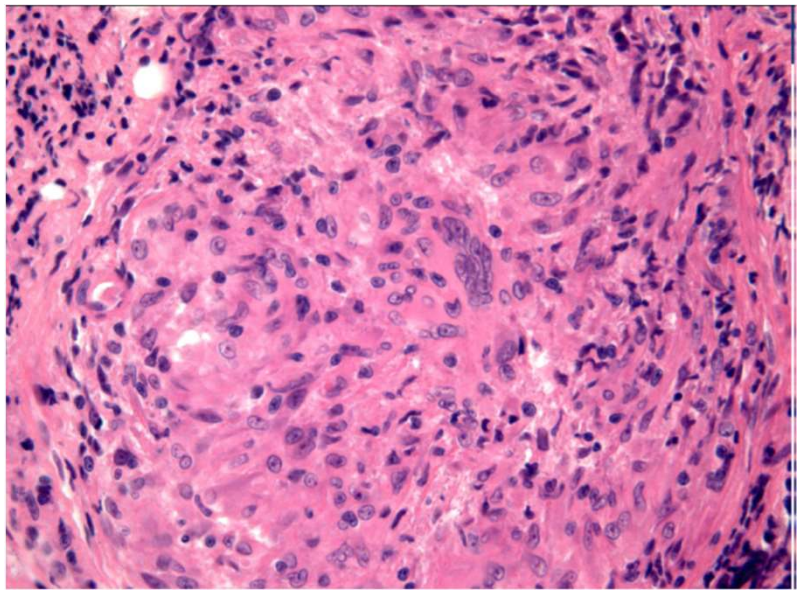


CROHN'S DISEASE : microscopy, active

- Discontinuous crypt distortion, > 10%
- Focal chronic inflammation
  - One or more foci, ≠ normal lymphoid aggregates
- Granulomas
  - Collection of epithelioid histiocytes
  - Not associated with crypt injury
  - With / without giant cells; usually no necrosis
- At least 3 features / at least 1 and a granuloma

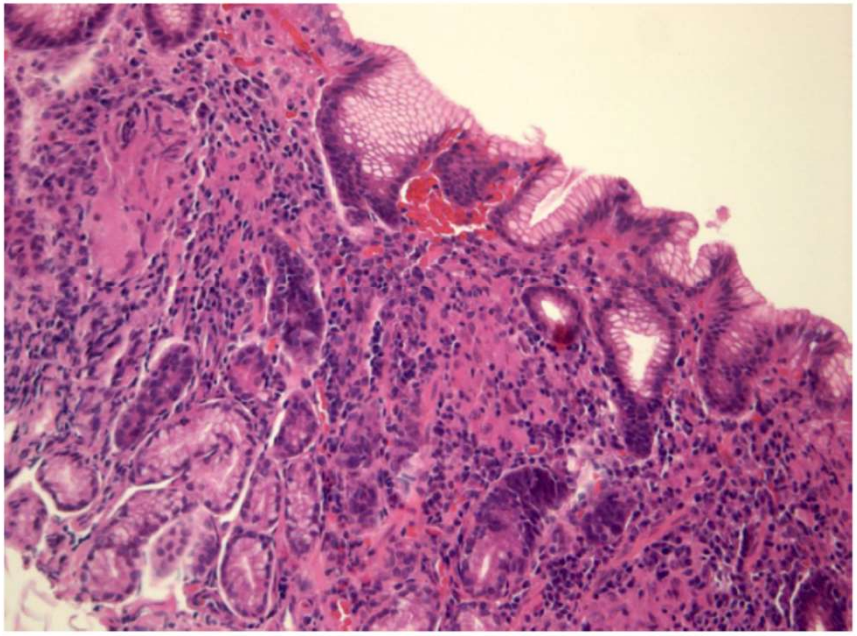






CROHN'S DISEASE : children

- Compared with adults:
  - When < 10 yrs of age : more colitis, less ileitis
  - All biopsies may show chronic inflammation (is it patchy ?)
  - Granulomas are more frequent in children (also upper GI !)



IBD UNCLASSIFIED ?

- "Indeterminate colitis (IC)" = for surgical specimens
  - With features overlapping between UC and CD
    - Relative rectal sparing, fissuring ulceration, transmural lymphoid inflammation
    - Usually in fulminant UC with extensive mucosal ulceration
- "IBD unclassified (IBDU)" = for endoscopic biopsies
  - When surely IBD but distinction UC / CD can't be made
- Both IC and IBDU are "temporary diagnoses"
  - Review all previous biopsies
  - Scheduled follow-up procedures
  - Most ultimately behave like UC …

How accurate are we on endoscopic biopsies?

- Evaluation of multiple changes in topographical context
- "Expert" GI pathologists : 74% UC, 64% CD
- Recommendations:
  - Take multiple biopsies, especially if you suspect CD
    - Rectal alone is not enough !
  - Accuracy is lower in CD than in UC
    - Because crucial features in the deeper bowel wall cannot be assessed
  - Upper endoscopy may help, especially in children
  - Provide clinical information
  - Discuss difficult cases with your pathologist

Table 2 Microscopic features used for the diagnosis of IBD.

	Ulcerative colitis	Crohn's disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse(continuous)	Focal (discontinuous)
	Decrease proximally	Variable
Patchiness	Uncommon	Common
Localization	Superficial	Transmural
	Transmucosal	
	Sometimes in submucosa	
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

Suggested reading, PMIDs

- 10048734
- 17324129
- 23870728
- 24942757
- 28158501
- 29659081

PART 2
HISTOPATHOLOGICAL SCORING OF IBD (UC)

Ulcerative Colitis: FDA Clinical Trial Endpoints Guidance for Industry

"Mucosal healing (based on the Mayo Endoscopy subscore) has been included as a secondary endpoint in many clinical trials. In many clinical trials, mucosal healing has been defined as Mayo Endoscopic subscore of less than or equal to 1 point. However, **a claim of mucosal healing would not be supported through endoscopy that provides only an assessment of the visual appearance of the mucosa**. Any claim related to findings on endoscopy, in the absence of validated histological assessment of the mucosa, would be limited to the endoscopic appearance of the mucosa."

FDA Guidance for Industry (Ulcerative Colitis) Draft Guidance document August 2016
https://www.fda.gov/

Comparison of the EMA and FDA Guidelines on Ulcerative Colitis Drug Development

EMA: mucosal healing is defined as “absence of macroscopic signs of active inflammation as judged by endoscopy”

EMA: histology is recommended to help establish the diagnosis of UC and pouchitis, and could be a secondary endpoint or a component of a secondary endpoint.

FDA: considers EMA’s definition of mucosal healing = endoscopic healing, stating specifically that “endoscopy alone only provides only an assessment of the visual appearance of the mucosa.”

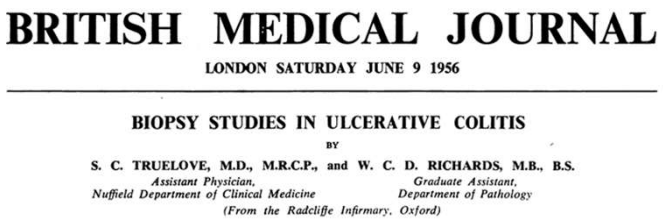
FDA: emphasizes the value of histology for the claim of mucosal healing.

Reinisch et al. Clin Gastroenterol Hepatol. 2019;17:1673-79.

The long history of histology scores in UC

- The approach of using both endoscopic and histologic endpoints in clinical trials in IBD has been present for **sixty years**
  - Truelove et al. (1956) used both clinical, endoscopic and histologic endpoints in a clinical trial for corticosteroids in UC

- Over the years, **over 30 different histologic scoring systems for UC** have been created



BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 9 1956

BIOPSY STUDIES IN ULCERATIVE COLITIS

BY

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(From the Radcliffe Infirmary, Oxford)

Why is histological healing important in Ulcerative Colitis?

Established value as predictor of

- Disease relapse in IBD
- Risk of hospitalization/surgery
- Risk of colorectal cancer

Established value as screening tool

- Identify those at risk for dysplasia and neoplasia

Histological remission/healing

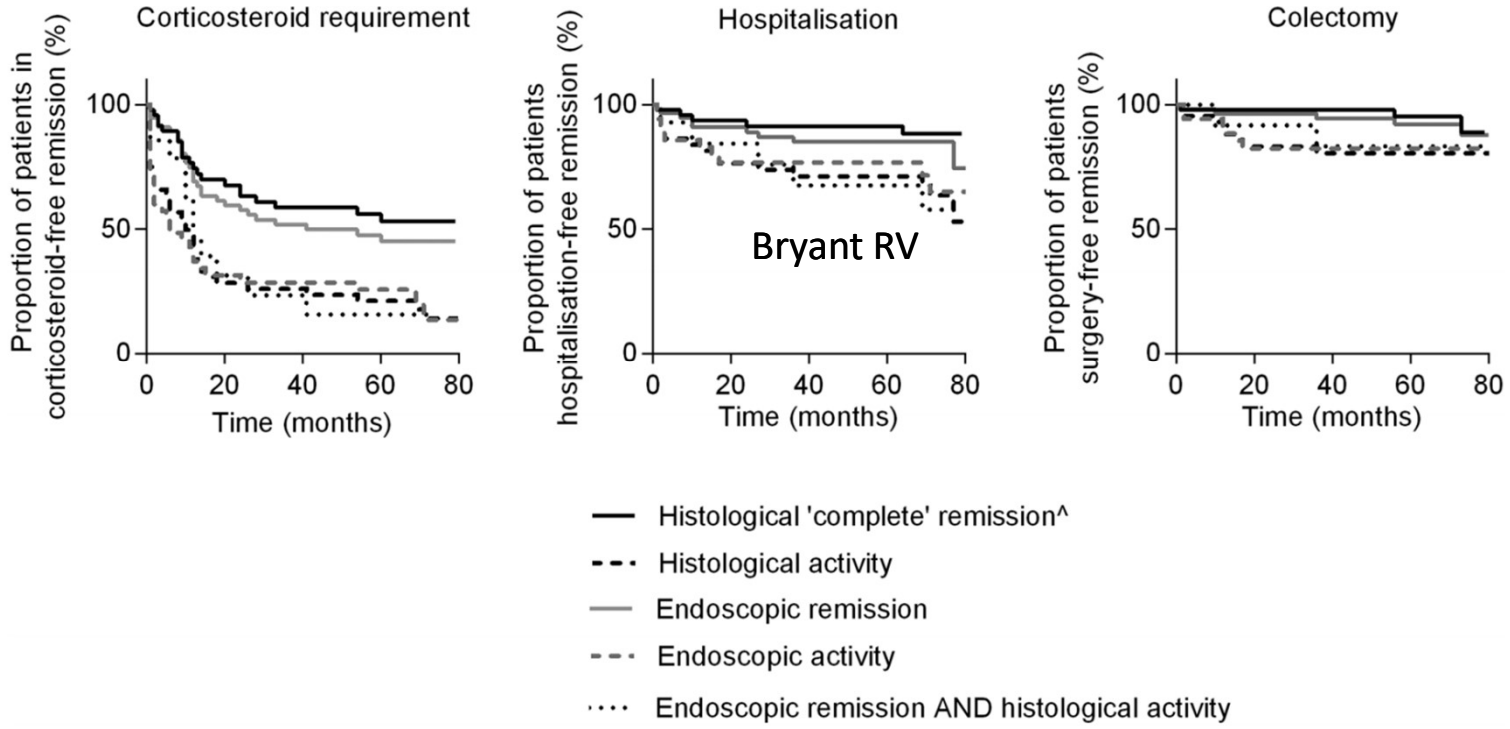
- It is an area of increasing research focus and holds promise of being an important marker of treatment efficacy in UC
- Further studies are warranted to define its potential for disease modification

Questions to be answered

- What is the required degree of histological healing?
- Should therapy be optimized based on histological assessment?

Histologic Remission Versus Endoscopic Remission in Predicting Clinical Outcomes

Kaplan-Meier Graph of Endoscopic, Histological and Clinical Outcomes in UC Patients



Most well-known histologic indices in UC

- (Modified) Riley Score: (M)RS
- Geboes Score: GS
- Nancy Histologic Index: NHI
- Robarts Histopathology Index: RHI

Most “validated”: Nancy and Robarts indices

Features used in the 4 most often used histologic scoring indices

- **Modified Riley**: mild (1-3: neutrophil infiltrate); moderate (4-6: crypt involvement); severe (7: ulcers)
- **Geboes**: 0 (structural change only) to 5 (erosions or ulcers)
- **Nancy**: 0 (no histologic significant disease) to 4 (severe [ulcers])
- **Robarts**: four components (chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium and erosions/ulcerations
    - Weighted component scores lead to a range of 0-33

Similar histologic features come back in every score!

(Modified) Riley Index

- The Initial Riley Score was described in 1988. Pathologists independently graded inflammation according to five levels which subjectively categorize tissue samples based on the degree of chronic inflammation and tissue destruction (Riley 1988).

- Riley 1991 subsequently described the widely used Riley Score in a clinical trial designed to predict relapse in clinically and endoscopically quiescent UC patients. This score incorporates six histologic features
  - acute inflammatory cell infiltrate (neutrophils in the lamina propria),
  - crypt abscesses,
  - mucin depletion,
  - surface epithelial integrity,
  - chronic inflammatory cell infiltrate (round cells in the lamina propria), and
  - crypt architectural irregularities.

  Each feature was graded on a four-point scale as none, mild, moderate, or severe (Riley 1991).

- The Modified Riley Score removed features of chronicity that were thought to be resistant to responsiveness (Feagan 2005).

Riley SA et al. Gut. 1991 Feb;32(2):174-8.

Feagan B et al. New England Journal of Medicine 2005;352(24):2499-507.

The Geboes Score (GS)

The Geboes Index includes five features:

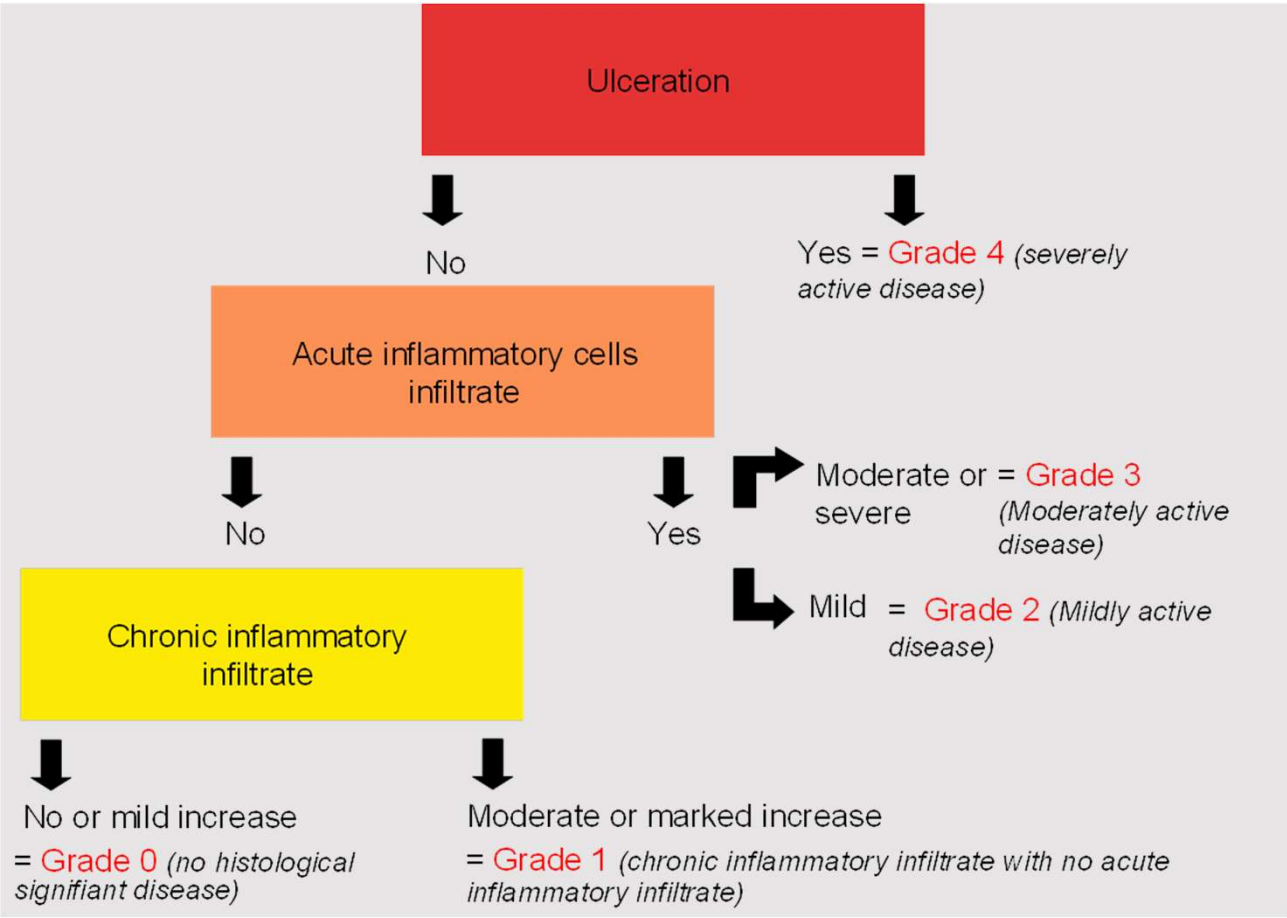
1. architectural change
2. lamina propria neutrophils and eosinophils
3. neutrophils in epithelium
4. crypt destruction
5. erosion or ulceration

Geboes et al. Gut. 2000;47:404-9

Different grades used for evaluation of disease severity in ulcerative colitis

Grade 0	**Structural (architectural change)**
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	**Chronic inflammatory infiltrate**
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	**Lamina propria neutrophils and eosinophils**
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
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 crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	**Erosion or ulceration**
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

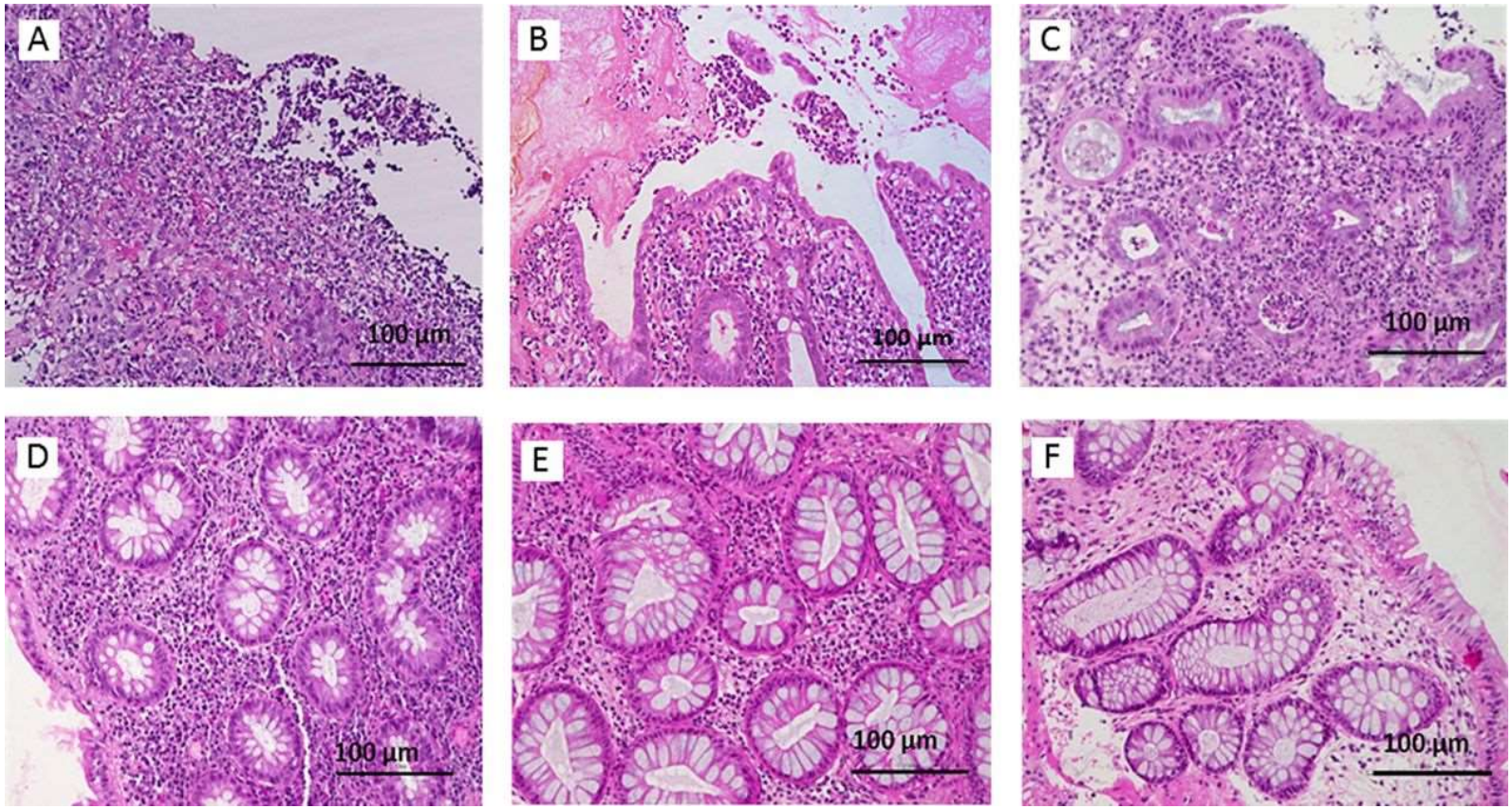
The Nancy Index



Marchal-Bressenot et al. Development and validation of the Nancy histological index for ulcerative colitis. Gut 2015.

Aude Marchal-Bressenot et al. Gut 2016;65:1919-1920

GUT



(A) (B) Ulceration with inflamed granulation tissue or neutrophils in fibrin = *grade 4*
(C) Presence of multiple clusters of neutrophils in lamina propria and/or in epithelium that are easily apparent = *grade 3*
(D) Presence of few or rare neutrophils in lamina propria or in the epithelium that are difficult to see = *grade 2*
(E) No neutrophils and presence of a moderate-to-severe increase in mononuclear inflammatory cells = *grade 1*
(F) Biopsy specimen showing a mild increase in mononuclear cells = *grade 0*

Robarts Histological Index

$$\begin{aligned}\text{RHI} = {} & 1 \times \text{chronic inflammatory infiltrate level (4 levels)} \\ & + 2 \times \text{lamina propria neutrophils (4 levels)} \\ & + 3 \times \text{neutrophils in epithelium (4 levels)} \\ & + 5 \times \text{erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2).}\end{aligned}$$

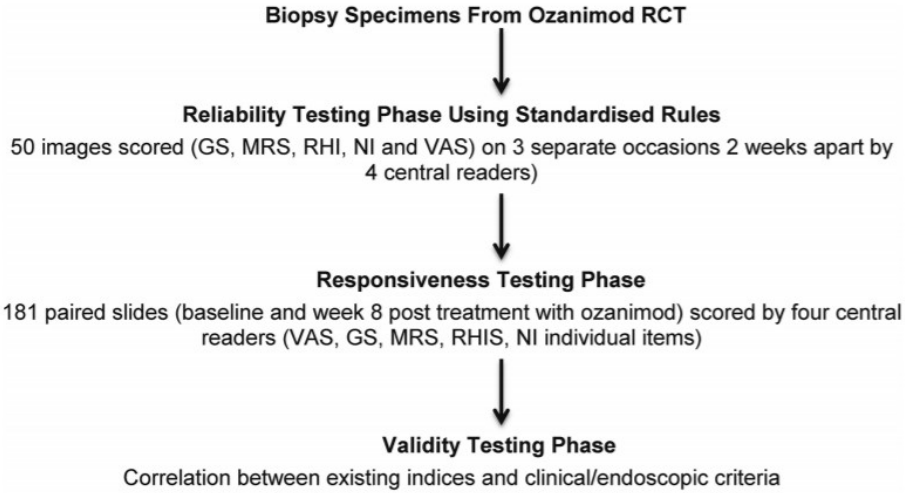
The total score ranges from 0 (no disease activity) to 33 (severe disease activity)

Good index for a short-term indication of disease activity

- Chronic inflammatory infiltrate
  - 0=No increase
  - 1=Mild but unequivocal increase
  - 2=Moderate increase
  - 3=Marked increase
- Lamina propria neutrophils
  - 0=None
  - 1=Mild but unequivocal increase
  - 2=Moderate increase
  - 3=Marked increase
- Neutrophils in epithelium
  - 0=None
  - 1=<5% crypts involved
  - 2=<50% crypts involved
  - 3=>50% crypts involved
- Erosion or ulceration
  - 0=No erosion, ulceration or granulation tissue
  - 1=Recovering epithelium+adjacent inflammation
  - 1=Probable erosion—focally stripped
  - 2=Unequivocal erosion
  - 3=Ulcer or granulation tissue

How do the scoring indices compare relative to one another?

- *Post hoc* analysis of the **TOUCHSTONE trial** (phase II RCT of ozanimod-197 pts-moderate to severe UC)
- Disease activity was blindly assessed by four pathologists to compare the following histologic scoring indices: Geboes, Modified Riley, Robarts, Nancy index and VAS
- Reliability was assessed with **Intraclass Correlation Coefficients (ICCs)**



Index	Intra-rater reliability	Inter-rater reliability
Geboes Score (GS)	0.94 (0.90 to 0.97)	0.88 (0.82 to 0.92)
Modified Riley Score (MRS)	0.93 (0.88 to 0.95)	0.88 (0.80 to 0.90)
Robarts Histopathology Index (RHI)	0.94 (0.91 to 0.96)	0.86 (0.82 to 0.92)
Nancy Histological Index (NHI)	0.92 (0.88 to 0.95)	0.80 (0.73 to 0.85)
Visual analogue scale (VAS)	0.93 (0.89 to 0.95)	0.71 (0.61 to 0.79)

Substantial to almost perfect inter-rater reliability (ICC>0.61) observed for all indexes

Overview of the Histologic Scoring indices

Scoring system	Reference, date	Histological changes	Classification of Activity	HR
GS	Geboes et al, 2000	(1) Architectural changes (2) chronic inflammatory infiltrate (3) lamina propria eosinophils (4) lamina propria neutrophils (5) epithelial neutrophils (6) crypt destruction (7) erosions or ulcerations	Six grades subdivided into 4 categories. Scoring from 0 to 5.4	0–1 (structural change only-chronic inflammation)
RS	Riley et al, 1991	(1) Presence of an acute inflammatory cell infiltrate (2) Crypt abscesses (3) mucin depletion (4) surface epithelial integrity (5) chronic inflammatory cell infiltrate (6) crypt architectural irregularities	Each histologic feature graded 0–3 (none, mild, moderate, severe)	Not defined
MRS	Feagan etal, 2005	Items derived from original RS responsive to changes in acute inflammation (neutrophils in epithelium, lamina propria neutrophils, erosion/ulcer)	Scores range from 0 (normal/inactive colitis) to 7 (severe acute inflammation)	Not defined
NHI	Marchal-Bressenot et al, 2017	(1) Chronic inflammatory cell infiltrate (2) acute inflammatory cell infiltrate (3) ulceration	Stepwise index ranging from 0 (no histologic significant disease)to 4 (severely active disease)	Grade 0–1
RHI	Mosli et al, 2017	Derived from GS; (1) chronic inflammatory cell infiltrate (2) lamina propria neutrophils (3)epithelial neutrophils (4)erosions or ulcerations	Each variable scored independently. The total sum ranges from 0 (no activity) to 33 (severe activity)	Score< 6

MRS, Modified Riley Score; NHI, Nancy Histologic Index;
RHI, Roberts Histopathology Index; RS, Riley score; GS, Geboes score.

How can histologic remission / improvement be defined?

- It is not clear or universally agreed upon what a “histological response” is.

- If you are very strict, you can require **complete normalization of histology**.
  -> In my experience that almost never happens
  (except perhaps in a very small group of children with proctitis only, treated early in their disease and moreover with great success).

- You can also ask “histological improvement”. The definition is very broad:

(1) **Lose all the neutrophils.**
  -> Minority of the patients. So strict that it is not accepted by most clinicians. Can’t be met by most tested medications in the short term that is usually under consideration in clinical trials (8 tot 12 wks).

(2) **Lose all the neutrophils in the epithelium + there should be no residual epithelial damage.**
  -> How many neutrophils are acceptable in the lamina propria? Few or many? A few often occurs & may be due to either UC or to other factors such as bowel preparation, scope passage, infection, …

(3) **Minimal epithelial neutrophilic infiltration in the epithelium without epithelial damage is acceptable.**
  -> At least one study based on histology data from a large clinical trial has proposed this as a measure of histologic improvement. When combined with endoscopic remission (reaching Mayo endoscopic subscore 0 or 1), it is even relevant as a predictor for a better long-term prognosis. (Li K, et al. JCC 2019;13:1025-35)

Limitations of Histologic Scoring Indices For Evaluation of Disease Activity in Ulcerative Colitis

- Need for invasive sampling procedure (risk of complications/cost/inconvenient for patients)
- Sampling effect for histological assessment (higher in CD due to discontinuous disease)
- Results depend on # of samples, correct cutting technique and orientation of biopsies
- In routine clinical practice, pathologists do not use scoring indices (little experience)
- Lack of validation/standardization of histological reporting, scoring and definition of remission
- UC disease duration affects changes in distribution and nature of microscopic change
- Confirmation of histologic healing, beyond or independent of mucosal healing alone remains needed

Suggested reading, PMIDs

- 10940279
- 13316140
- 26464414
- 26475633
- 28542712
- 29338066