MAYO CLINIC

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Biopsy interpretation in chronic inflammatory bowel disease

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Outline

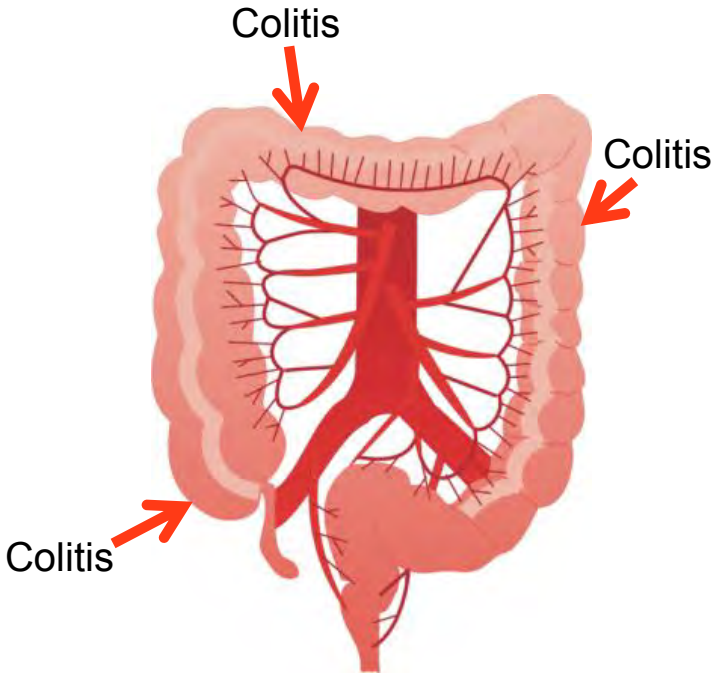
- Evaluation of colitis and ileitis
  - Patterns of injury in the lower GI tract
  - Differential diagnosis of IBD
- What to do when looking at biopsies from known IBD patients
  - Reporting histologic disease activity in IBD: Does it even matter?
  - The concept of mucosal and histologic healing

Evaluation of Colitis/Ileitis

- What do we need as pathologists?
  - Pertinent clinical history including medications
  - Endoscopic impression
    - Review of endoscopic images would be best
  - Appropriate biopsies
    - Appropriate number and location
    - Biopsies before institution of any therapy
- What to provide in our report?
  - More than just a descriptive diagnosis
  - Summary statement indicating what you think is going on (IBD, infection, ischemia, medication injury, etc.)

Where to biopsy: The importance of the endoscopic impression

Endoscopic impression: Patchy colitis



- Where to biopsy?
  - Just the abnormal areas?
  - Biopsy according to location (including both abnormal and normal if present)

Ideally, if IBD is considered, a full ileocolonoscopy should be done with ~5 biopsy jars (ileum, ascending colon, transverse, descending/sigmoid, and rectum)

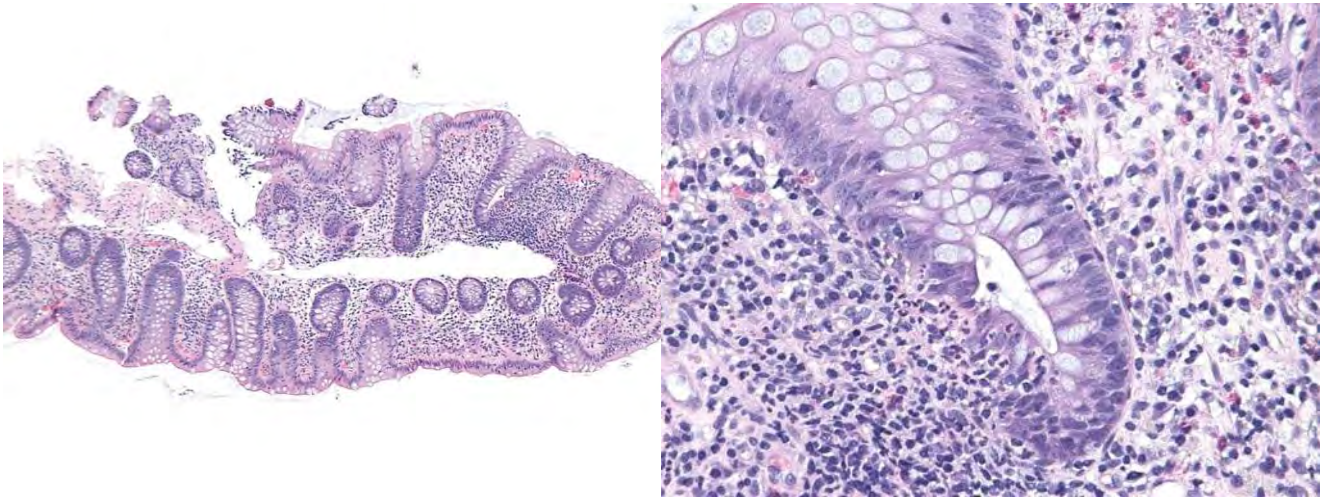
Diagnostic terminology to describe active colitis/ileitis in pathology reports

- ***Focal active colitis/ileitis***
  - Use this when there is only scattered cryptitis (<50% of biopsy) with no features of chronicity.
- ***[Mildly, moderately, severely] active colitis/ileitis***
  - Use this when there is frequent cryptitis with no features of chronicity.
- ***[Mild, moderate, severe] chronic active colitis/ileitis***
  - Use this when there is definite chronic injury and neutrophilic inflammation
- ***Inactive (quiescent) chronic colitis/ileitis***
  - Use this when there is chronic mucosal injury but no neutrophils

- **Terms to avoid: Nonspecific chronic colitis/ileitis, colonic/ileal mucosa with chronic inflammation, acute and chronic colitis/ileitis**

Case 1:

- 60 yo male undergoing a screening colonoscopy. A patchy of erythema was seen in the descending colon



Focal active colitis pattern of injury

- FAC can be seen in the colon of patients with definitive features of Crohn's disease elsewhere.
- What does isolated FAC in adults mean? Children?

Shetty S, Anjarwalla S M, Gupta J, Foy C J W, Shaw I S, Valori R M & Shepherd N A
(2011) *Histopathology* **59**, 850–856

Focal active colitis: a prospective study of clinicopathological correlations in 90 patients

Table 1. Clinical categorization for all cases of focal active colitis (FAC)

Clinical category	Male	Female	Total
IBD	3	11	14
Infectious-type colitis	7	10	17
Drugs	8	14	22
IBS	9	21	30
Incidental	4	3	7
Total	31	59	90

IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

Table 3. A comparison of the four studies correlating focal active colitis (FAC) with clinical categorization

Authors and year of publication	Location, numbers and patient group	C Infective/ self-limited	A Drugs	U IBS	S Incidental	E CIBD	S Other
Greenson *et al.*, 1997	USA 42 cases adults	39%	39% on NSAIDs	14%	22%	0%	4% ischaemic colitis
Volk *et al.*, 1998	USA 31 cases adults	48%	?	?	29%	13% (all CD)	10% ischaemic colitis
Xin *et al.*, 2003	USA 31 cases children	31%	0%	0%	27.6%	31% (8 CD; 1 UC)	6.5% allergic colitis; 3.2% Hirschsprung's d
Shetty *et al.*, 2011	UK 90 cases adults	19%	24%	33%	8%	16% (10 CD, 2 UC, >2 IBDU	–

NSAIDs, non-steroidal anti-inflammatory drugs; CIBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease, IBDU, inflammatory bowel disease, unclassified.

Is focal active colitis of greater clinical significance in pediatric patients? A retrospective review of 68 cases with clinical correlation

Human Pathology (2018) 74, 164–169

Allison Osmond MD[a], Dhandapani Ashok MD[b], Courtney A Francoeur[b], Michael Miller[b], Joanna C Walsh MB, BCh[a,*]

- 24% diagnosed with IBD
- 11% with IBD when you exclude TI inflammation
- 49% were unexplained

Table 1 Breakdown of final clinical diagnoses, N = 68

Final clinical diagnosis	N (%)	Female/male	Clinical criteria used for diagnosis
IBD	16 (24%)	8:8	Subsequent clinical diagnosis of IBD
Crohn's disease	14		
Ulcerative colitis	2		
IBD unclassified	0		
Infectious colitis	2 (3%)	1:2	Positive stool or blood culture
Allergic colitis	6 (9%)	2:4	Documented cow's milk protein or other allergy
Other definitive diagnosis possibly accounting for active colonic inflammation[a]	11 (16%)	6:5	
Idiopathic FAC	33 (49%)	7:9	Included a final clinical diagnosis of irritable bowel syndrome or functional abdominal pain, and those with "no clinical diagnosis"

[a] Henoch-Schonlein purpura, recent antibiotic use, post-transplant lymphoproliferative disorder, common variable immunodeficiency, lymphocytic colitis, juvenile polyposis, solitary rectal ulcer syndrome, chronic constipation, hemorrhoids and fissure.

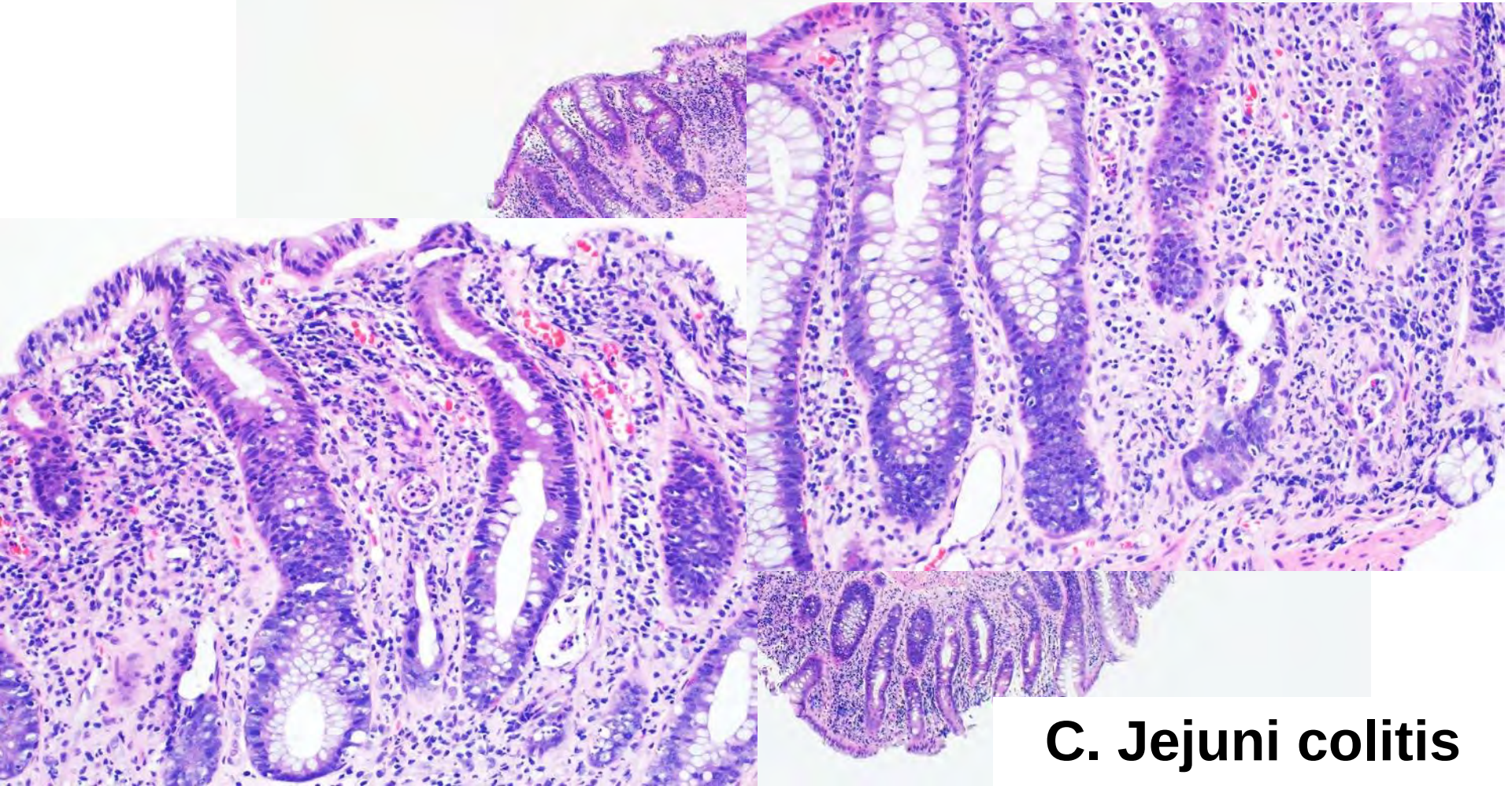
Table 3 Bivariate relations between clinical and histopathologic features and a final diagnosis of IBD

	IBD (16/68)	*Non-IBD (52/68)*	*Test value*	*P*
Elevated serum inflammatory marker(s)	10/15	10/49	$\chi^2 = 11.44$	***.001**
Positive family history of IBD	6/16	14/52	$\chi^2 = 0.66$	.532
>1 fragment involved	7/16	26/52	$\chi^2 = 0.19$	.662
Number of crypts involved	Mean = 4 Range = 0–18	Mean = 5.7 Range = 0–41	r = −.110	.419
Maximum number of neutrophils per crypt	Mean = 4.69 Range = 0–14	Mean = 6.6 Range = 0–41	r = −.131	.300
Aphthous inflammation	8/16	22/52	$\chi^2 = 0.29$	.588
Crypt abscesses	6/16	6/52	$\chi^2 = 5.67$	***.027**
TI inflammation	10/14	4/36	$\chi^2 = 20.27$	*** < .001**
Upper GI inflammation	7/10	12/24	$\chi^2 = 1.15$	.451

Case 2:

- 53 year old female with multiple sclerosis who presents with a several week history of diarrhea, nausea, fever, and vomiting. CT scan revealed pan-colitis. Colonoscopy was performed

Active colitis

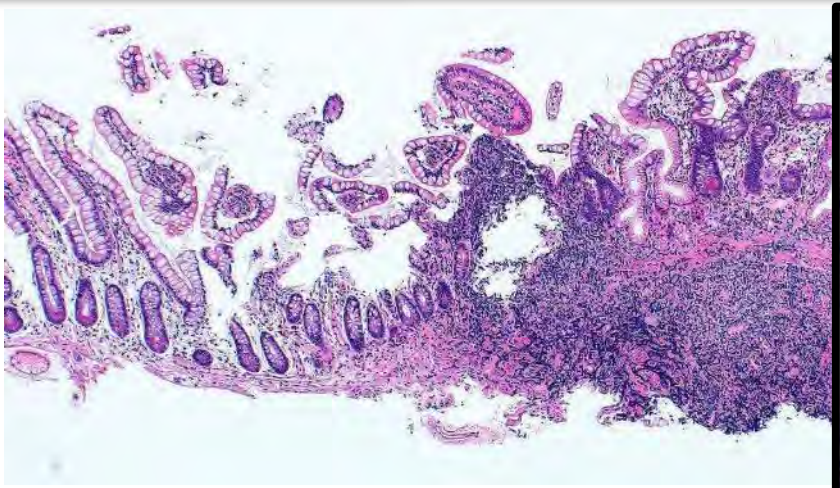


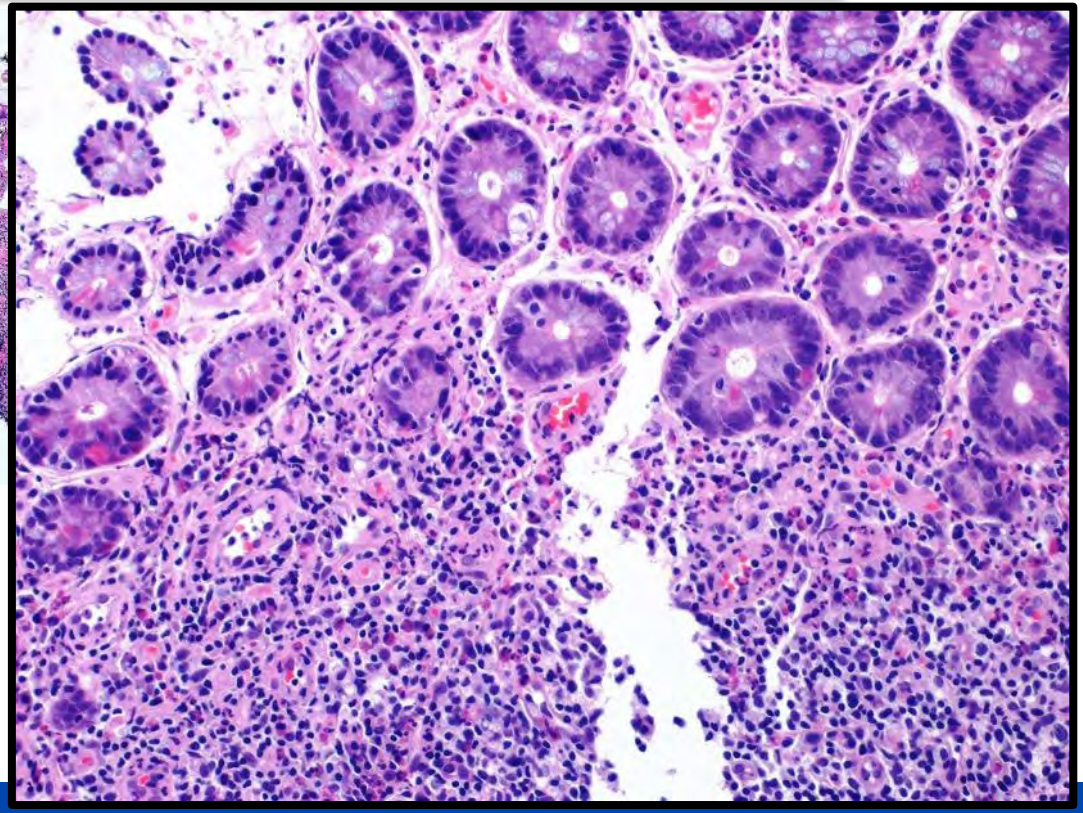
C. Jejuni colitis

Active colitis without chronicity

- Broad differential diagnosis
- Must rule out infection:
  - Shigella, Salmonella, Campylobacter, Yersinia
  - Always consider amebiasis, mycobacteria, fungal and other parasitic infections
- Often no organisms isolated on culture or stool PCR: probable viral or other as yet unrecognized agents (hence the clinical term acute self-limited colitis)
- **Comment:** Active colitis without features of chronicity is a non-specific pattern that is most commonly related to medication injury or an infectious process. If the patient remains symptomatic, repeat examination of the colon and terminal ileum may be of value.

What about isolated ileitis?





Clinicians invariably want to know if this Crohn's disease?

Isolated Asymptomatic Ileitis Does Not Progress to Overt Crohn Disease on Long-term Follow-up Despite Features of Chronicity in Ileal Biopsies

Am J Surg Pathol • Volume 33, Number 9, September 2009

TABLE 3. Morphologic Findings and Clinical Presentation as Predictors of Progression to CD in Patients With an Isolated Ileitis

	Outcome = CD	Outcome = No CD
Blinded Morphological Categorization		
CAI—favor CD (n = 15)*	7 (47%)	8 (53%)
FAI—not diagnostic of Crohn disease (n = 14)	3 (21%)	11 (79%)
Clinical Presentation		
Asymptomatic (n = 14)		
CAI present (n = 11, 79%)	0	11 (100%)
CAI absent (n = 3, 21%)	0	3 (100%)
Symptomatic (n = 15)†		
CAI present (n = 10, 67%)	8 (80%)	2 (20%)
CAI absent (n = 5, 33%)	2 (40%)	3 (60%)

*Morphologic categorization into CAI or FAI was not a statistically significant predictor of progression to CD ($P = 0.24$; 2-tailed Fisher exact test).

†The presence of symptoms at the time of index colonoscopy was a significant predictor of progression to CD in patients with an isolated ileitis ($P < 0.001$). None of the asymptomatic group patients progressed to CD.

CAI indicates chronic active ileitis, favor CD; CD, Crohn disease; FAI, focal active ileitis, not diagnostic of CD.

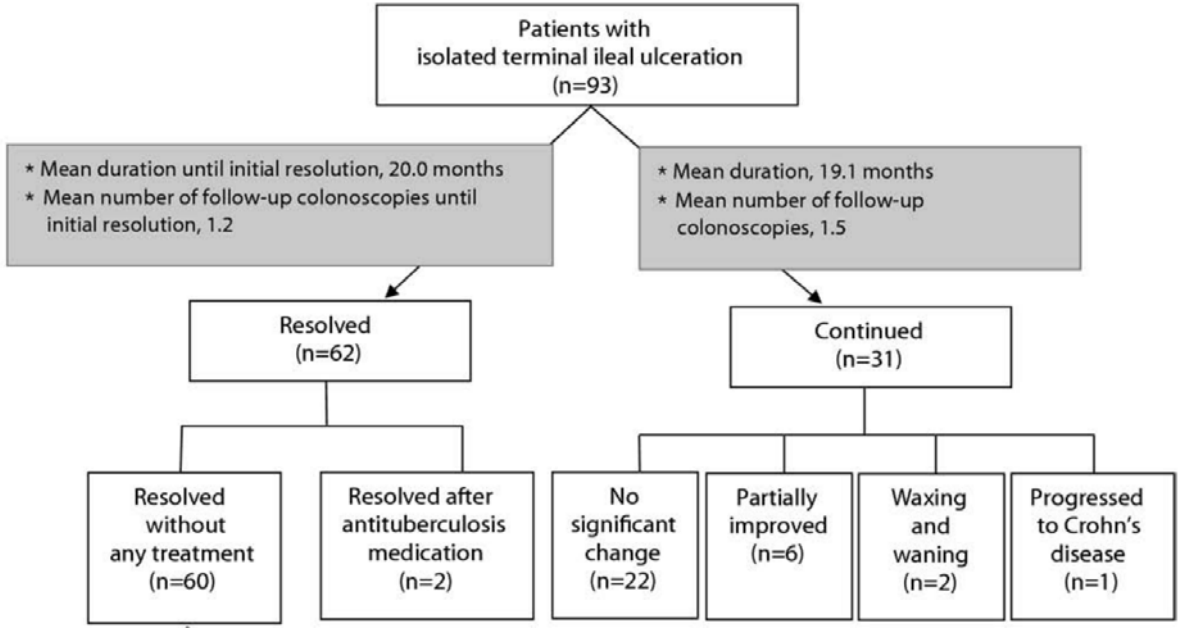
Isolated terminal ileal ulcerations in asymptomatic individuals: natural course and clinical significance

Hye-Sook Chang, MD, Don Lee, MD, Jong Cheol Kim, MD, Hye-Kyung Song, MD, Hyun Ju Lee, MD, Eun-Ju Chung, MD, Tae Hyup Kim, MD, Hye-Won Park, MD, Jeong-Sik Byeon, MD, Suk-Kyun Yang, MD, Jae-Won Choe, MD (Gastrointest Endosc 2010;72:1226-32.)

Seoul, South Korea

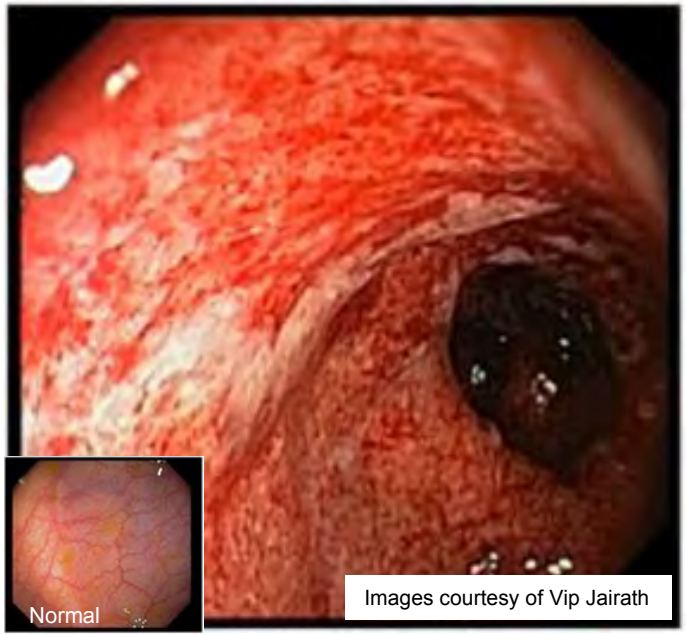
Excluded:

- Colorectal symptoms
- NSAIDs
- Colorectal surgery
- Oral or genital ulcerations



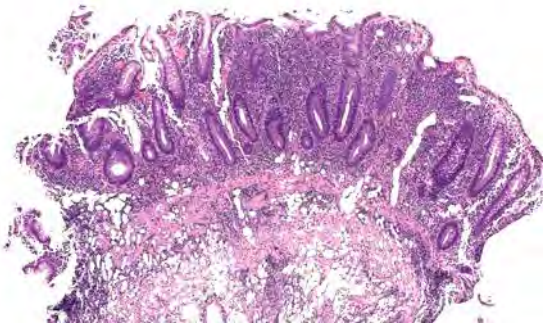
IBD diagnosis requires correct clinical scenario

30 year old male with rectal bleeding and cramping rectal pain

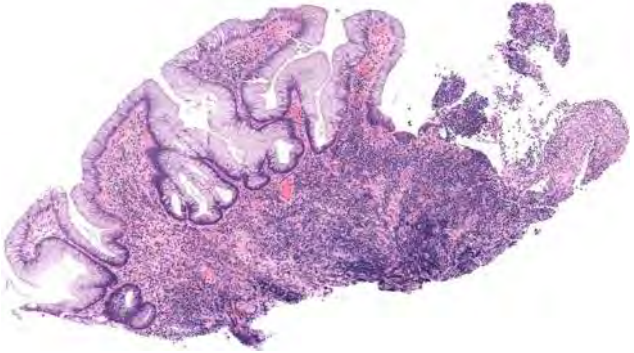


- Endoscopically consistent with pancolitis
- Biopsies were taken from multiple colonic segments.

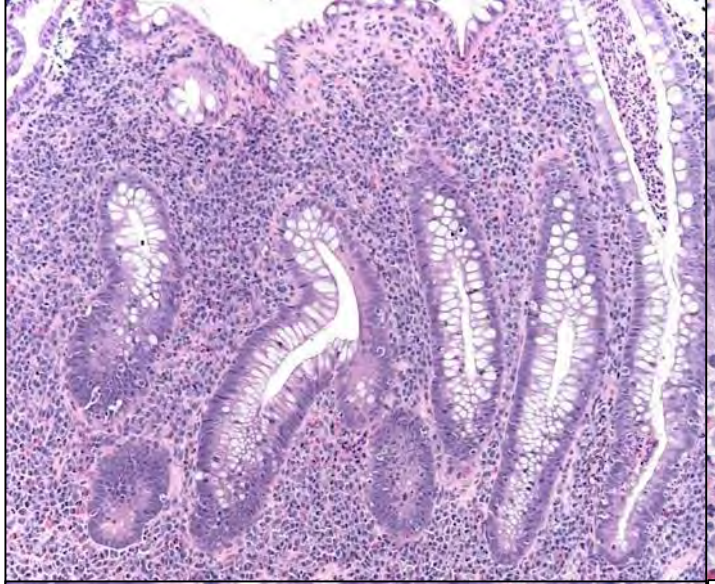
Chronic active colitis

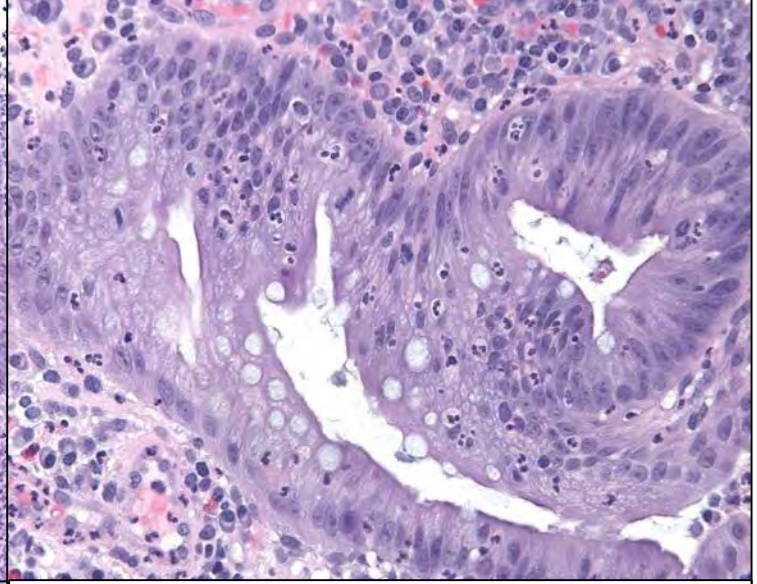


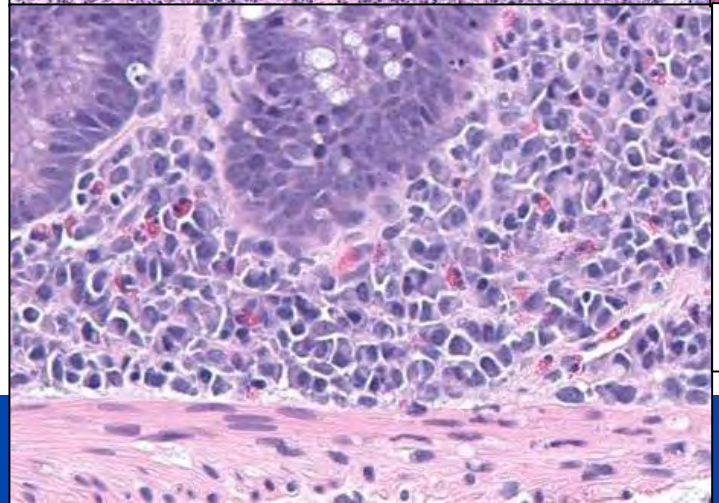
Proximal colon



Sigmoid colon



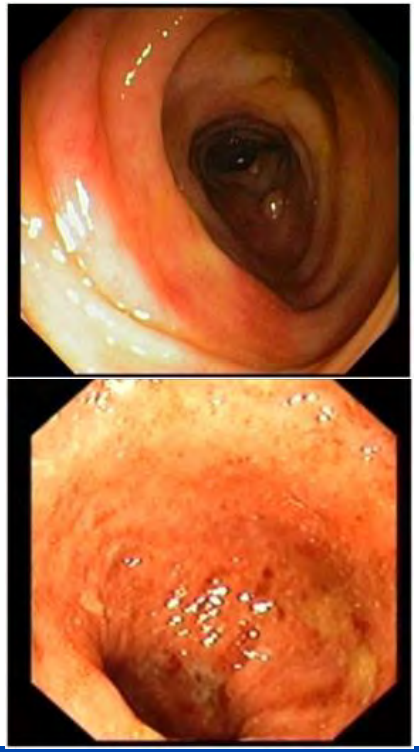


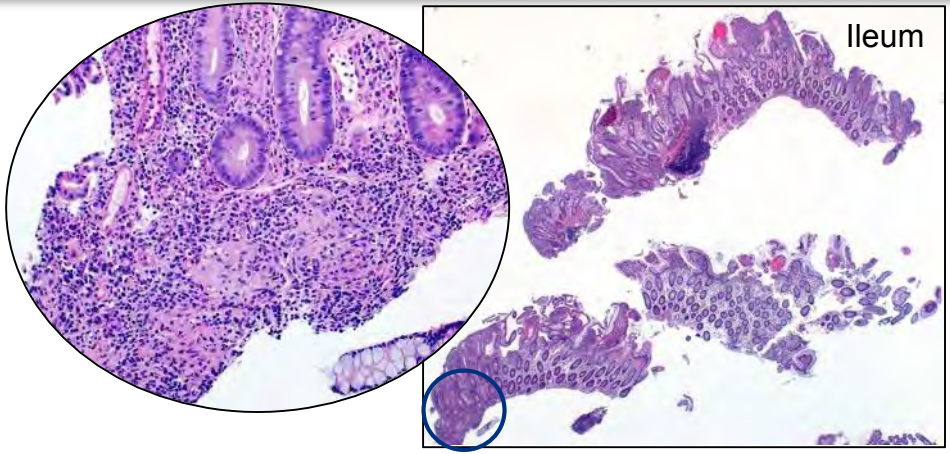


Chronic active colitis:

1. Active (neutrophilic inflammation)
2. Crypt architectural distortion
3. Expanded lamina propria with basal plasmacytosis

IBD diagnosis requires correct clinical scenario



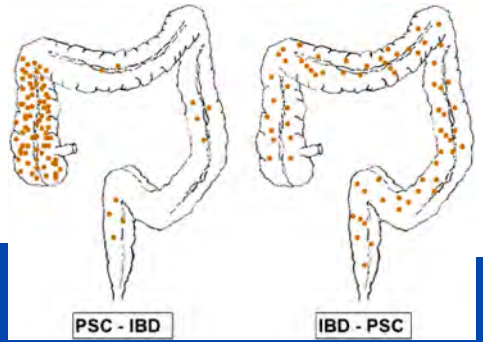


21 year old female with long-standing history of abdominal pain

Crohn's disease

Unusual IBD patterns: be careful!

- Backwash ileitis in pan-UC (can show CAI pattern)
- Proximal inflammation in the setting of left-sided UC
- Relative rectal sparing in pediatric UC
- Patchiness after institution of medical therapy – almost never diagnose CD in the setting of treated UC
- Mild upper GI tract inflammation in these setting of UC
- IBD in the setting of primary sclerosing cholangitis



- PSC diagnosed before IBD: right sided predominance
- PSC diagnosed after IBD: usually pancolitis

Dig Dis Sci. 2013 Sep;58(9):2608-14.

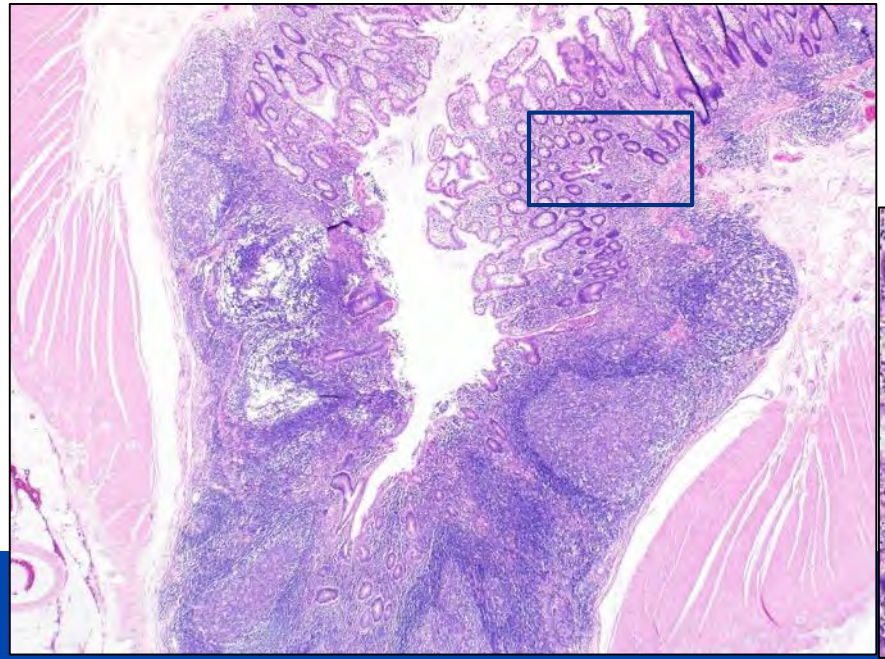
Mimics of inflammatory bowel disease

CLASSIC MIMICS

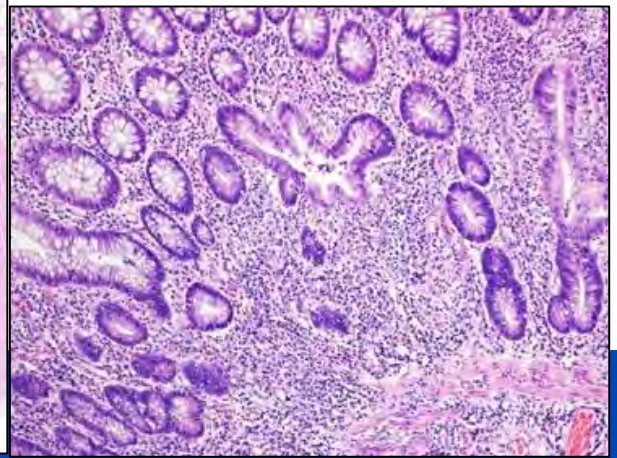
- Infection
- Chronic NSAID injury
- Diverticular disease associated colitis
- Solitary rectal ulcer syndrome/mucosal prolapse
- Lymphocytic and collagenous colitis
- Diversion colitis

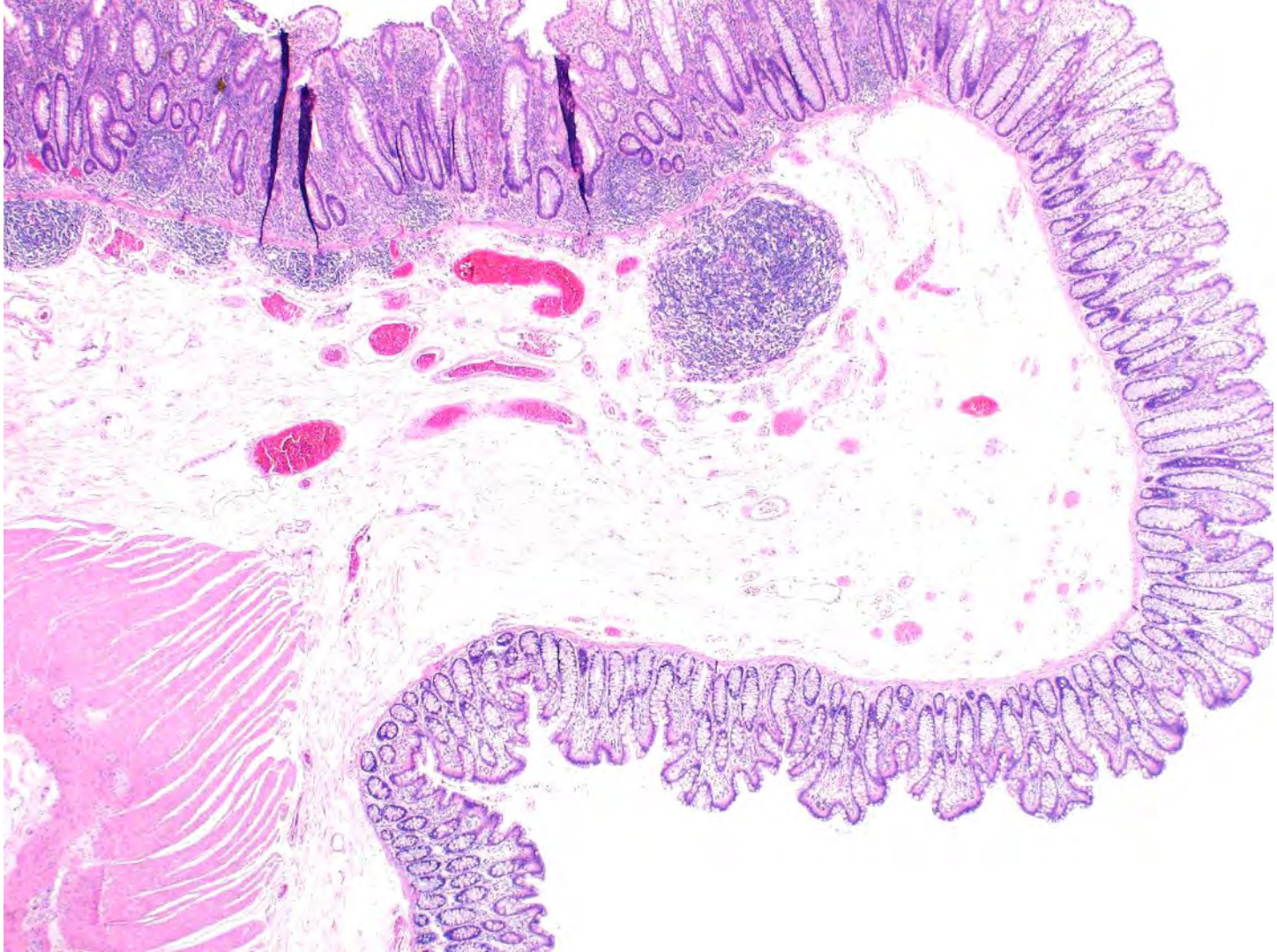
Case 3:

- 57 yo male with medically refractory ulcerative colitis diagnosed on outside biopsies not sent for review.
- Total abdominal colectomy was performed.

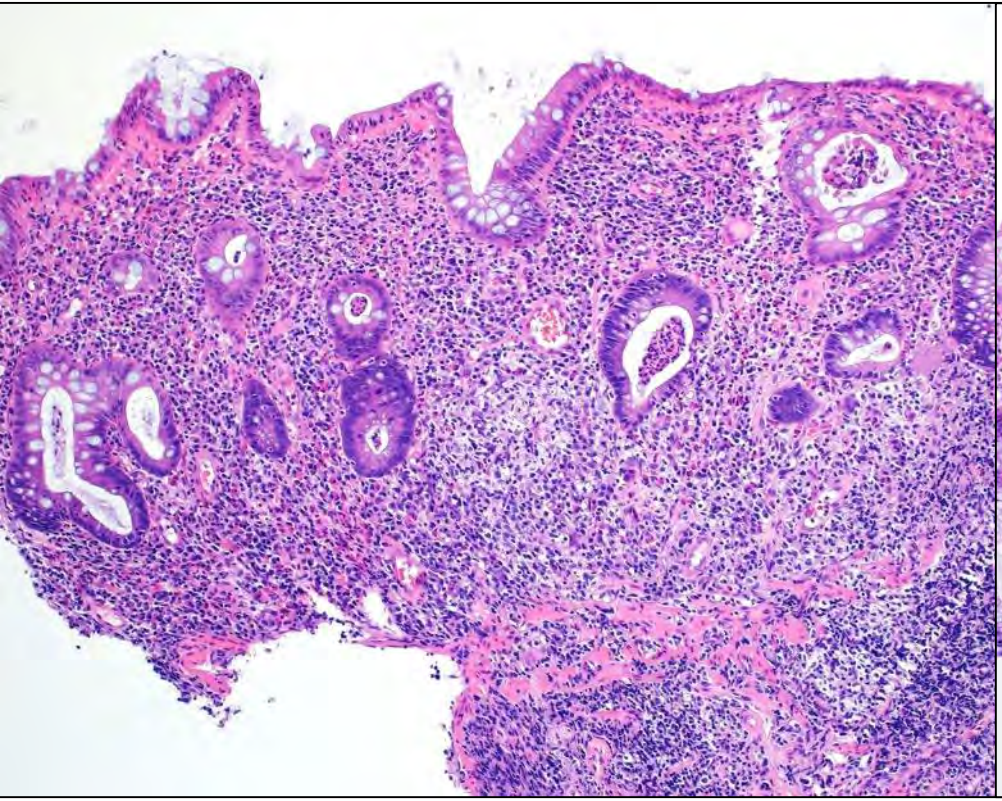


Chronic active colitis within and near diverticula

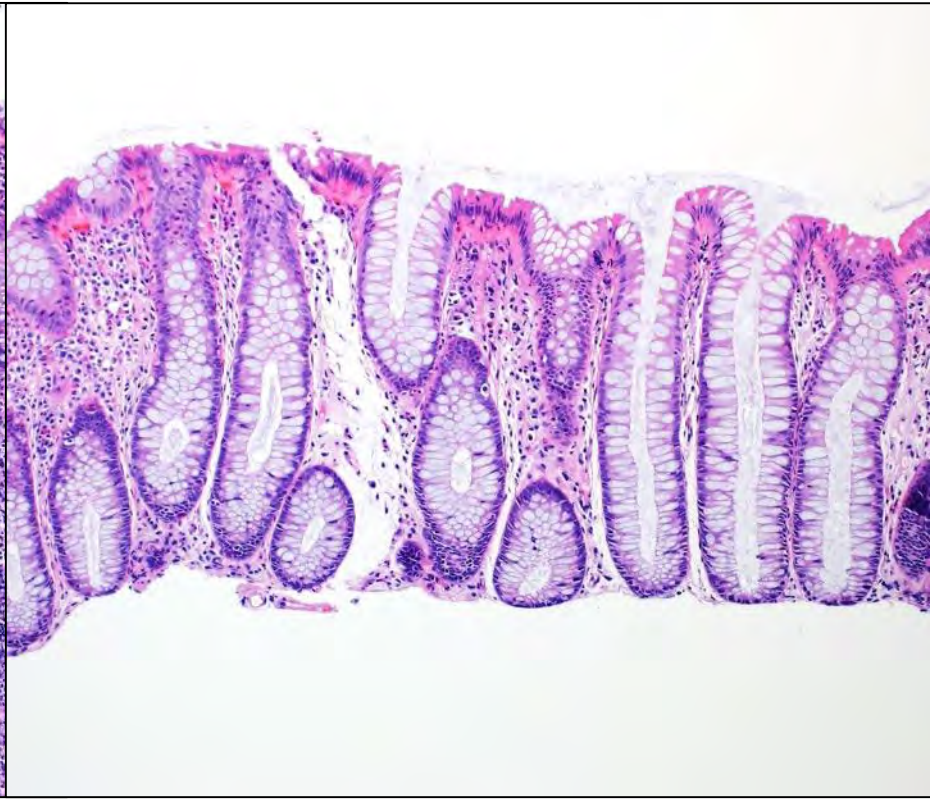




Sigmoid colon



Rectum



Diverticular disease-associated colitis

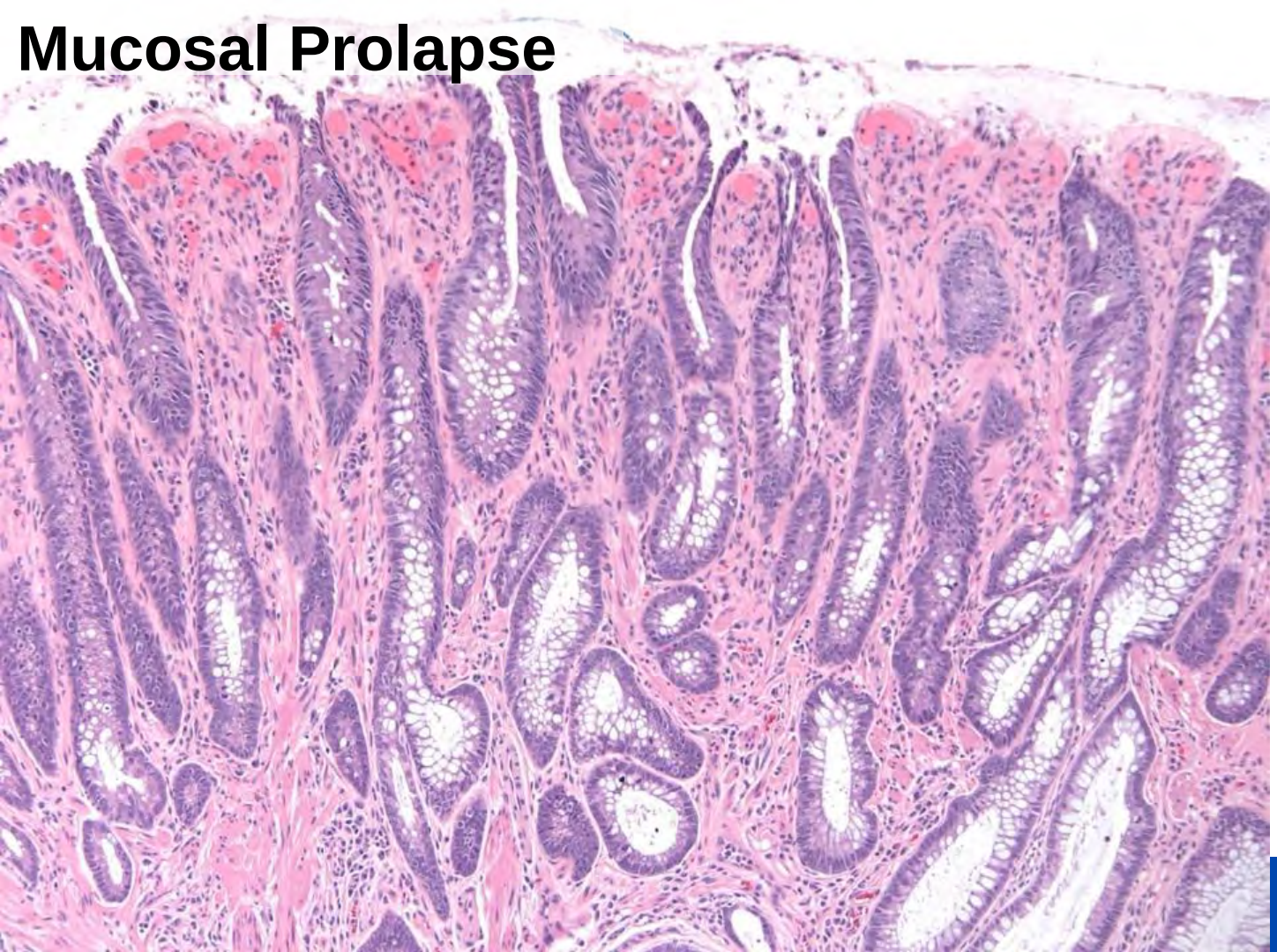
Diverticular disease-associated colitis

- Also known as segmental colitis associated with diverticulosis
- Predominantly sigmoid.
- Diffuse inflammation of mucosa between and surrounding diverticula.
- Often a chronic active colitis pattern
- May show features of prolapse similar to solitary rectal ulcer syndrome.
- Biopsies of the rectum are helpful (diverticula do not occur in the rectum).

Solitary rectal ulcer–Mucosal Prolapse syndrome

- Young adults (less commonly pediatric and elderly) with rectal bleeding with mucus and rectal pain
- Secondary to mucosal prolapse, mucosal trauma
- Tjandra JJ, et al. Clinical and pathologic factors associated with delayed diagnosis in solitary rectal ulcer syndrome. Dis Colon Rectum. 1993 Feb;36(2):146-53
  - 98 patients with mucosal prolapse.
  - 25 patients (26%) had an initially incorrect diagnosis.
  - In 10 patients, the biopsies were diagnostic but the features were not recognized.
  - ***In 7/10 patients, the biopsies were incorrectly interpreted as IBD (Crohn's and UC).***

Mucosal Prolapse

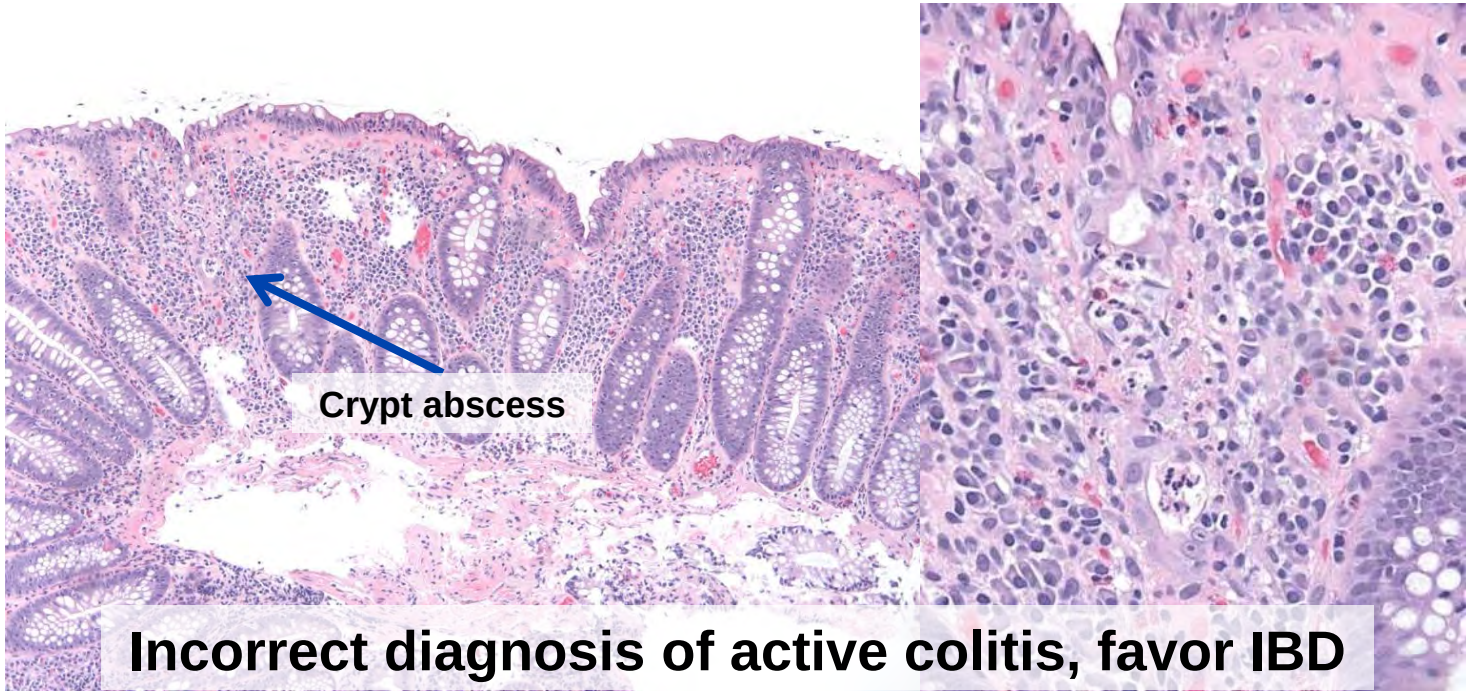


Characteristic histologic features:

- Fibromuscular hyperplasia of the lamina propria – perpendicularly oriented smooth muscle bundles
- Distorted crypts (may resemble serrated polyp)
- Villiform change to mucosal surface
- Surface ulceration and granulation tissue

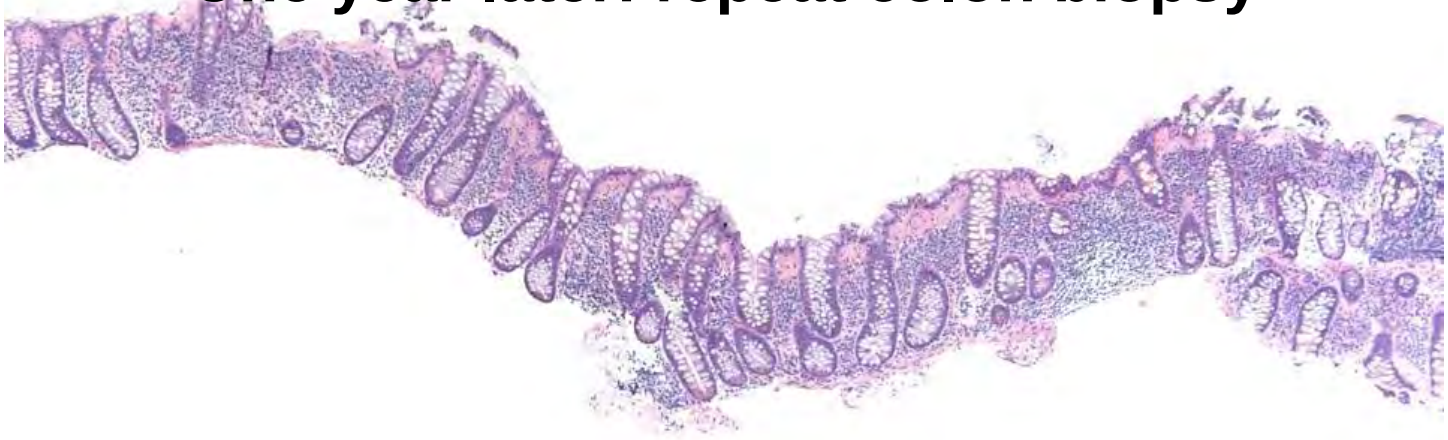
Case 4:

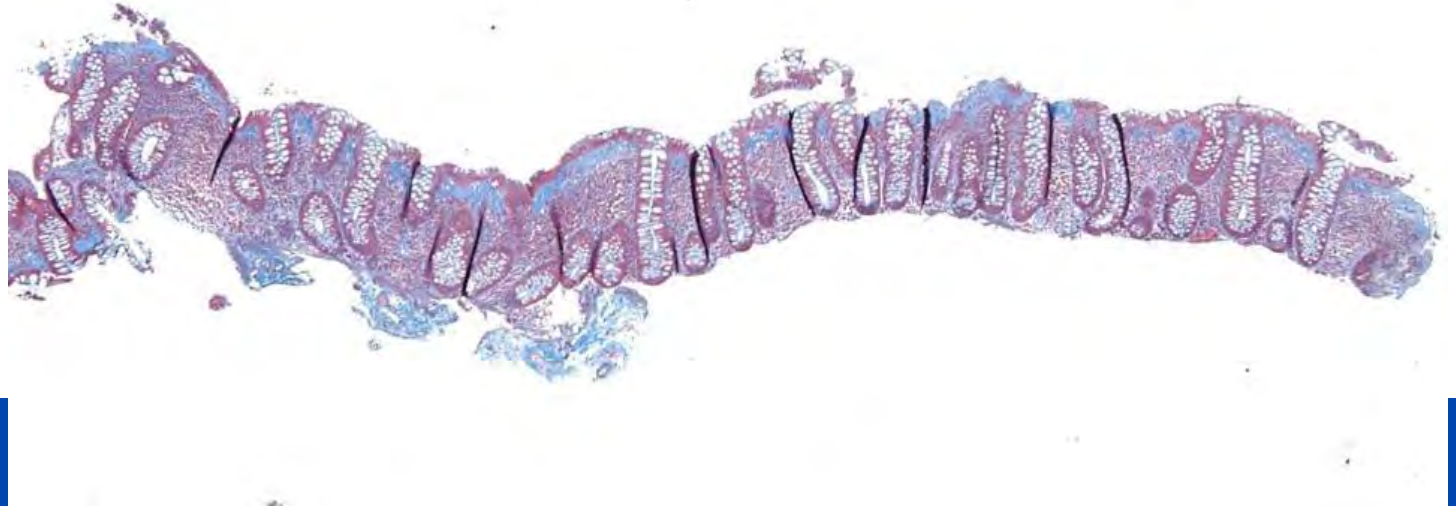
- 60 yo female with diarrhea.



Incorrect diagnosis of active colitis, favor IBD

One year later: repeat colon biopsy





Prevalence and Significance of Inflammatory Bowel Disease-Like Morphologic Features in Collagenous and Lymphocytic Colitis

American Journal of Surgical Pathology. 2002. Nov;26(11):1414-23.

Gamze Ayata, M.D., Sarathehandra Ithamukkala, M.D., Heidi Sapp, M.D., Beth H. Shaz, M.D., Tom P. Brien, M.D., Helen H. Wang, M.D., Dr.Ph., Donald A. Antonioli, M.D., Francis A. Farraye, M.D., M.Sc., and Robert D. Odze, M.D., F.R.C.P.C.

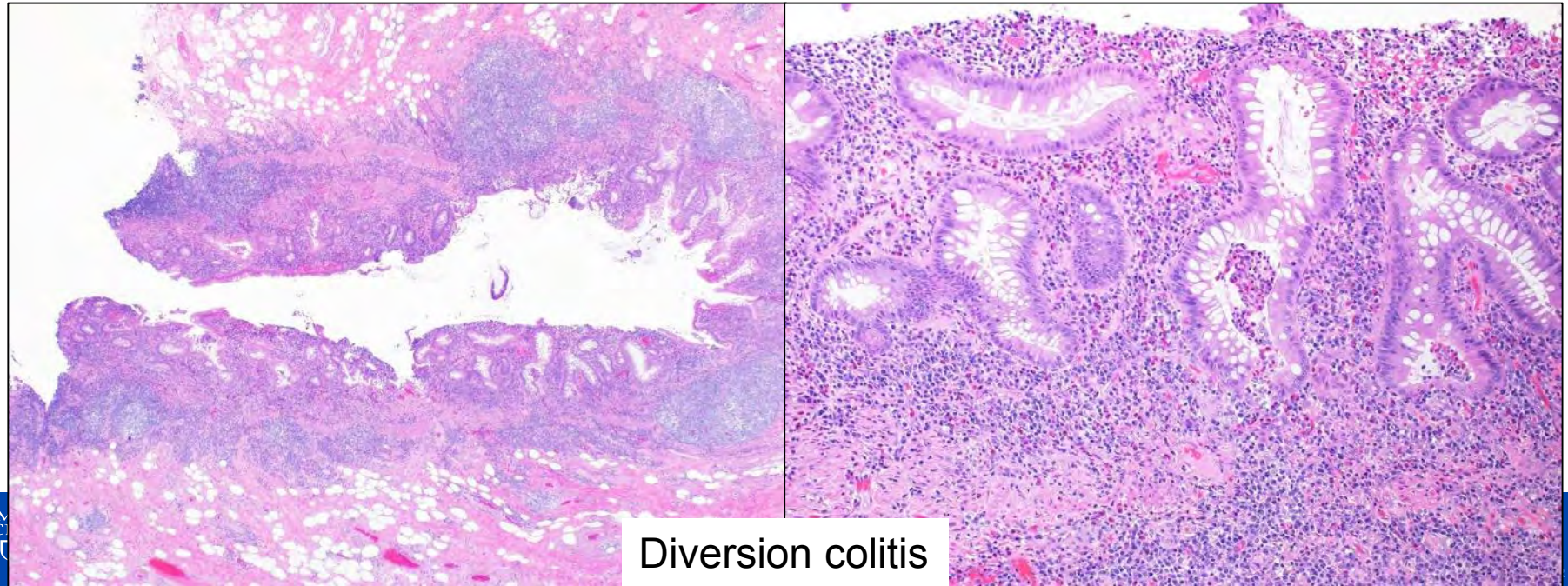
TABLE 2. *Summary of histologic features in patients with collagenous or lymphocytic colitis*

Feature	Collagenous colitis (No. of patients [%])	Lymphocytic colitis (No. of patients [%])
Active crypt inflammation	24/79 (30%)	27/71 (38%)
Cryptitis only	20/24	25/27
Cryptitis and crypt abscess	4/24	2/27
Surface ulceration	2/79 (2.5%)	0/71 (0%)
Paneth cell metaplasia	32/72 (44%)	9/63 (14%)*
Crypt atrophy or irregularity	6/79 (7.6%)†	3/71 (4.2%)†
Lymphoid nodules	51/79 (65%)	49/71 (69%)
Mixed inflammation	0	0
Basal Plasmacytosis	0	0
Basal lymphoid aggregates	0	0
Mean Subepithelial collagen thickness	15 ± 10	NA
No. of cases >10 IEL/100 ECs	54/79 (68%)	71/71 (100%)

* p <0.001 for CC vs LC.
† Includes two patients in the CC group and 1 patient in the LC group with atrophy.
NA, not applicable.

Case 5:

- 45 yo paraplegic male due to a car accident in his 20s that required a total abdominal colectomy. Undergoes completion proctectomy.



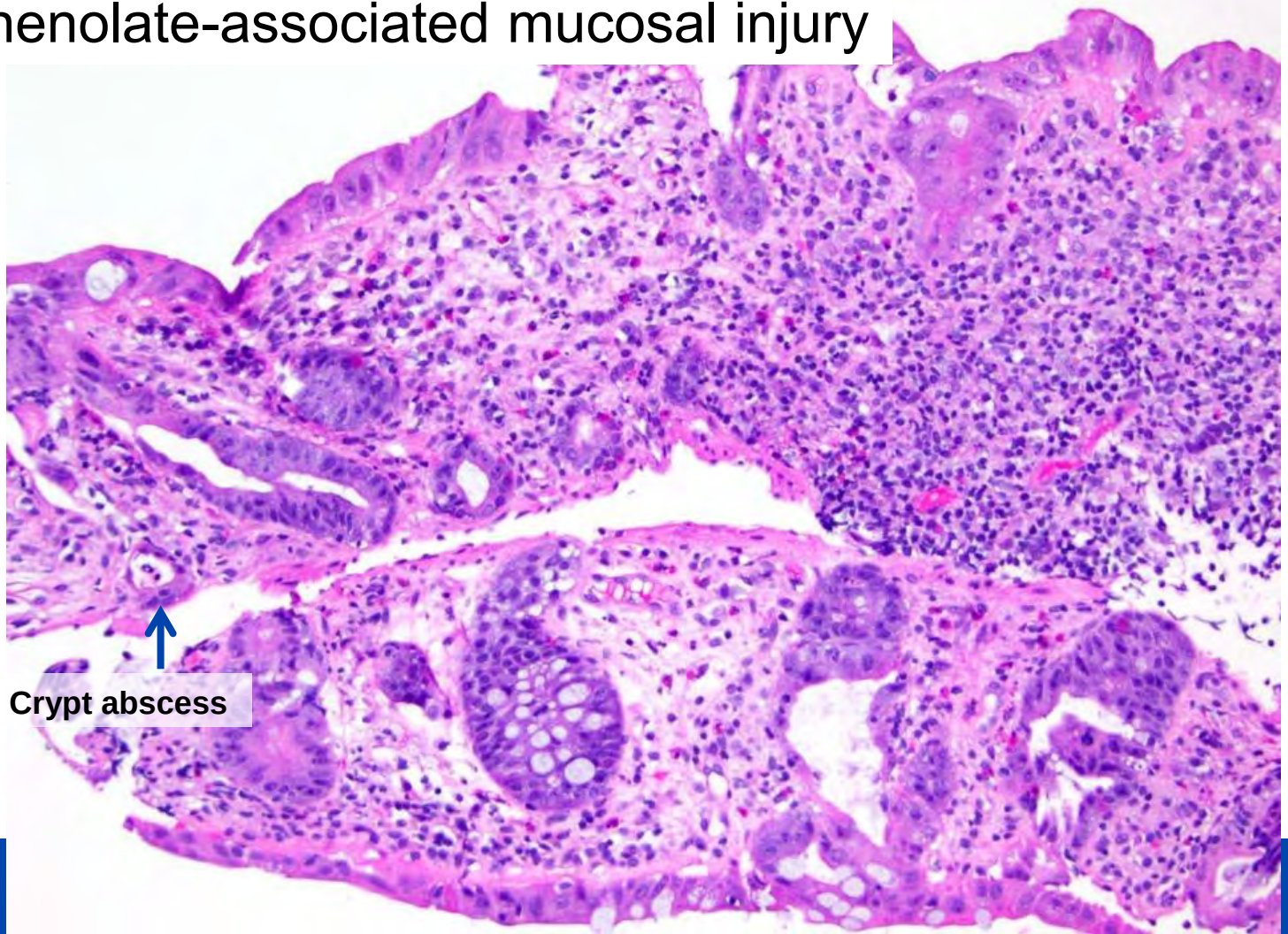
Diversion colitis

Mimics of inflammatory bowel disease

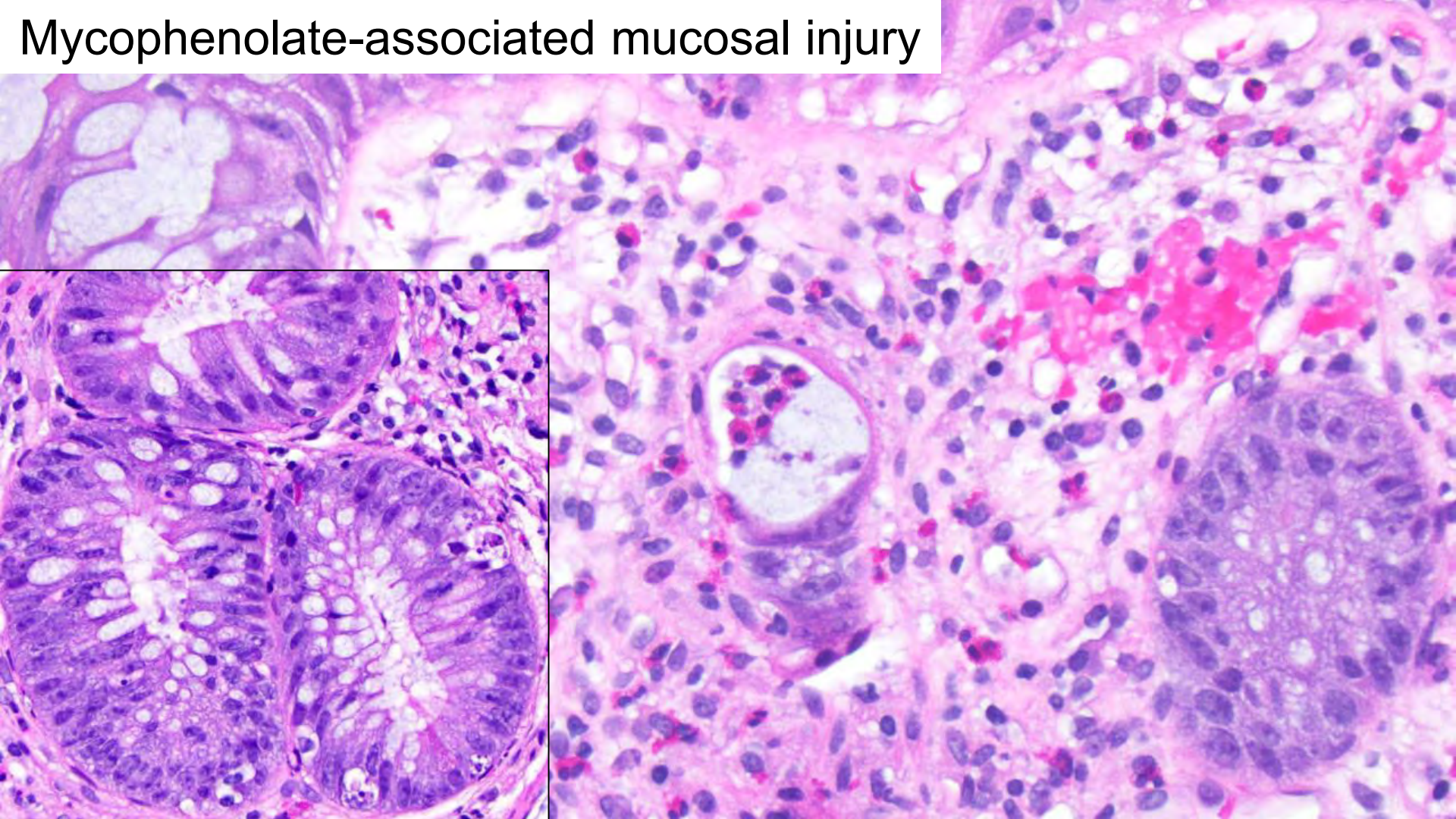
NEW AND RARE MIMICS

- Medication-associated mucosal injury (partial list)
  - Mycophenolate mofetil (CellCept) colitis
  - Colitis associated with cancer immunotherapy
  - Idelalisib-associated colitis
  - Medication resin-associated mucosal injury
- Chronic granulomatous disease
- Autoimmune enteropathy
- Common variable immunodeficiency
- Sexually transmitted infection (STI)-associated colitis
- Systemic mastocytosis
- Vascular disease
- Cord-colitis syndrome

Mycophenolate-associated mucosal injury



Mycophenolate-associated mucosal injury



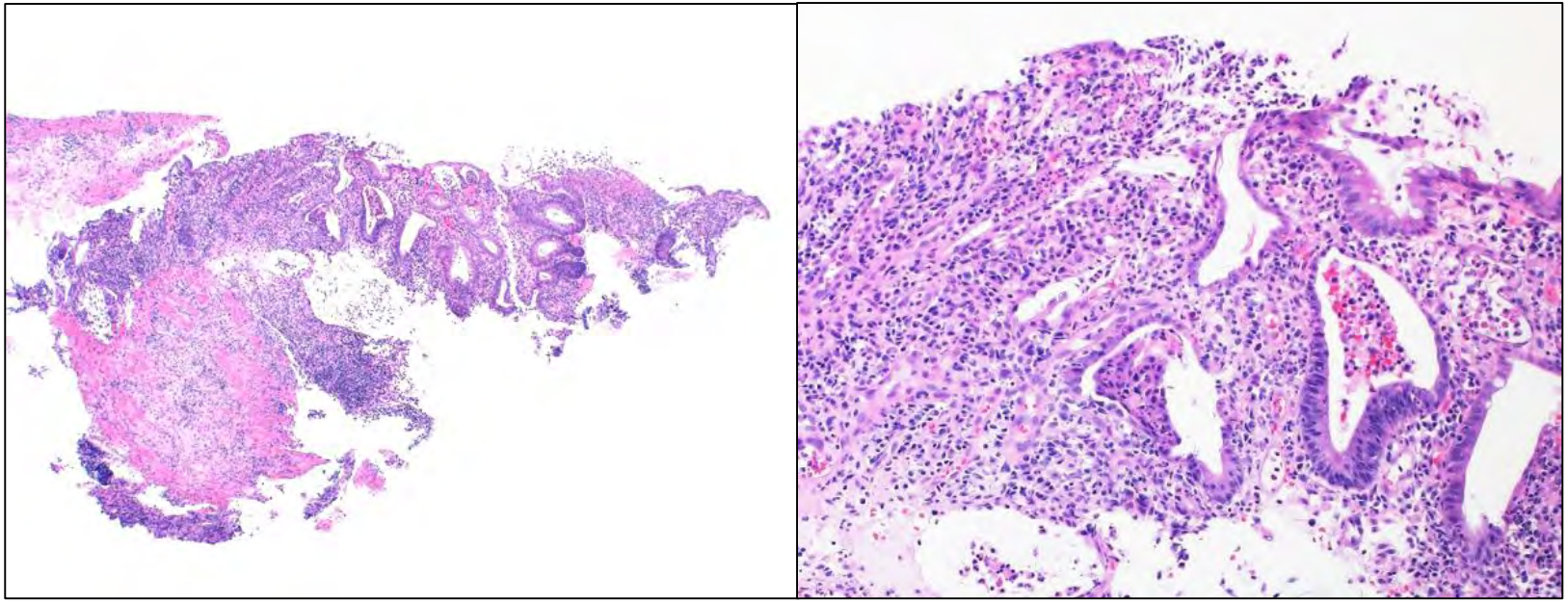
Mycophenolate injury

- Can mimic inflammatory bowel disease.
  - Crypt architectural distortion and lamina propria chronic inflammation seen in ~70-80% of cases.
- Histologic clues to the diagnosis:
  - Crypt epithelial apoptoses.
  - Dilated damaged (hypereosinophilic) crypts.
  - Increased lamina propria eosinophils (not specific).
- Most important: clinical and medication history.

1. Selbst MK et al. Mod Pathol 2009;22:737-743.
2. Parfitt JR et al. Am J Surg Pathol 2008;32:1367-1372.
3. Star KV et al. Am J Surg Pathol 2013;1319-1328.

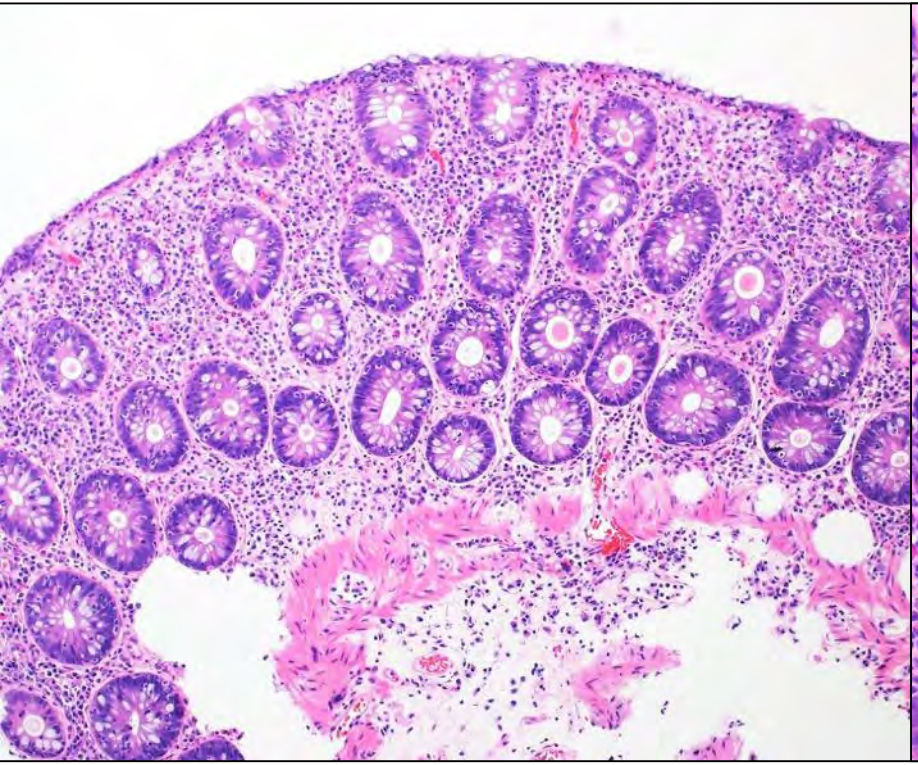
Case 6:

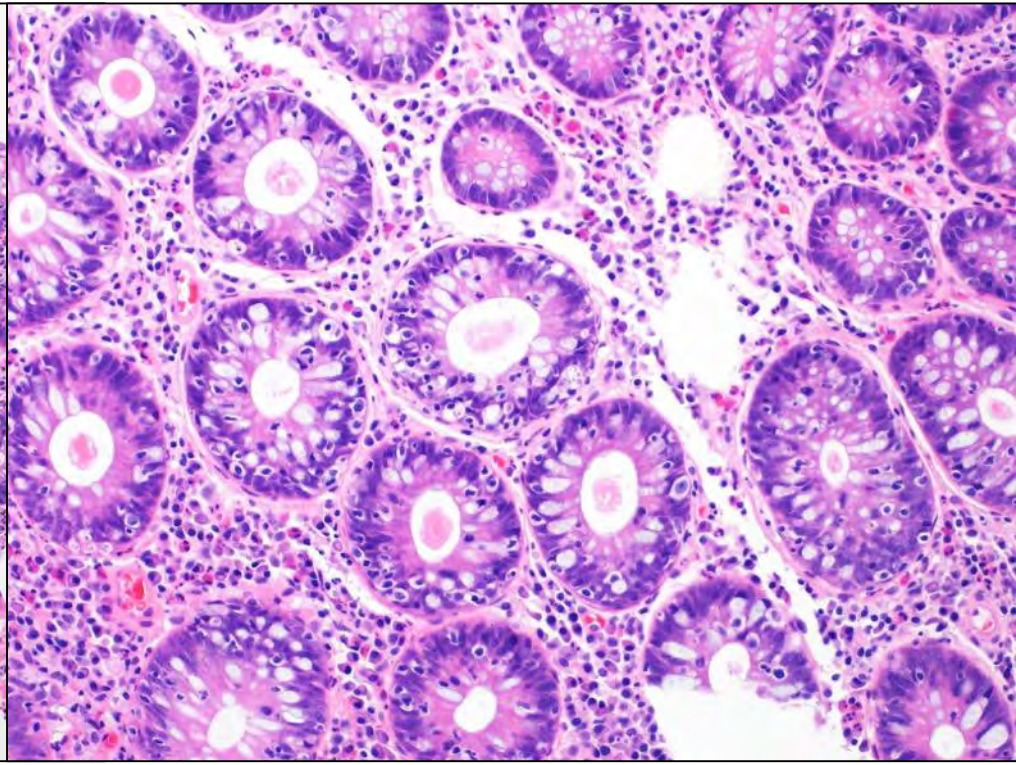
- 67 yo male with history of metastatic renal cell carcinoma presents with diarrhea



Checkpoint inhibitor colitis: on pembrolizumab (anti-PD1)

Patient with metastatic melanoma on pembrolizumab





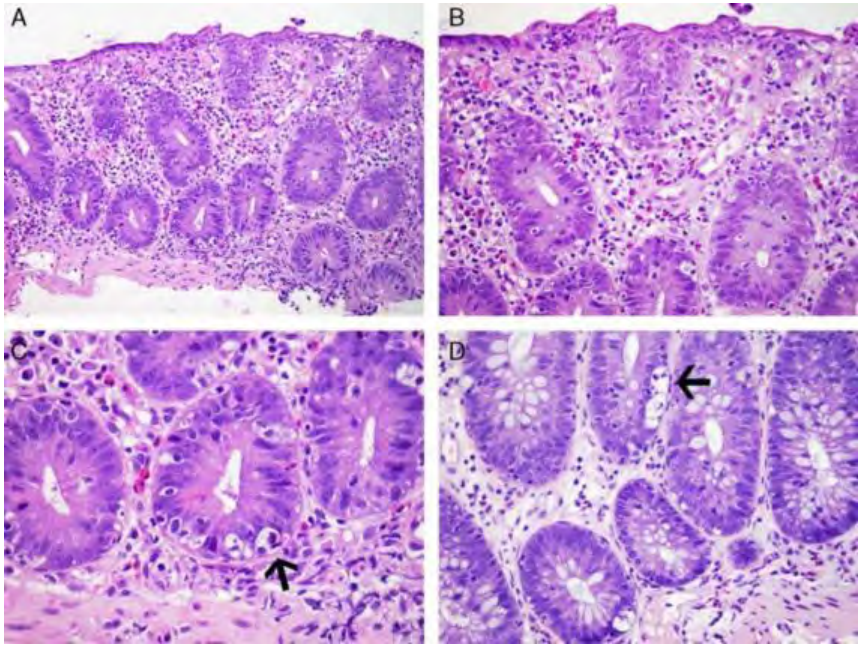
Checkpoint inhibitor associated injury

- Monoclonal antibodies that block T-cell inactivation (anti-CTLA4, anti-PD1, anti-PD-L1)
- Two common histologic patterns:
  1. Active colitis pattern that can resemble IBD:
     - Crypt architectural distortion and lamina propria chronic inflammation (seen in ~40% of cases).
     - Cryptitis and crypt abscess formation is common.
     - Can present with fulminant perforating colitis w/ extensive ulceration.
  2. Lymphocytic colitis-like pattern:
     - Intraepithelial lymphocytosis (~70% of cases).
     - Crypt epithelial apoptoses (~20% of cases).
- Treatment with corticosteroids.

1. Verschuren EC et al. Clin Gastroenterol Hepatol 2015;14:836-842.
2. Oble DA et al. Am J Surg Pathol 2008;32:1130-1137.
3. Mitchell KA et al. J Clin Gastroenterol 2013;47:781-785.
4. Chen JH et al. Am J Surg Pathol. 2017 May;41(5):643-654

Idelalisib associated injury

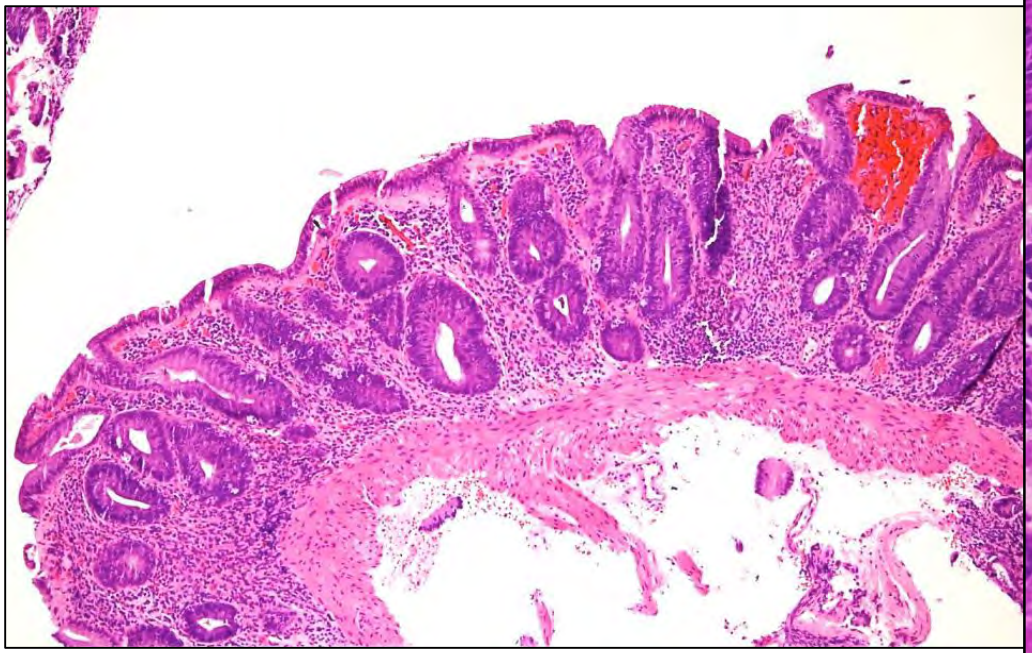
- Idelalisib: small molecule PI3Kδ inhibitor used in CLL/SLL and follicular lymphoma therapy.
- Histologic Features:
  - Increased intraepithelial lymphocytes (~80-90%).
  - Crypt epithelial apoptoses (~80%).
  - Cryptitis and architectural distortion often seen.

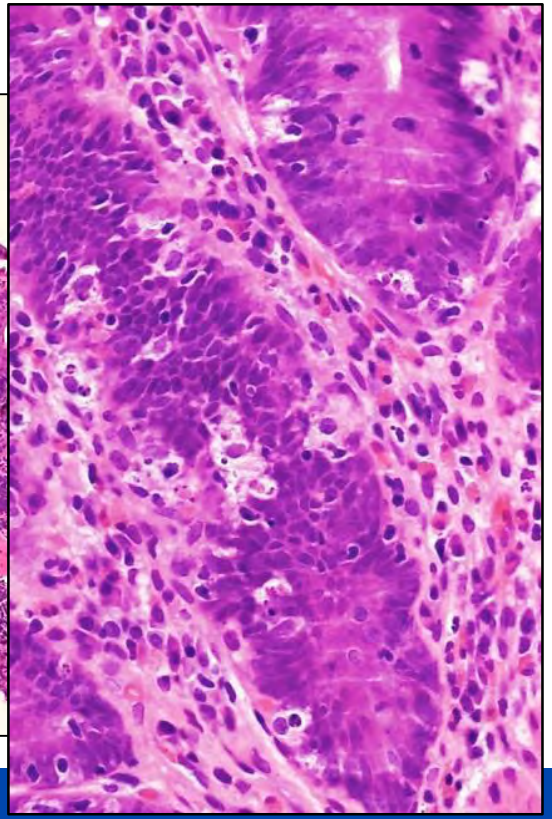


1. Weidner A et al. Am J Surg Pathol 2015;39:1661-1667.
2. Louie CY et al. Am J Surg Pathol 2015;39:1653-1660.

Case 7:

54 year old man with history of thymoma and several month history of diarrhea and weight loss.





Autoimmune enterocolitis (thymoma related):
Complete absence of goblet cells and increased crypt epithelial apoptosis

Autoimmune enterocolitis

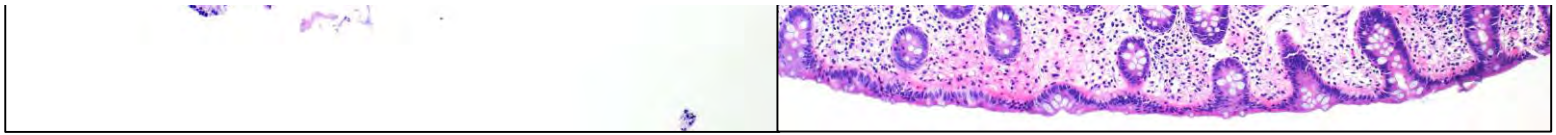
- Two types
- Pediatric autoimmune enterocolitis
  - APECED (Autoimmune Phenomena, Polyendocrinopathy, Candidiasis, and Ectodermal Dystrophy)
    - Mutations in *AIRE*
  - IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
    - Mutation in *FOXP3*
  - Immunodeficiency (CVID)
- Adult onset autoimmune enterocolopathy
  - May be secondary
    - Thymoma-associated
- Autoantobodies against goblet cells and enterocytes are present in the majority of patients, but not required for the diagnosis.

1. Masia R et al. Am J Surg Pathol 2014;38:1319-1329.
2. Singhi AD et al. Mod Pathol 2014;27:543-553.

CVID: Diverse histologic features

TABLE 2. Percentage of Patients Showing Histologic Abnormality

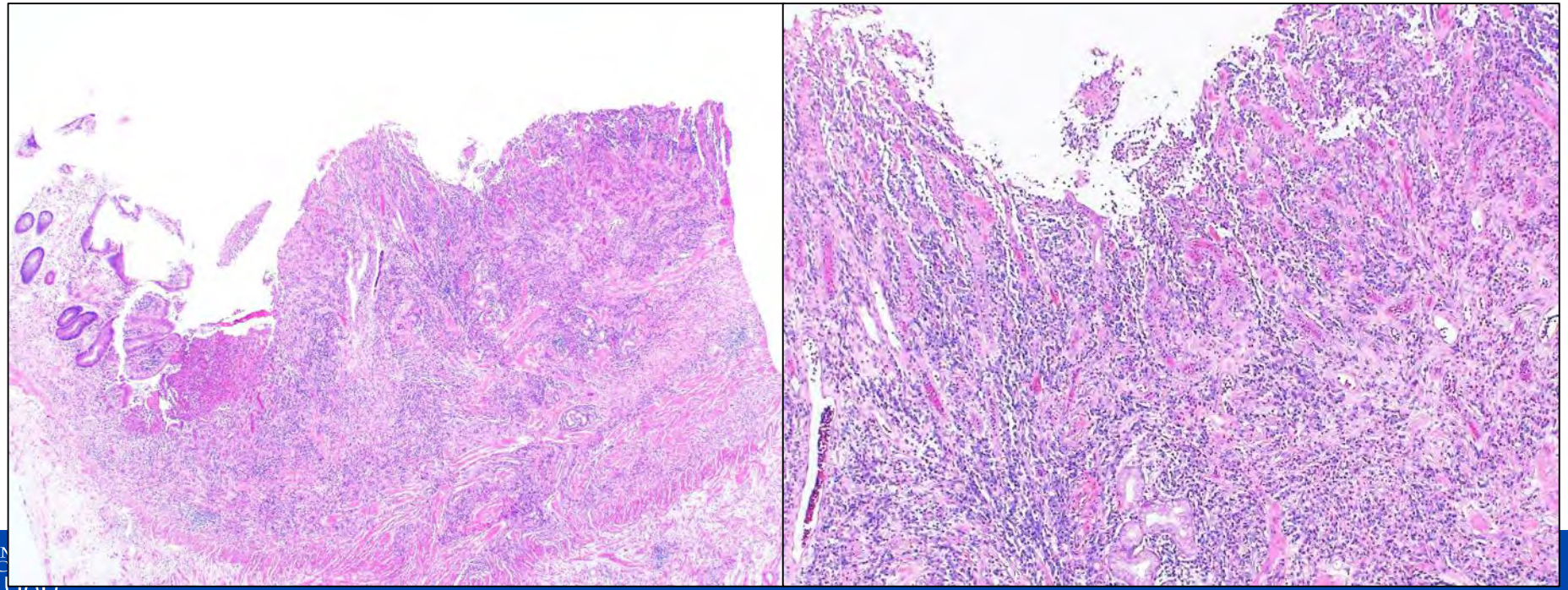
Histologic Findings	Esophagus	Stomach	Small Intestine	Colon	Appendix	Gallbladder
Decreased plasma cells	N/A	12/18 (67%)	13/19 (68%)	10/16 (63%)	1/1 (100%)	1/2 (50%)
Lymphoid aggregates	N/A	11/18 (61%)	9/19 (47%)	13/16 (81%)	0/1 (0%)	0/2 (0%)
Increased apoptosis	1/10 (10%)	6/18 (33%)	4/19 (21%)	8/16 (50%)	1/1 (100%)	0/2 (0%)
Intraepithelial lymphocytosis	5/10 (50%)	4/18 (22%)	12/19 (63%)	6/16 (38%)	0/1 (0%)	0/2 (0%)
Villous blunting*	N/A	N/A	10/12 (83%)	N/A	N/A	N/A
Collagenous pattern*	N/A	0/4 (0%)	0/12 (0%)‡	2/6 (33%)	N/A	N/A
Granulomas	0/10 (0%)	1/18 (6%)	2/19 (11%)	3/16 (19%)	0/1 (0%)	0/2 (0%)
Intraepithelial neutrophils	4/10 (40%)	8/18 (44%)	6/19 (32%)	14/16 (88%)	0/1 (0%)	1/2 (50%)
Crypt Distortion†	N/A	N/A	N/A	6/14 (43%)	0/1 (0%)	N/A
Infections†	4/4 (100%) Candida	2/8 (25%) CMV; 1/8 (13%) HP; 1/8 (13%) Crypto	1/19 (5%) CMV; 1/19 (5%) Crypto	1/14 (7%) CMV	0/0 (0%)§	0/1 (0%)
Cancer	0/10 (0%)	1/18 (6%) AdenoCA	0/19 (0%)	0/16 (0%)	0/1 (0%)	0/2 (0%)



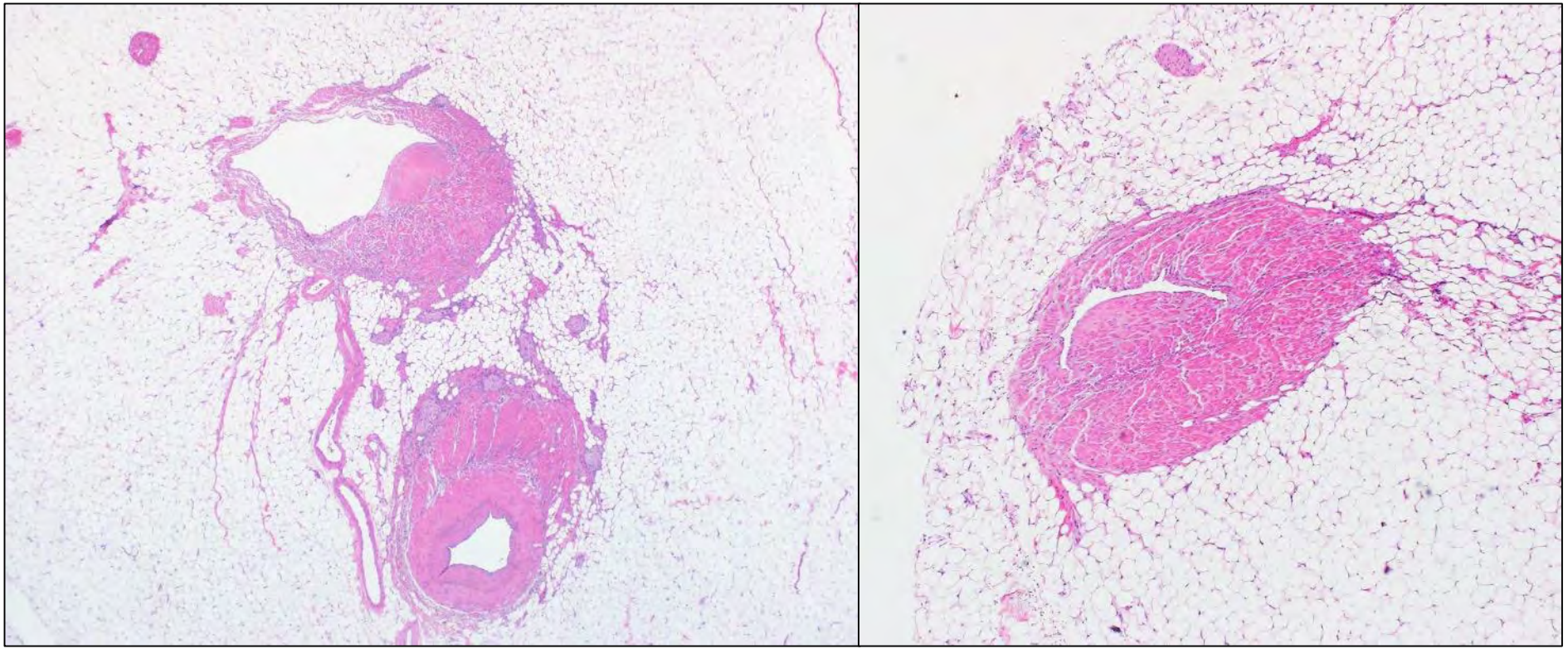
Am J Gastroenterol. 2019 Apr;114(4):648-655
Am J Surg Pathol. 2007 Dec;31(12):1800-12.

Case 8:

- 60 yo female undergoes resection of a larger uterine leiomyoma. An incidental small bowel stricture was identified.



Mesenteric arteriovenous dysplasia/vasculopathy

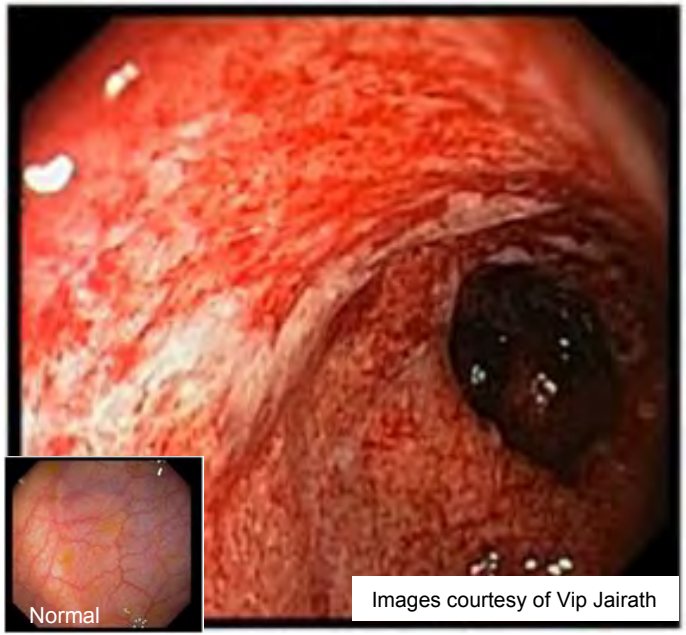


MAYO CLINIC

Am J Surg Pathol. 2016 Oct;40(10):1316-25.

Typical clinical scenario: Ulcerative colitis (UC)

30 year old male with rectal bleeding and cramping rectal pain

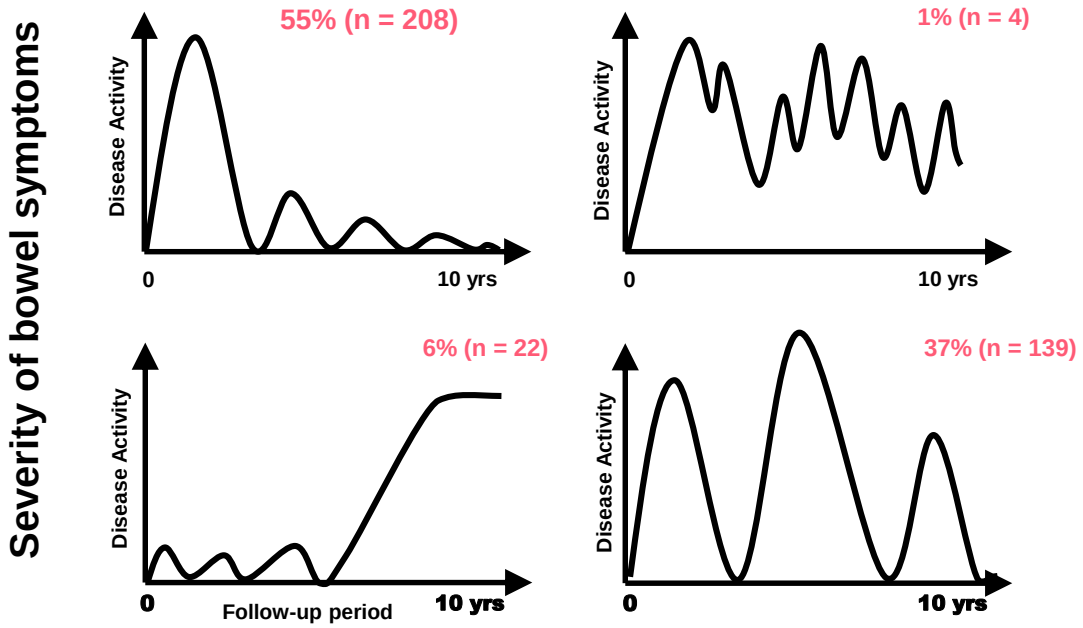


- Endoscopically consistent with pancolitis
- Mucosal biopsies show “severe chronic active colitis, consistent with inflammatory bowel disease (ulcerative colitis)”
- Patient started on medical therapy
- Clinical remission is achieved initially
- Patient has a few flares over the next few years but able to get back into clinical remission
- Endoscopic surveillance for dysplasia begins 8 years after diagnosis

IBSEN

A Personalized Management Strategy is Essential for Patients with UC

Potential UC Disease Course Over First 10 Years



~45% of UC pts potentially will have an unfavorable disease course

IBSEN-Study: A 10-year IBD population-based follow-up study

Solberg et al. Clin Gastroenterol Hepatol 2007;5:1430-1438
Solberg et al. Scan J Gastroenterol 2009;44:431-440

Traditional uses of mucosal biopsies in IBD

1. Help establish the initial diagnosis of IBD
2. Help confirm the presence of disease flare
3. Exclude the presence or absence of dysplasia in long-standing IBD

Can we do better?

1. Are there alternative ways to measure treatment response and disease activity in addition to assessing clinical symptoms +/- endoscopic appearance?
2. Are there ways to predict those patients in clinical remission and/or endoscopic remission who will relapse?
   - Maybe these patients are better served by another medication?
3. Can we better predict those patients at high risk for dysplasia and carcinoma?

Serial Rectal Biopsy in Ulcerative Colitis During the Course of a Controlled Therapeutic Trial of Various Diets

Vol. 11, No. 11, 1966

RALPH WRIGHT, M.D., D.PHIL., M.R.C.P., and
SIDNEY R. TRUELOVE, M.D., F.R.C.P.

Each specimen was given a code number and the histologic sections were examined by one of us without any knowledge of the clinical activity of the ulcerative colitis or the nature of the diet. Only the code number was known

Sidney Truelove

TABLE 2. RECTAL BIOPSY FINDINGS AND SIGMOIDOSCOPIC FINDINGS

	Degree of inflammation on biopsy specimen				
Sigmoidoscopic grading	*None*	*Mild*	*Moderate*	*Severe*	*Total*
Normal	166	103	2	1	272
Mild	30	83	22	1	136
Moderate	11	87	44	23	165
Severe	2	31	38	14	85
TOTAL	209	304	106	39	658

39% of patients with normal sigmoidoscopy had inflammation on biopsy

Am J Dig Dis. 1966 Nov;11(11):847-57

Serial Rectal Biopsy in Ulcerative Colitis During the Course of a Controlled Therapeutic Trial of Various Diets

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RALPH WRIGHT, M.D., D.PHIL., M.R.C.P., and
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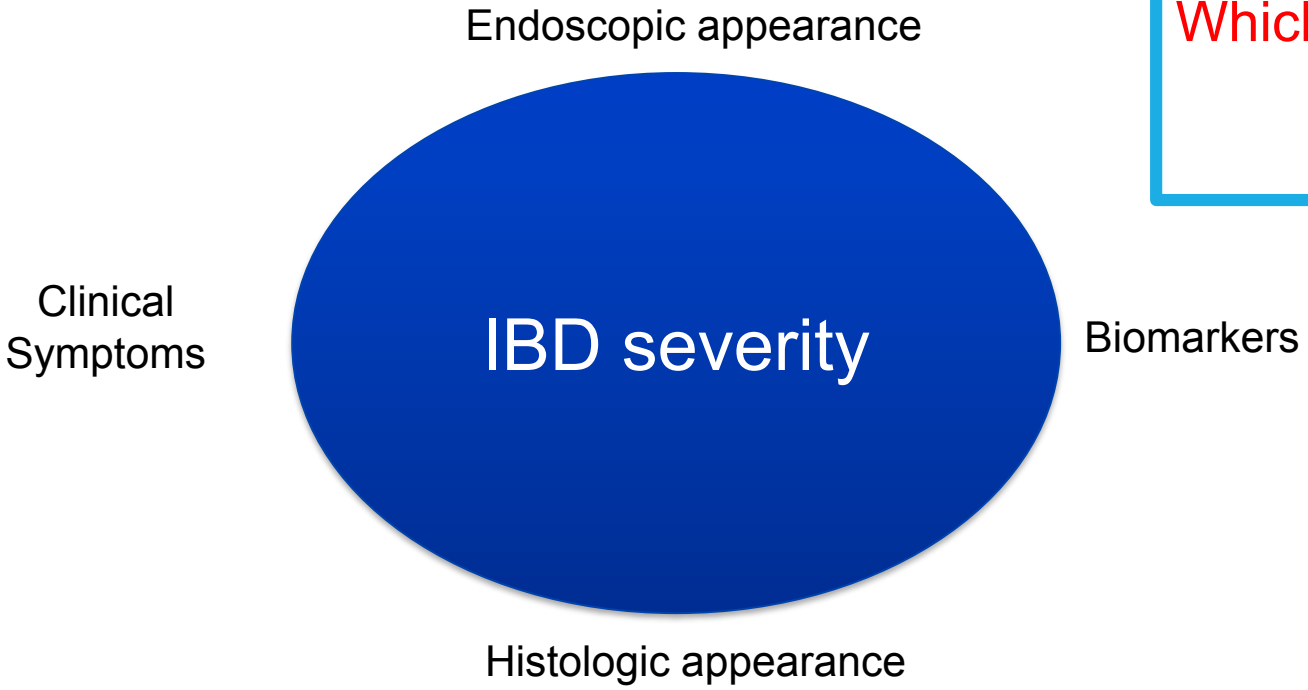
trial year. Table 3 shows the results of sigmoidoscopy at 2 months after entry into the trial in relation to the number of relapses subsequently suffered. It will be seen that among the patients with normal sigmoidoscopic findings at that time, 39.5% remained symptom-free during the remainder of the trial period, compared with 17.9% of those with abnormal sigmoidoscopic findings. The results are consistent for the 3 dietary groups.

Table 4 shows comparable data for the rectal biopsy findings at 2 months after entry into the trial. It will be seen that 57.9% of the patients with no significant inflammation in the biopsy specimen remained symptom-free during the rest of the year, compared with only 16.7% of those with evidence of inflammation in the biopsy specimen. In other words, the rectal biopsy has greater predictive value than the sigmoidoscopic findings.

Disease activity measurements in IBD



Which measurement is the gold standard?

What is the goal of UC therapy?

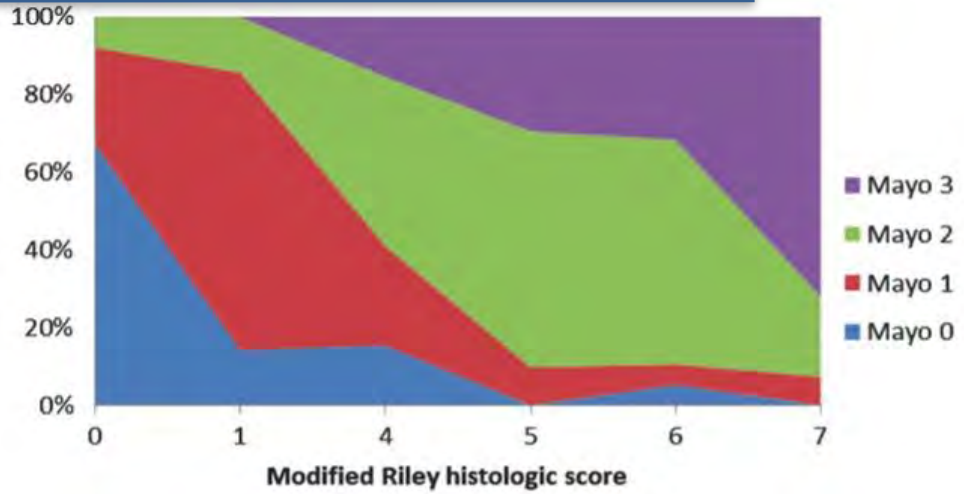
Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastro 2015:110:1325

Recommendation	Voting results	
	Strength of recommendation[a]	Percentage votes at last ballot
Clinical		
1. Resolution of rectal bleeding and normalization of bowel habit should be the target	8.1	95
2. Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions	7.4	75
All attendees agreed that resolution of clinical symptoms and inflammation are the goals of treatment that define the term "remission". Mucosal healing was recommended as the therapeutic goal in clinical practice, because it is associated with better outcomes in both cohort studies and randomized controlled trials.		
Endoscopic		
1. A Mayo endoscopic subscore of 0 is the optimal target. A Mayo endoscopic subscore of 1 should be a minimum target	7.8	92
2. Endoscopic assessment should be performed 3–6 months after the start of therapy for a patient with symptoms	8.0	92
The endoscopic Mayo subscore is currently recommended for UC, rather than the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), because its predictive value is well established. While a Mayo subscore of 0 may be defined as the target, there is currently insufficient evidence to recommend it in all patients and only a Mayo subscore of 0–1 can be systematically recommended in clinical practice.		
Histologic		
1. Histopathology is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility	7.5	80
The attendees felt that the level of evidence was insufficient to recommend histologic remission as a target in UC in clinical practice. However, it was considered important to acknowledge the role of histopathology in the evaluation of inflammation in patients with UC.		

Correlation between Endoscopic and Histologic Score in Assessing the Activity of UC

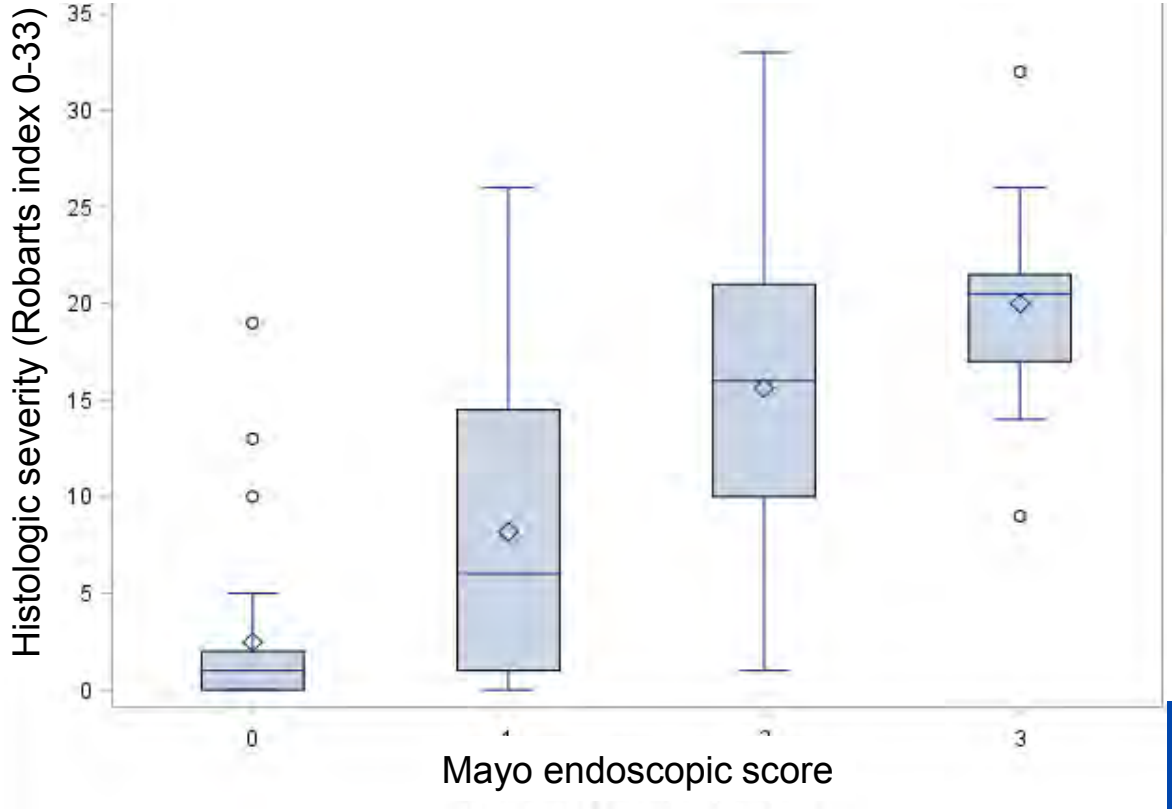
Lemmens et al. Inflamm Bowel Dis 2013:19:1194-1201

- In general, there is a moderate correlation between endoscopy and histology
- 263 biopsies were taken from 131 patients with ulcerative colitis



	Mayo score 0 (normal)	Mayo score 1 (mild)	Mayo score 2 (moderate)	Mayo score 3 (severe)
Any histologic activity	14%	51%	93%	100%
Ulcers/erosions	0%	14%	20%	68%

Histologic and endoscopic correlation



Correlation between histologic and endoscopic measurements in 137 patients treated with 6weeks of vedolizumab

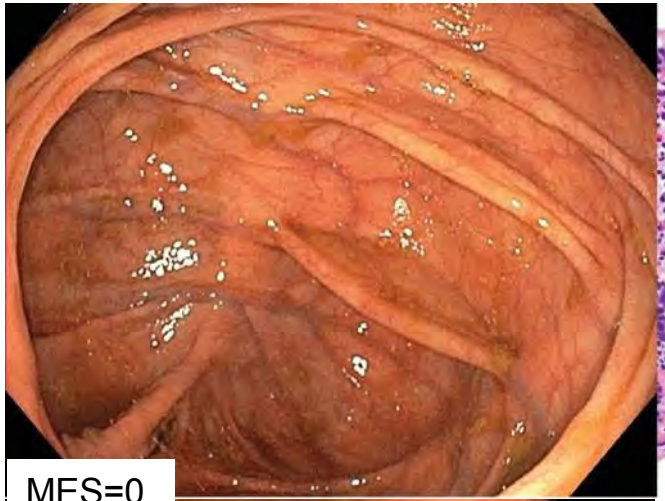
Unpublished data

Endoscopy does not tell the whole story

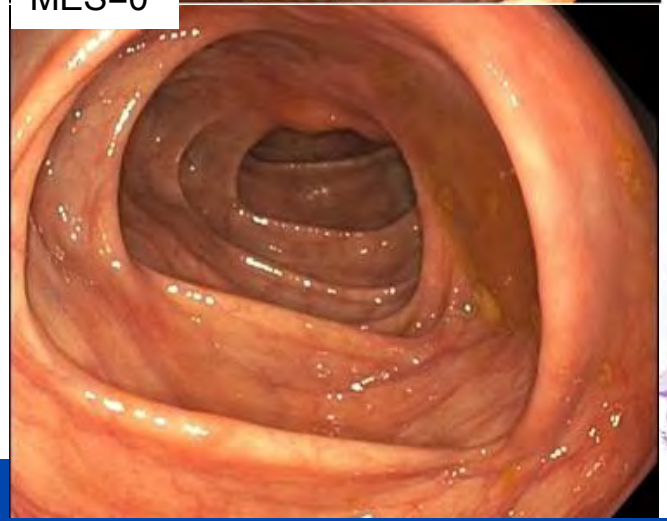
Histology is more sensitive than endoscopy at detecting disease activity

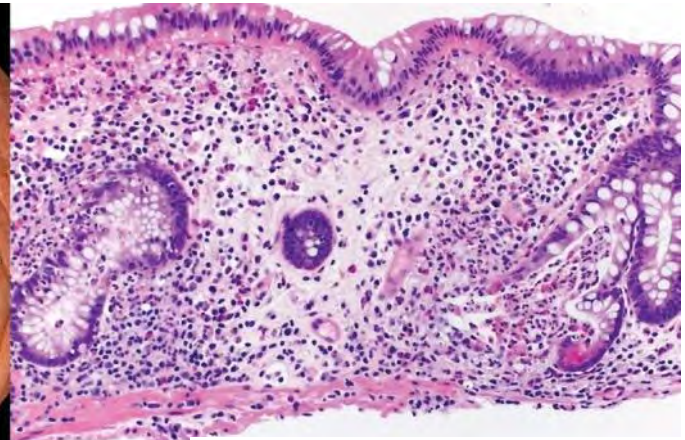
Study	Endoscopic evaluation	Histologic active disease
Truelove and Richards 1956	Normal sigmoidoscopy	37%
Lemmens 2013	Mayo endoscopy score 0	14%
Bessissow 2012	Mayo endoscopy score 0	40%
Theede 2015	Mayo endoscopy score ≤ 1	30%
Bryant 2016	Baron score ≤ 1	27%
Baars 2012	Normal endoscopy	33%
Calafat 2017	Mayo endoscopy score 0	15%
Christensen 2017	Mayo endoscopy score 0	12%
Christensen 2017	Mayo endoscopy score 1	27%
Lobaton 2018	Mayo endoscopy score 0	13%
Lobaton 2018	Mayo endoscopy score 1	43%

POST-THERAPY

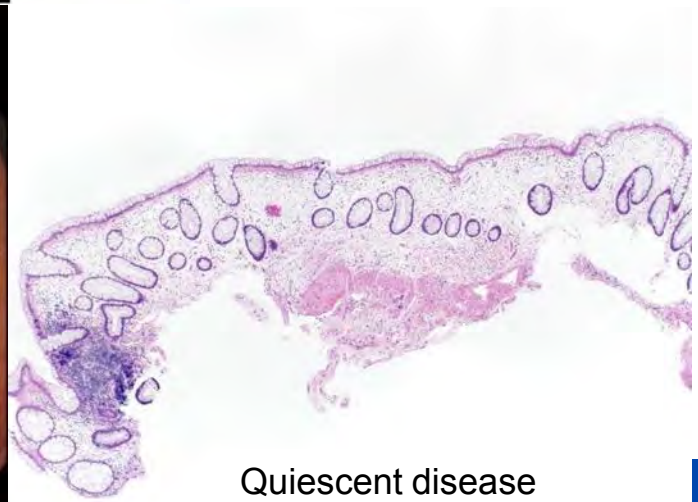


MES=0





Active disease with cryptitis



Quiescent disease

Prognostic value of serological and histological makers on clinical relapse in UC patients with mucosal healing

Bessissow et al. Am J Gastroenterol 2012:107:1684-92

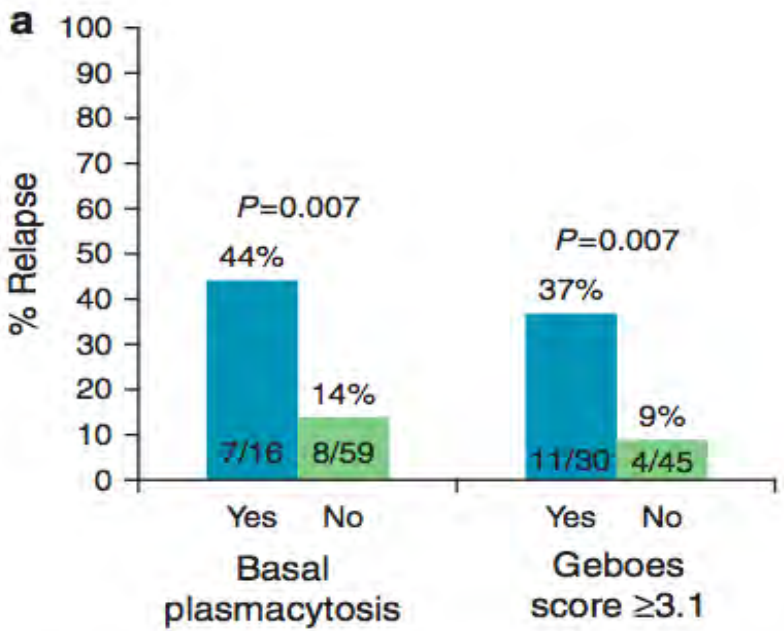
Table 2. Baseline characteristics of cohort

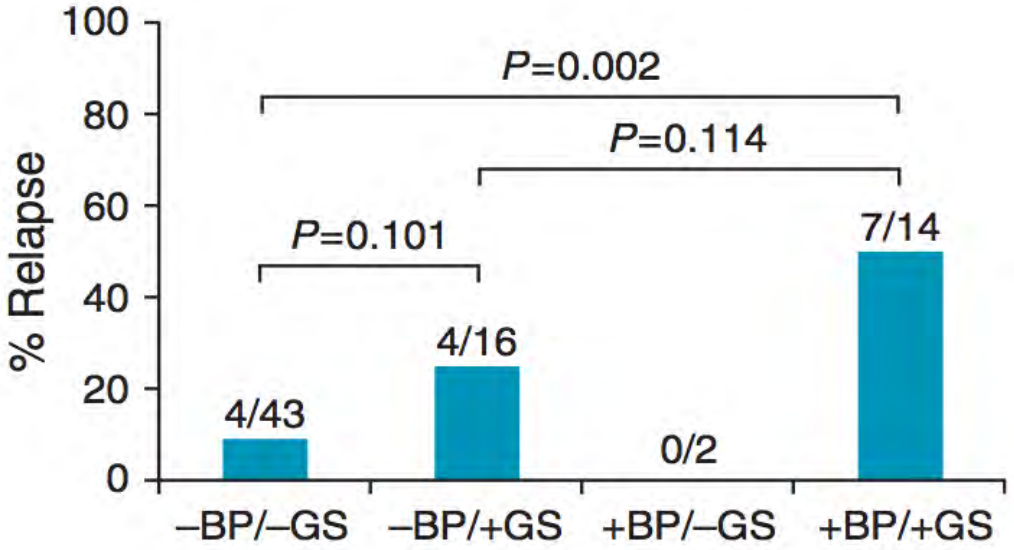
	Value
No. of patients	75
Male sex (%)	40 (53)
Median age (years)	47 (36–58)[a]
Median duration of remission before study (months)	34 (12–70)[a]
Appendectomy (%)	4 (5)
Active smoking (%)	12 (16)
Pancolitis (%)	56 (75)
Medications	
Oral mesalamine (%)	53 (71)
Immunomodulators[b] (%)	27 (36)
Biologicals[c] (%)	40 (53)
CRP (>5 mg/l) (%)	10 (15)
Geboes score ≥3.1 with MH(%)	30 (40)
Basal plasmacytosis	16 (21)
Focal (%)	10 (13)
Diffuse (%)	6 (8)
Median no. of biopsies per patient	4 (1–6)[a]

- 15 patients experienced relapse of UC
- CRP was slightly elevated in relapsers (p=0.045)
- Use of biologics were somewhat protective of relapse (p=0.083)

Does Histologic Activity Predict Relapse?

Bessissow et al. Am J Gastroenterol 2012:107:1684-92





(Neutrophilic cryptitis)

Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study

Am J Gastroenterol 2016; 111:685–690

Table 1. Characteristics of enrolled cohort at baseline (*N*=179)

Mean age (STD)	43 (14)
Female	48%
Current smoker	1%
Disease phenotype	
Pancolitis	46%
Extraintestinal manifestations	7%
Disease duration >10 years	25%
Clinical remission >6 months	83%
Current medications	
5-ASA	76%
Thiopurine	18%
Anti-TNF	6%
Inflammatory parameters (STD)	
Mean SCCAI score	0 (1)
Mean WCC	6.8 (2.2)
Mean Hct	41 (5)
Mean ESR	11 (12)
Mean CRP	3.4 (4.7)

ASA, aminosalicyclic acid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; SCCAI, simple colitis clinical activity index; STD, standard deviation; TNF, tumor necrosis factor; WCC, white cell count.

Table 2. Distribution of inflammation scores in enrolled cohort at baseline (*N*=179)

	(%)
Endoscopy score (Mayo)	
0	55
1	32
2	12
3	1
Histology grade (Geboes)	
0	48
1	6
2	5
3	22
4	9
5	10

Relapse:

- SCCAI score >2 at 3, 6, or 12 months.
- Increase in stool frequency, blood in stool, or abdominal pain for >48 h, related to UC
- An escalation of colitis medications
- Hospitalization for UC relapse
- Colectomy for refractory UC

Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study

Am J Gastroenterol 2016; 111:685–690

- Only histologic inflammation was significantly associated with relapse on multivariate analysis
- Histologic inflammation was predictive of relapse even in Mayo ES 0 patients
- % relapse of patients in clinical and endoscopic remission at baseline = 42%.
- % relapse of patients in clinical, endoscopic, and histologic remission at baseline: 7%

Table 3. Univariate analysis of factors associated with clinical relapse

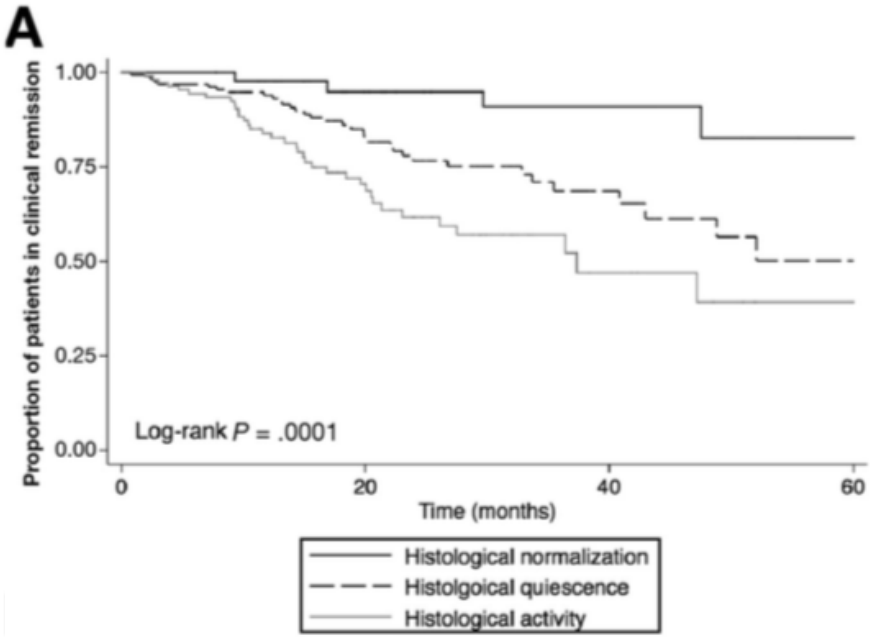
Dichotomous variables	OR	95% CI	*P* value
Male gender	0.9	0.4–1.8	0.8
Remission >6 months	0.6	0.2–1.4	0.2
Steroids within 12 months	0.8	0.2–2.1	0.3
Current thiopurine	0.8	0.3–2.2	0.7
Current mesalamine	0.5	0.2–1.1	0.08
Non-smoker	3.8	0.2–62	0.4
NSAID use	1.6	0.6–4	0.3
Extraintestinal features	0.8	0.2–3.4	0.9
Endoscopy score >0	**2.8**	**1.6–4.9**	**0.0002**
Histology score >3	**3.5**	**1.6–6.4**	**0.0001**
Continuous variables			
Age			0.9
White cell count			0.06
Hct			0.7
ESR			0.4
CRP			0.3
Histology score (0–22)			**0.0001**

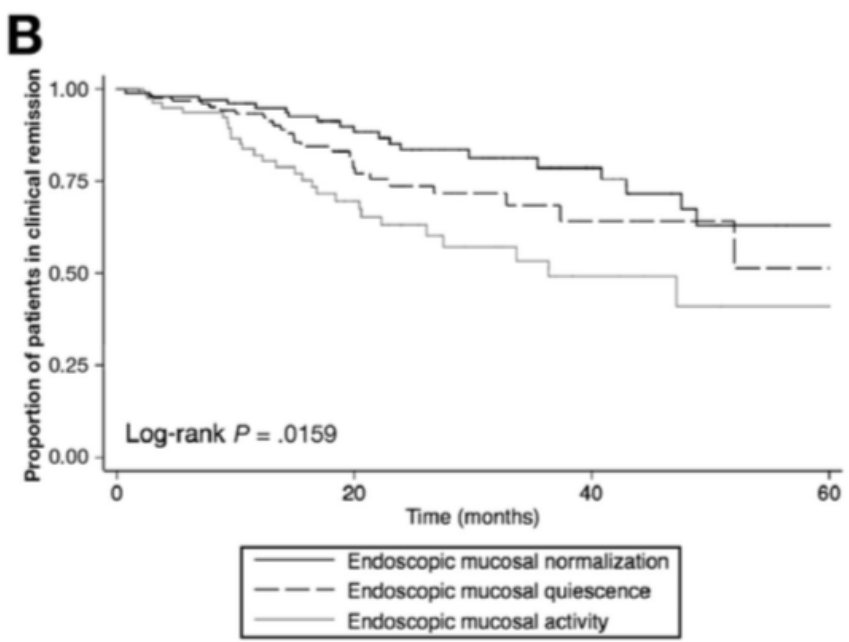
CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

Bold values are statistically significant.

Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes.

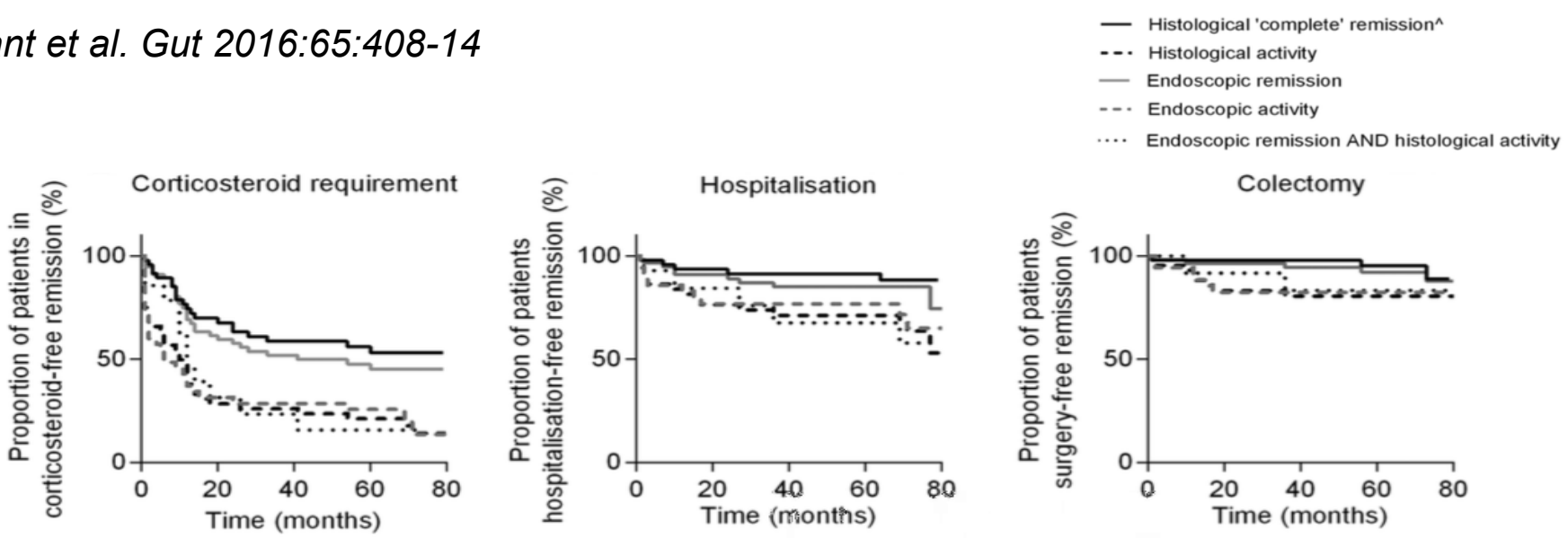
646 patients with UC. 310 in clinical remission. Endoscopy was measured by MES (0=normal, 1=quiescence, ≥2=active). Histology was divided into normal, quiescent, and active.





Christensen B, et al. Clin Gastroenterol Hepatol. 2017 Oct;15(10):1557-1564

Bryant et al. Gut 2016:65:408-14



Multivariate analysis

Variable	Corticosteroid requirement	Hospitalization for severe colitis	Colectomy
Disease extent	n.s.	3.21, p=0.02	**4.06, p=0.02**
Histologic remission	**0.42, p=0.02**	**0.21, p=0.02**	0.36, p=0.22
Endoscopic remission	0.86, p=0.65	0.83, p=0.74	0.71, p=0.64
Histo and Endo Remission	**0.38, p=0.02**	**0.24, p=0.04**	0.46, p=0.39

Histologic Activity and Neoplasia

Flores et al. Gastro Endosc 2017. 86:1006

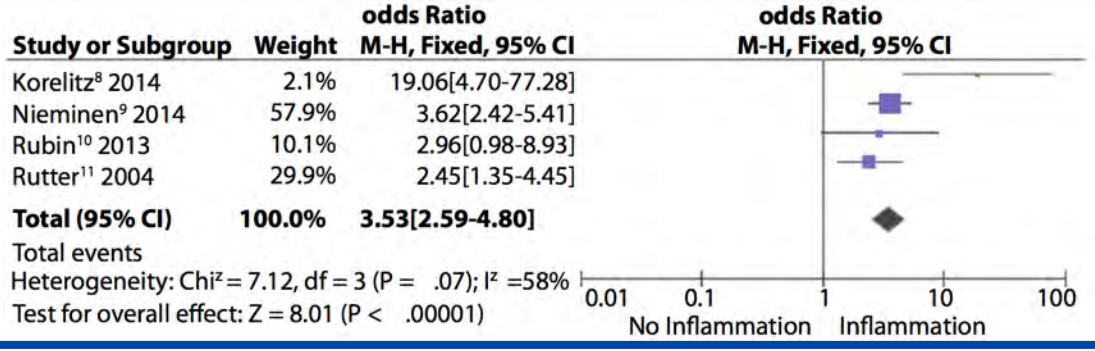
TABLE 1. Characteristics of included studies (papers)

Author	Design	N (number of patients in study)	No. cases	Definition of dysplasia	Inflammation score	Definition of inflammation	Duration of follow-up, y
Gupta[7]	Retrospective observational cohort	418	224	Low-grade dysplasia, high-grade dysplasia, cancer	Histologic activity index: grade 0-3	Score of 1 or greater	6.7
Korelitz[8]	Retrospective observational cohort	68	20	High-grade dysplasia, cancer	Microscopic inflammation in the absence of gross inflammation	Microscopic inflammation in the absence of gross inflammation	>20
Nieminen[9]	Retrospective case-control	506	168	Dysplasia, cancer	Histologic activity index: grade 0-3	Score of 1 or greater	12
Rubin[10]	Retrospective case-control	200	59	Neoplasia, cancer	Histologic inflammatory activity: grade 0-5	Score of 2 or greater	11
Rutter[11]	Retrospective case-control	204	68	Adenoma, low-grade dysplasia, high-grade dysplasia, cancer	Histologic inflammation: grade 0-4 Colonoscopic inflammation: grade 0-4	Unclear, assess at 1-unit increases	14
Rutter[12]	Retrospective case-control	204	68	Adenoma, low-grade dysplasia, high-grade dysplasia, cancer	Presence of scarring, post-inflammatory polyps, backwash ileitis, shortened colon, tubular appearance, featureless colon	Presence or absence of scarring, post-inflammatory polyps, backwash ileitis, shortened colon, tubular appearance, featureless colon	14

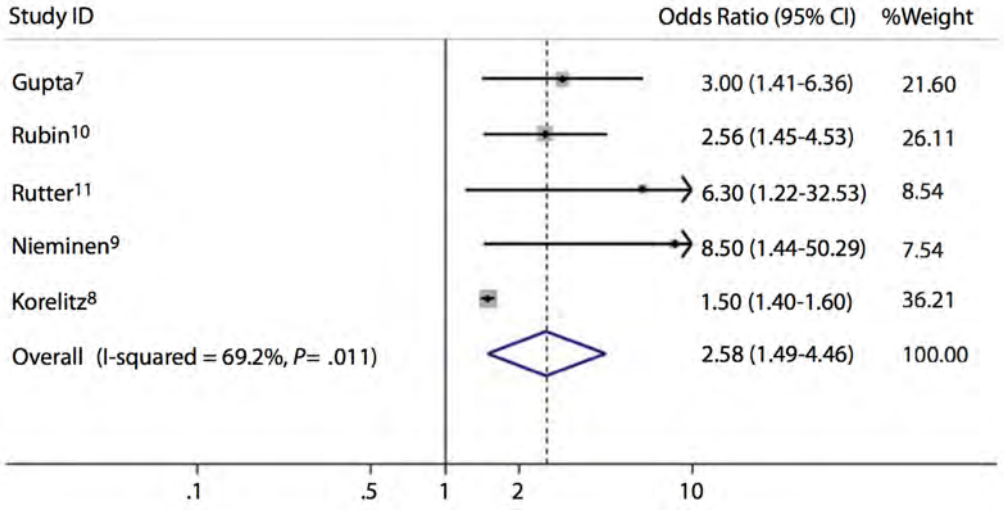
Histologic Activity and Neoplasia

Flores et al. Gastro Endosc 2017. 86:1006

Endo or Histo Activity



Histo Activity only



Cumulative burden of inflammation predicts colorectal neoplasia risk in ulcerative colitis: a large single-centre study

Choi C-HR, *et al*. *Gut* 2019;**68**:414–421.

987 patients with UC: Both severity and duration of inflammation influence neoplasia risk

Cumulative inflammatory burden (microscopic)

- *Sum* of mean microscopic inflammation severity between each interval x length of interval

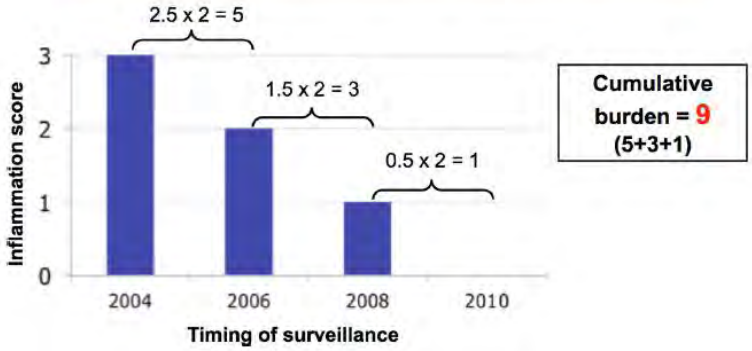


Table 4 Final multivariate model showing predictors associated with colorectal neoplasia

Variables	HR (95% CI)	P value
Cumulative inflammatory burden		
Endoscopic*	**2.1** (1.5 to 2.9)	**<0.001**
Histological*	**2.1** (1.4 to 3.0)	**<0.001**
Macroscopic features of chronicity		
Scarring only	1.4 (0.8 to 2.4)	0.3
Tubular, featureless or shortened colon	**1.8** (1.1 to 2.9)	**0.03**
Postinflammatory polyps	1.2 (0.8 to 1.8)	0.4
Colonic stricture	**3.2** (1.3 to 8.0)	**0.01**
Chromoendoscopy	1.0 (0.6 to 1.7)	1.0
Primary sclerosing cholangitis	**2.3** (1.1 to 4.7)	**0.02**
Age (at colonoscopy)	**1.02** (1.00 to 1.04)	**0.03**
Average number of biopsies	**1.14** (1.08 to 1.20)	**<0.001**
Average surveillance interval	**0.93** (0.91 to 0.96)	**<0.001**

*HR per 10-unit increase in cumulative inflammatory burden (equivalent of 10, 5 or 3.3 years of continuous mild, moderate or severe active disease, respectively). Statistically significant variables are highlighted in bold.

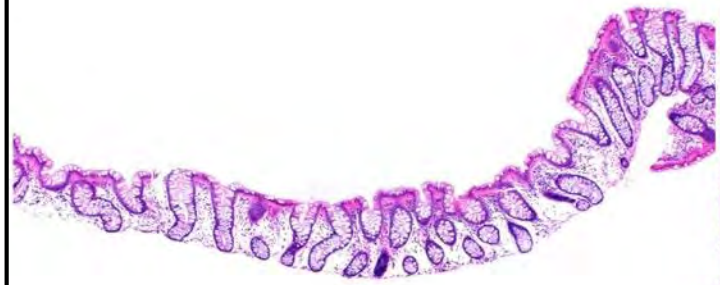
Histologic activity in IBD: Current state

- Histology is a sensitive way to measure disease activity in IBD
- Persistent histologic activity is the best predictor of adverse clinical outcomes (relapse, steroid use, hospitalizations, colectomy, dysplasia, etc.)
- Questions:
  - Can we use histology to measure response to therapy? How to measure?
  - What is the histologic target?

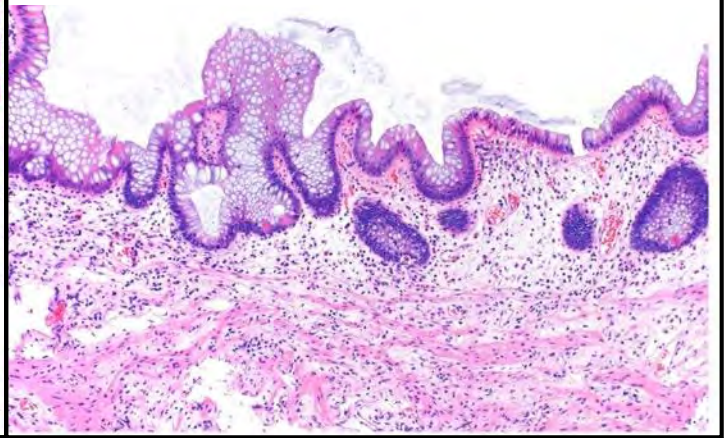
Histologic Targets in IBD

Histologic category	Proposed definition	Potential uses
Histologic healing	Complete normalization of the mucosa	Long term goal; maintenance therapy?

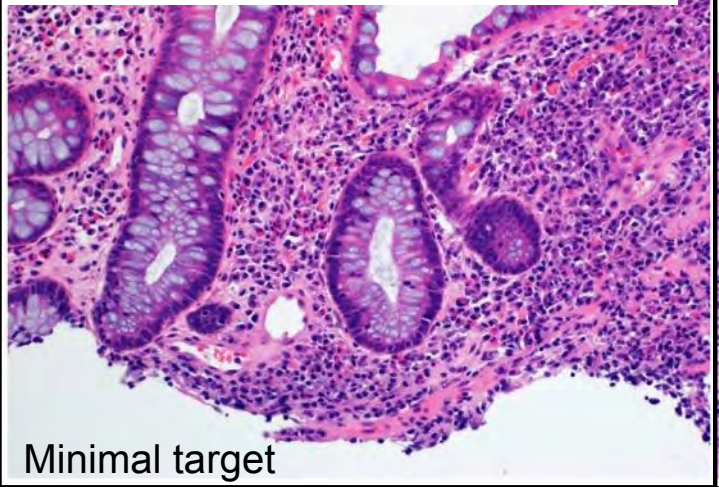
Normal



Remission: No PMNs, Eos, Basal plasmacytosis (IOIBD)

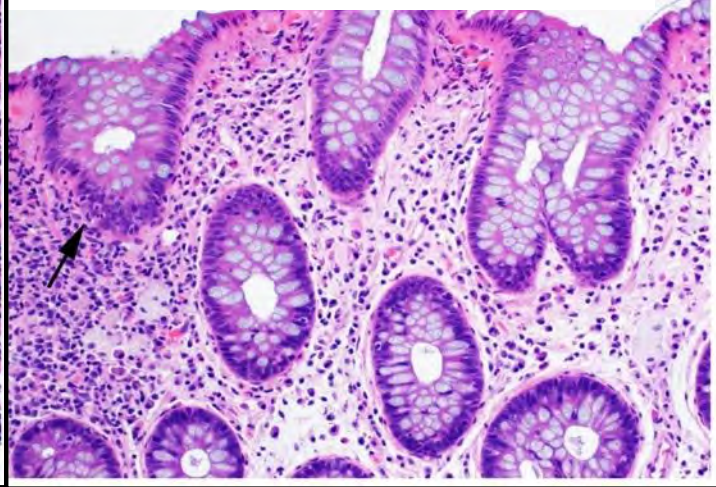


Remission: No PMNs, +Basal plasmacytosis



Minimal target

Near remission: Rare neutrophils only



Histologic activity in IBD

- How to measure severity of activity in IBD biopsie?
- 30(!) published histologic indices in ulcerative colitis
- Validated histologic indices:
  - Geboes score (2001): Measures all features seen in IBD, not designed to be used to measure response
  - Robarts Histopathologic index (2017): Designed to be responsive to therapy (0-33)
  - Nancy Histologic index (2017): Simple stepwise index (0-4)

Reliability of RHI, NI, and Geboes

Reliability of histologic scoring systems

	Intra-class Correlation Coefficient (95% CI)	
	Intra-rater	Inter-rater
Geboes Score	0.94 (0.90, 0.97)	0.88 (0.82, 0.92)
RHI	0.94 (0.91, 0.96)	0.86 (0.80, 0.90)
NI	0.92 (0.88, 0.95)	0.80 (0.73, 0.85)

ICC Interpretation
<0.00: Poor
0.00-0.20: Slight
0.21-0.40: Fair
0.41-0.60: Moderate
0.61-0.80: Substantial
0.81-1.00: Almost Perfect

Jairath V, et al. Gut. 2019. PMID: 30076171

Correlations between different activity measures

Histologic index	Clinical or Endoscopic measurement			
	Mayo Endoscopy Score	Mayo Total Score	Mayo RBS	PRO2
Geboes	0.46 (0.34, 0.57)	0.44 (0.32, 0.55)	0.32 (0.18, 0.44)	0.27 (0.12, 0.40)
RHI	0.48 (0.35, 0.58)	0.45 (0.32, 0.56)	0.33 (0.19, 0.45)	0.26 (0.11, 0.39)
Nancy	0.45 (0.33, 0.56)	0.43 (0.30, 0.54)	0.31 (0.17, 0.43)	0.22 (0.08, 0.36)

Pearson correlation coefficients: Strong correlation among all histologic indices, only moderate correlation with other measures

Jairath V, et al. Gut. 2019. PMID: 30076171

Histologic Healing Rates of Medical Therapies for Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Am J Gastroenterol 2019;114:733–745.

Robert Battat, MD[1,2], Marjolijn Duijvestein, MD, PhD[2,3], Leonardo Guizzetti, PhD[2], Daksh Choudhary, BSc[4], Brigid S. Boland, MD[1], Parambir S. Dulai, MD[1], Claire E. Parker, MA, MLIS[2], Tran M. Nguyen, MSc[2], Siddharth Singh, MD[1], Niels Vande Casteele, PharmD, PhD[1,2], Rish K. Pai, MD, PhD[5], Brian G. Feagan, MD[2,4,6], William J. Sandborn, MD[1] and Vipul Jairath, MD, PhD[2,4,6]

How good are current therapies?

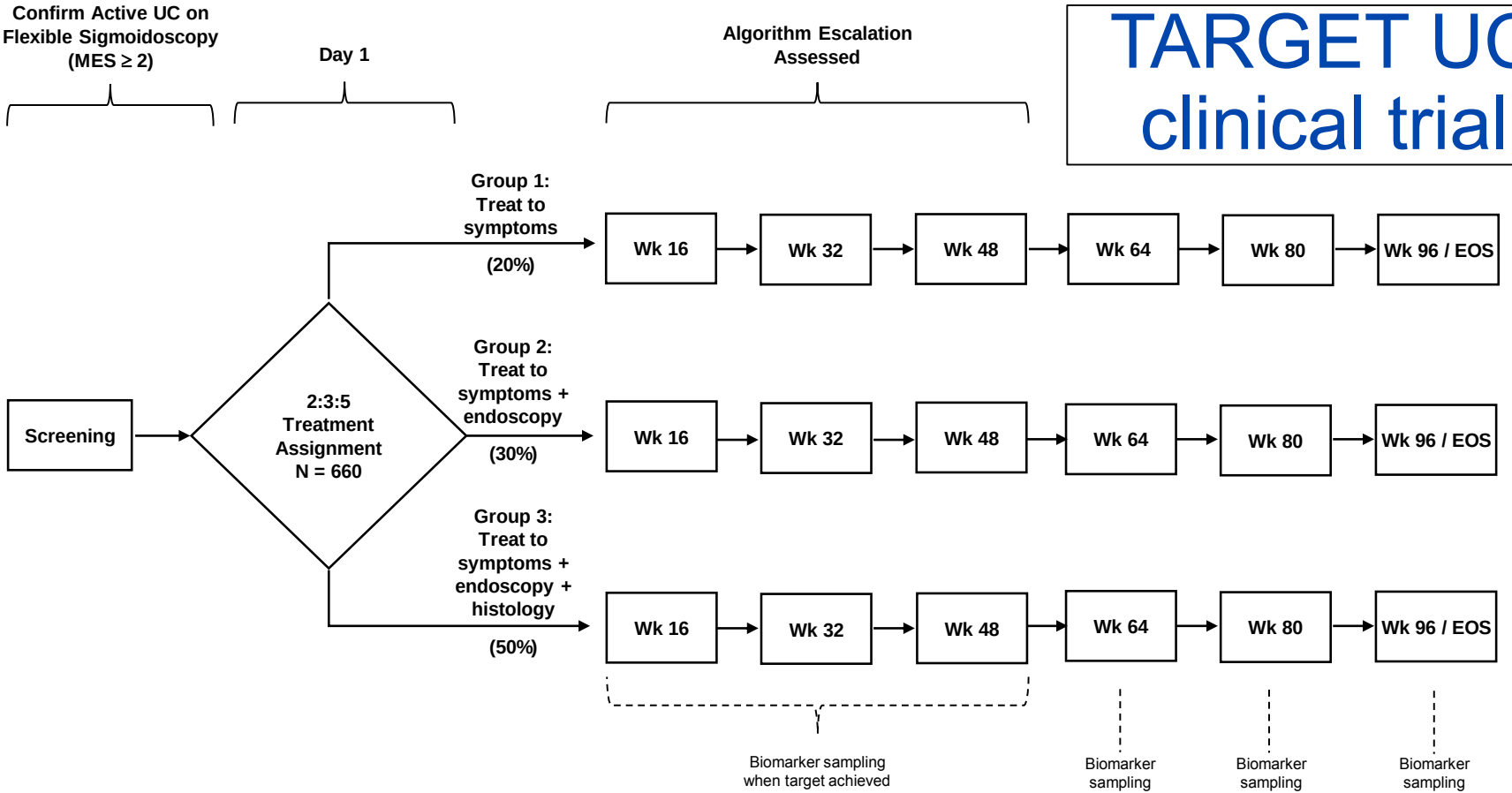
Drug class	Pooled Proportion (95% CI)	Studies	n / N	Het. Q	Het. I^2	Het. tau^2
Induc						
Oral A						
Histo						
Endo						
Topic						
Histo						
Endo						
ASA						
Histo						
Endo						
Oral,						
Histo						
Endoscopic Remission *	46.4 (42.0, 50.8)	5	224 / 483			
Budesonide MMX						
Histologic Remission *	15.0 (12.6, 17.9)	3	104 / 692			
Topical corticosteroids						
Histologic Remission	25.8 (17.3, 36.5)	8	130 / 511	36.18	80.2%	0.389
Endoscogic Remission	32.6 (22.1, 45.3)	10	431 / 1078	77.60	91.2%	59.600
Placebo						
Histologic Remission	10.4 (7.1, 15.2)	18	121 / 955	36.38	69.4%	0.450
Endoscopic Remission	21.0 (15.9, 27.2)	14	173 / 840	47.62	71.8%	0.285

Clinical Dilemma:
Should gastroenterologists escalate therapy in an asymptomatic patient with histologic activity?

UC
ot
logic

current therapies

TARGET UC clinical trial



*Periodic interim analyses to check allocation ratio and sample size based on achievement of target

*2 Interim analyses to describe cohort after 300 subjects enroll and after all subjects complete to Week 48

Primary Endpoint

What does this all mean?

EXPANDS ROLE OF PATHOLOGIC EVALUATION IN IBD

1. Help establish the initial diagnosis of IBD
2. Help confirm the presence of disease flare
3. Exclude the presence or absence of dysplasia in long-standing IBD
4. Measure response to therapy
5. Provide prognostic information regarding risk of adverse clinical outcomes (relapse, dysplasia, hospitalization, steroids, etc.)

Outline

- Evaluation of colitis and ileitis
  - Patterns of injury in the lower GI tract
  - Differential diagnosis of IBD
- What to do when looking at biopsies from known IBD patients
  - Reporting histologic disease activity in IBD: Does it even matter?
  - The concept of mucosal and histologic healing

