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Update in Inflammatory Bowel Disease (IBD)

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Disclosures

- NONE RELEVANT

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Objectives

- Understand current insights into the pathophysiology that underlies IBD
- Appreciate the therapies in IBD
- Become familiar with the risk:benefit ratio in treating IBD patients
- Be cognizant of the preventive care considerations for IBD patients

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Inflammatory Bowel Disease (IBD) vs. Irritable Bowel Syndrome (IBS)

- IBD = *Inflammatory Bowel Disease*
  - chronic intestinal ***inflammation***
  - Crohn disease, ulcerative colitis
- IBS = *Irritable Bowel Syndrome*
  - no tissue abnormality (yet…)
  - brain-gut dysregulation
    - motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, altered central nervous system (CNS) processing
  - Rome IV criteria
    - recurrent abdominal pain ≥ 6 months in duration averaging ≥1 day/week in last 3 months associated with ≥ 2 of:
      - related to defecation, associated with change in frequency of stool, associated with change in form (consistency) of stool
    - constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M) by Bristol

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Bristol stool chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, **Entirely liquid**

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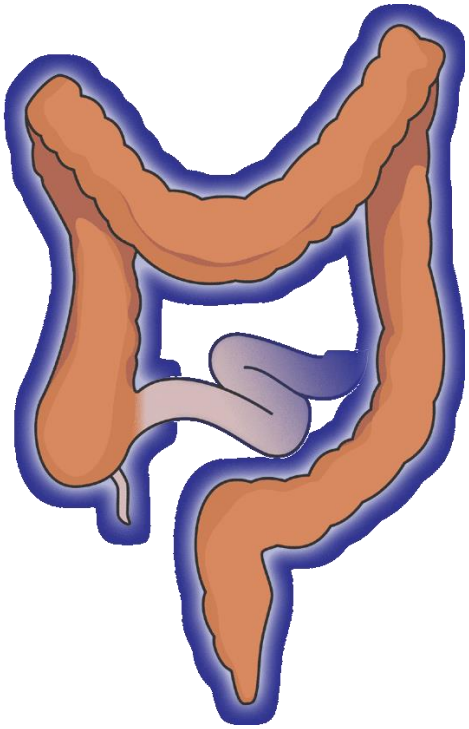
Inflammatory Bowel Diseases

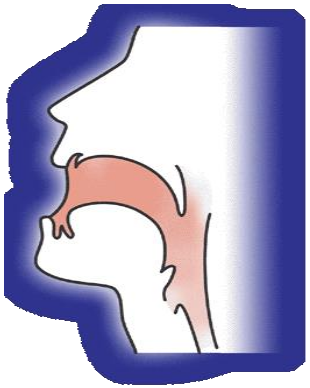
Ulcerative Colitis

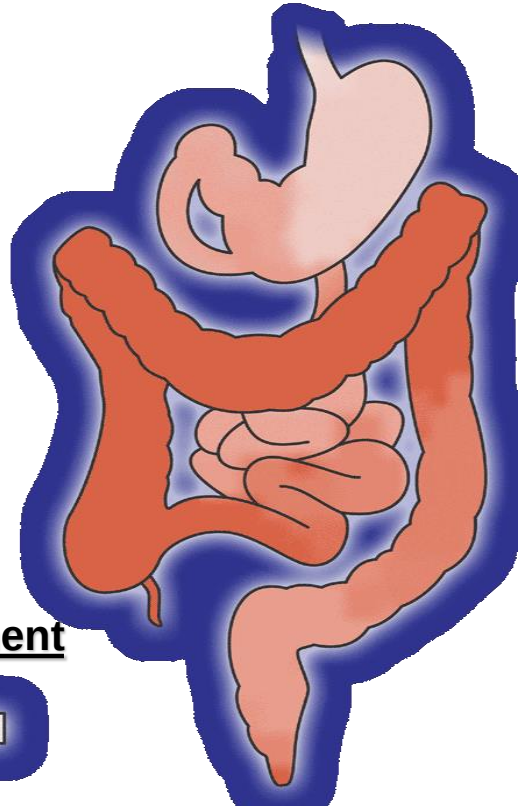
Confined to the colon



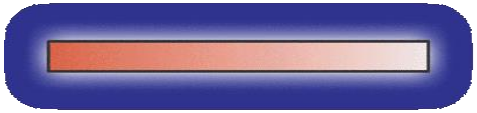
Crohn Disease

Any portion of the GI tract





Frequency of Involvement



Most ***Least***

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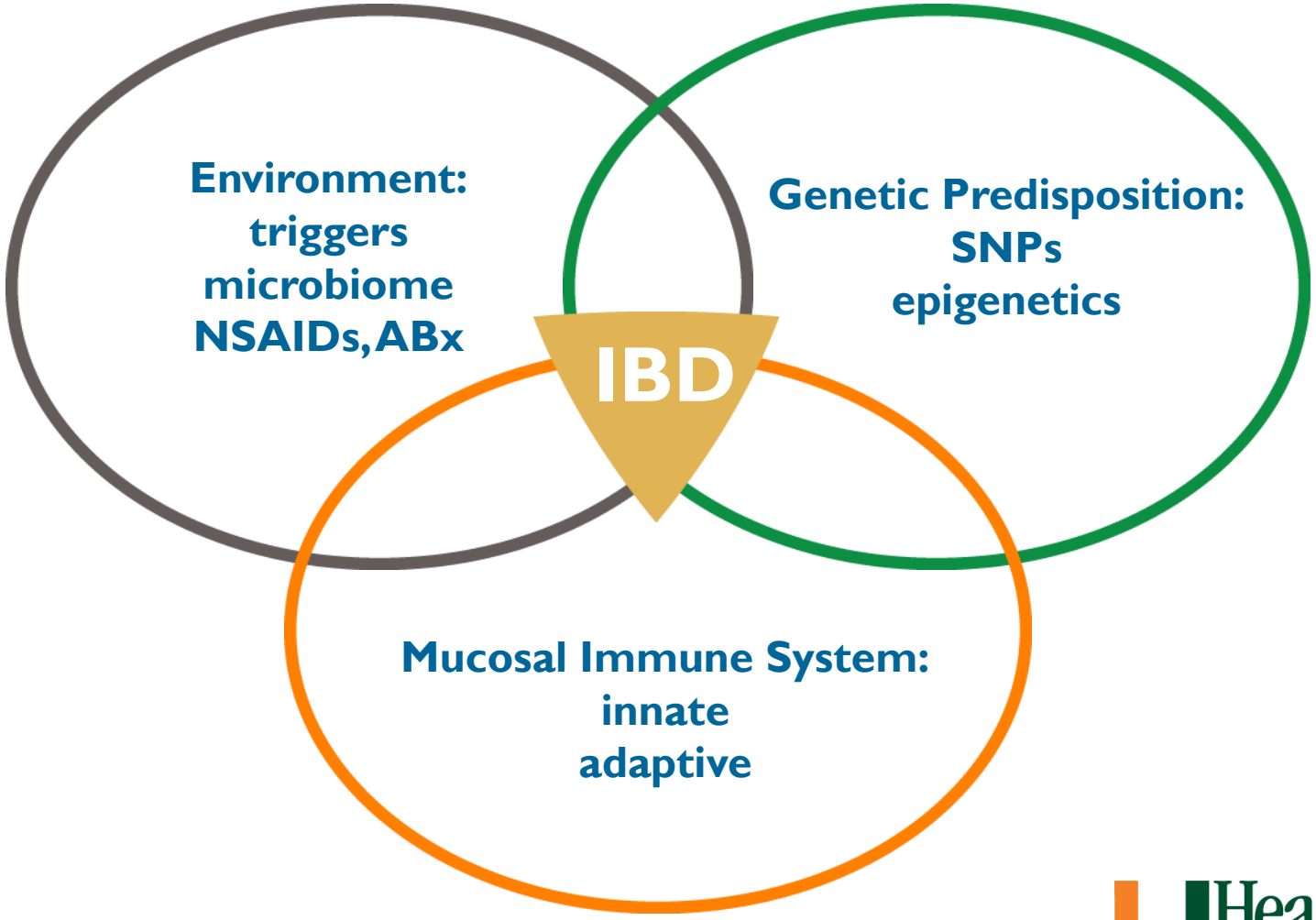
Etiologic Theory of Inflammatory Bowel Disease



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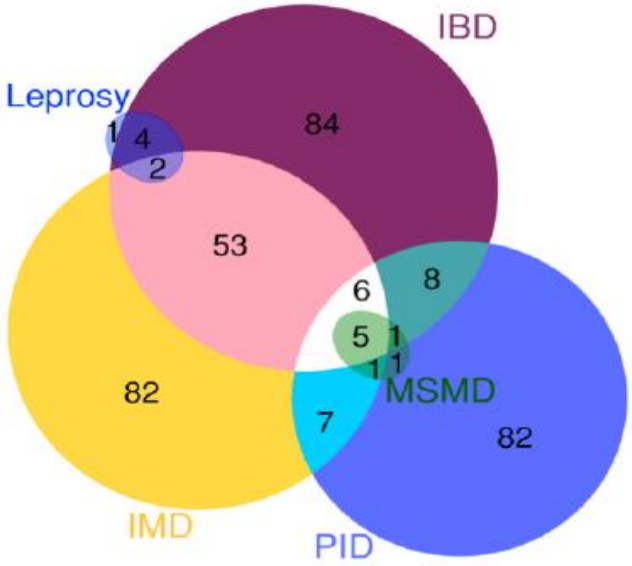
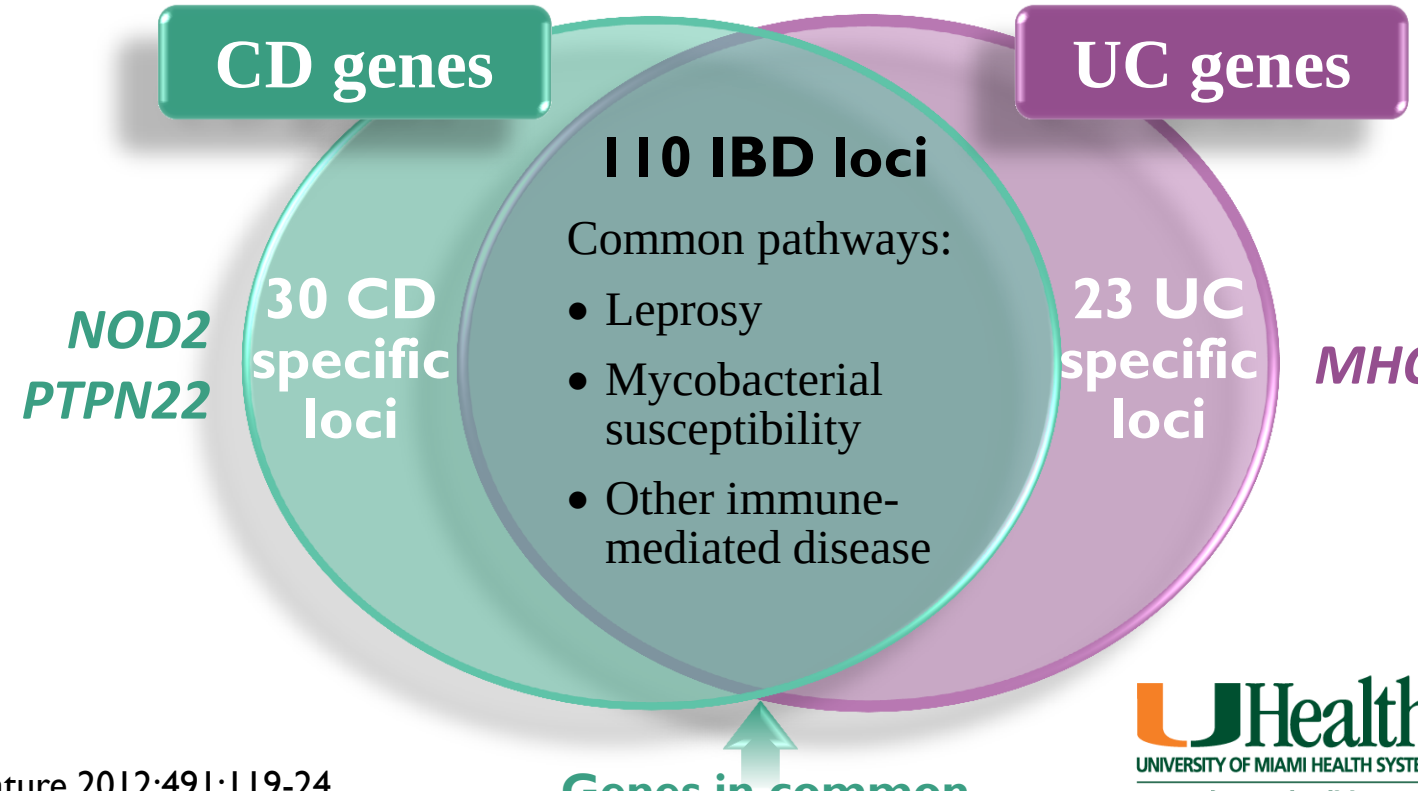
Genetics of IBD:

163 confirmed loci on meta-analysis of GWAS of CD and UC





Jostins L. Nature 2012;491:119-24.

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Genetics of IBD

As of early 2017, ~200 confirmed loci, number growing each year

Several immune-mediated diseases (IMD) show strong enrichment of overlap, with the largest being ankylosing spondylitis and psoriasis (14-fold)

Jostins L. Nature 2012;491:119-24.

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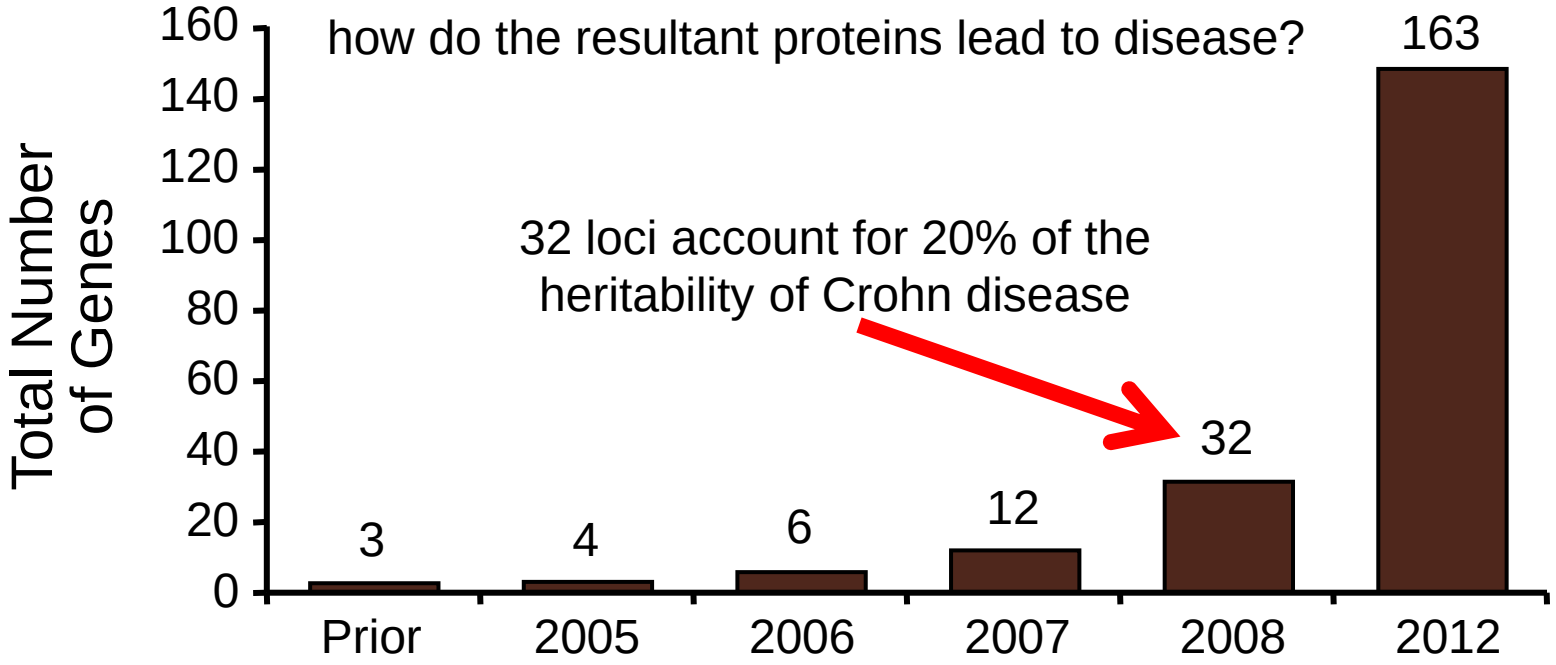
While IBD Genetics has made progress…

there is still a long way to go

how many more SNPs?
what about epigenetics?
what combinations are needed?
how do the resultant proteins lead to disease?



Barrett JC. Nat Genet 2008;40:955.
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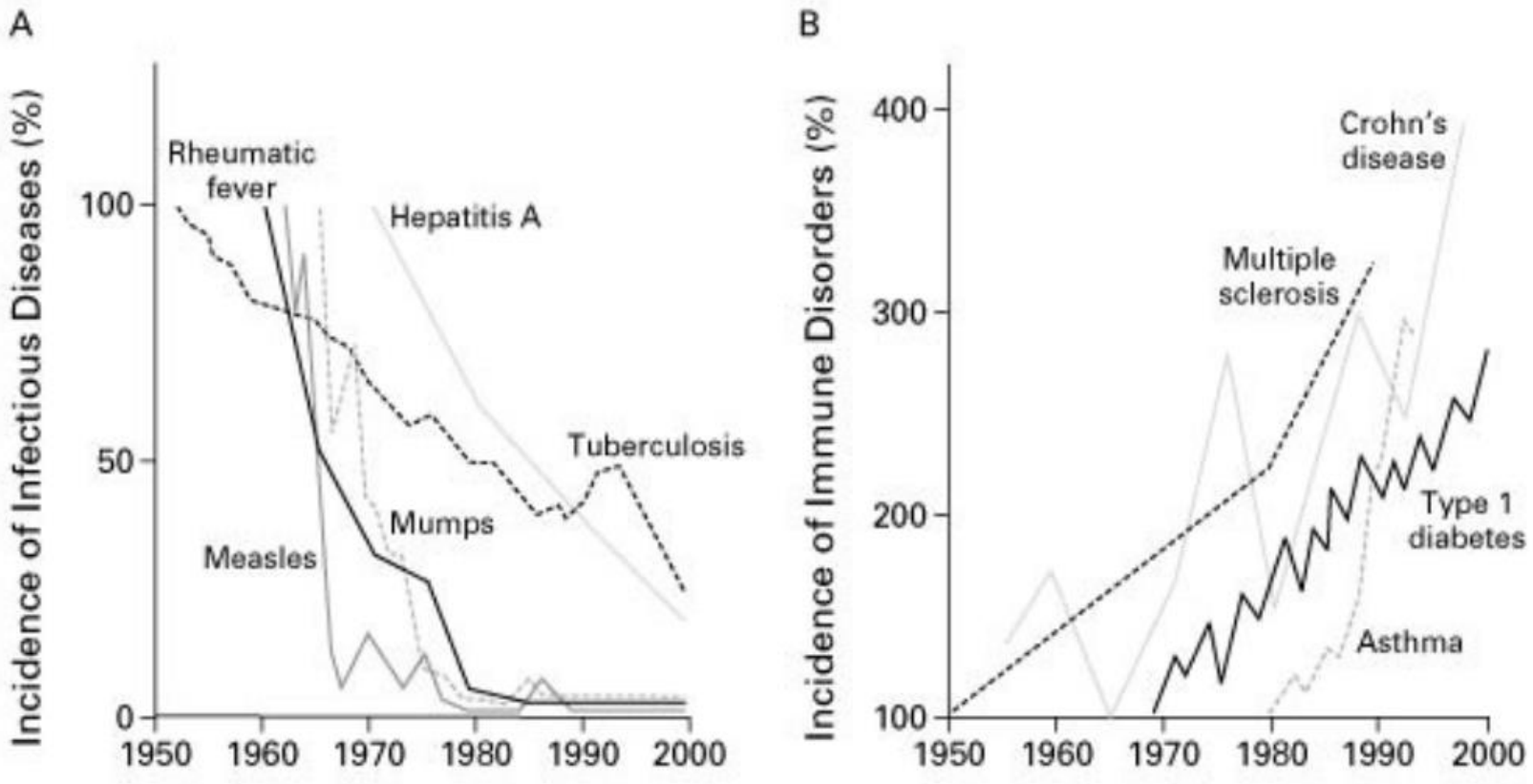
But not all genetics…

- Certainly familial
  - genetics vs epigenetics
- And monozygotic concordance > dizygotic
- But only about ½ of monozygotic twins of patients with Crohn disease will develop the disease too
  - almost all grew up together with similar but not identical environmental exposures
  - even lower for UC (~20%)

Ek WE. Ann Gastroenterol 2014;27(4):294-303.

Hygiene Hypothesis



Bach JF. N Engl J Med 2002;347(12):911-20.

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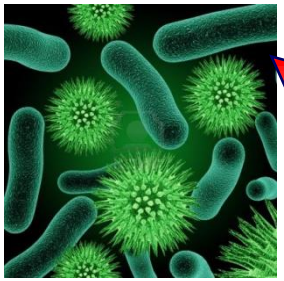
Environmental Triggers

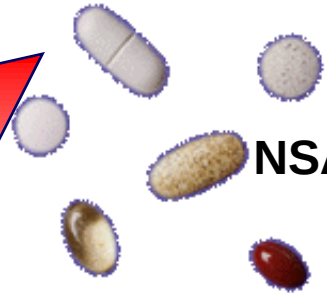
Change Flora



Microbiome/Infections
Mode of delivery?
Breastfeeding vs formula?
Antibiotics

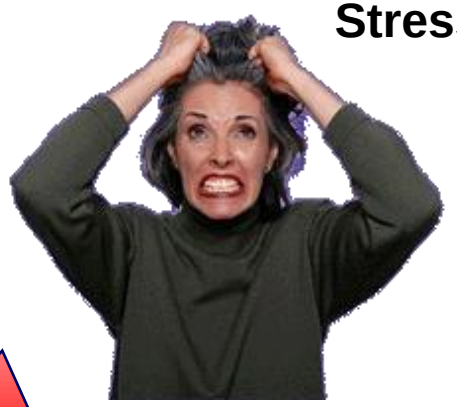
Food
Nutrition/Acculturation

Disrupt Mucosa



NSAIDs

Stress



Smoking

IBD

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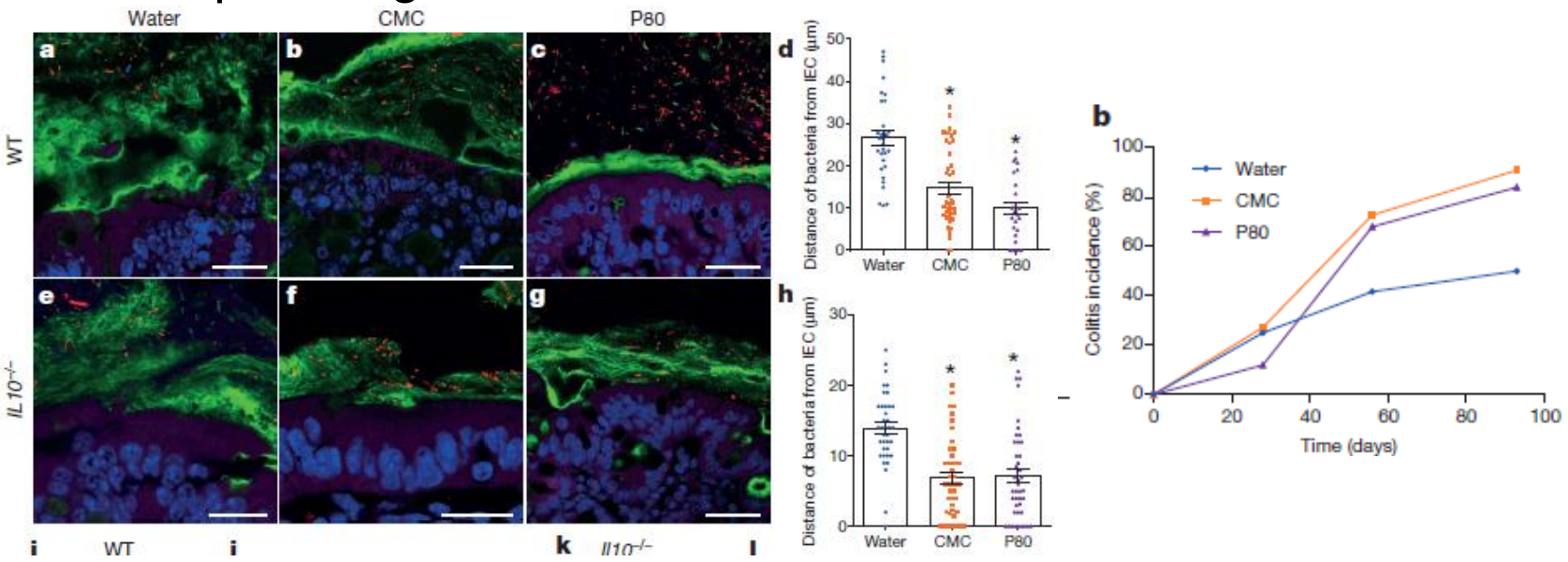
Not just hygiene

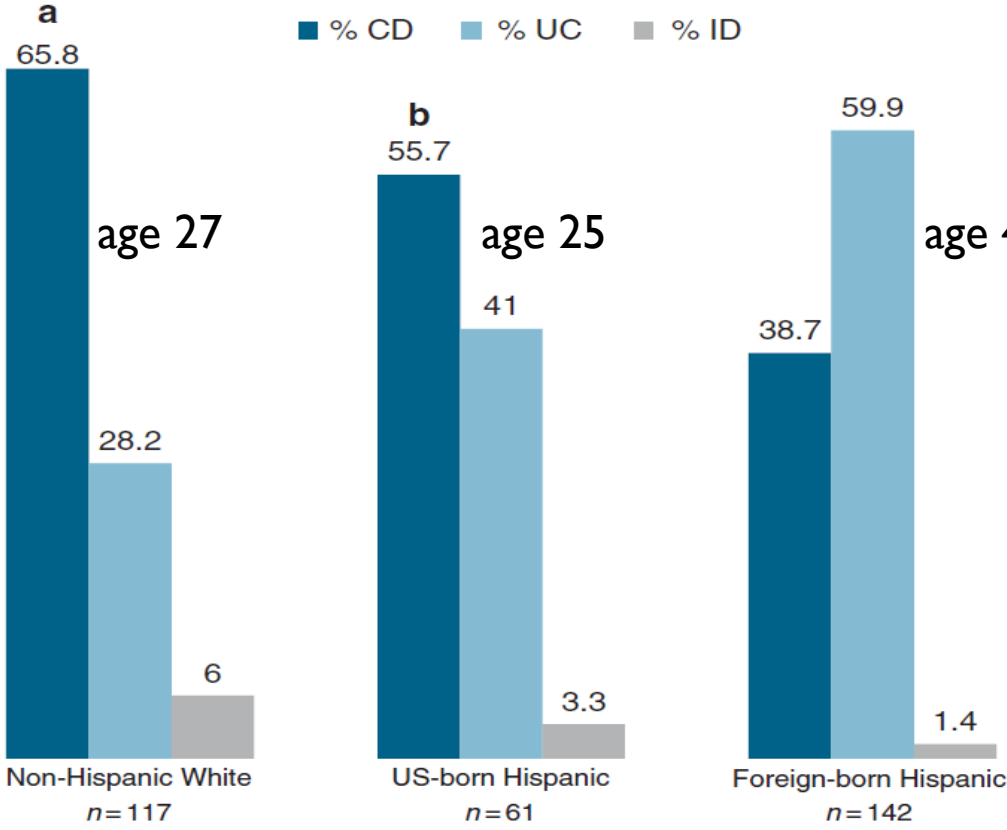
- Diet now has ABx-fed meat, processing, preservatives, and additives
- These by themselves can lead to changes (less mucus layer, closer distance of microbes to epithelium)
  - and they also change the microbiome with more mucolytic-producing bacteria



Chaissang B. Nature 2015;519(7541):92-6.

So…nature or nurture?

- Clea ences in IBD
  - age ent
  - mo ohn dise
  - ext ifferent
    - nc
  - mo d immunomodulators in non-Hispanic whites



Hispanics in Miami: foreign or American IBD phenotype?

Damas O. Am J Gastroenterol 2013;108(2):231-9.

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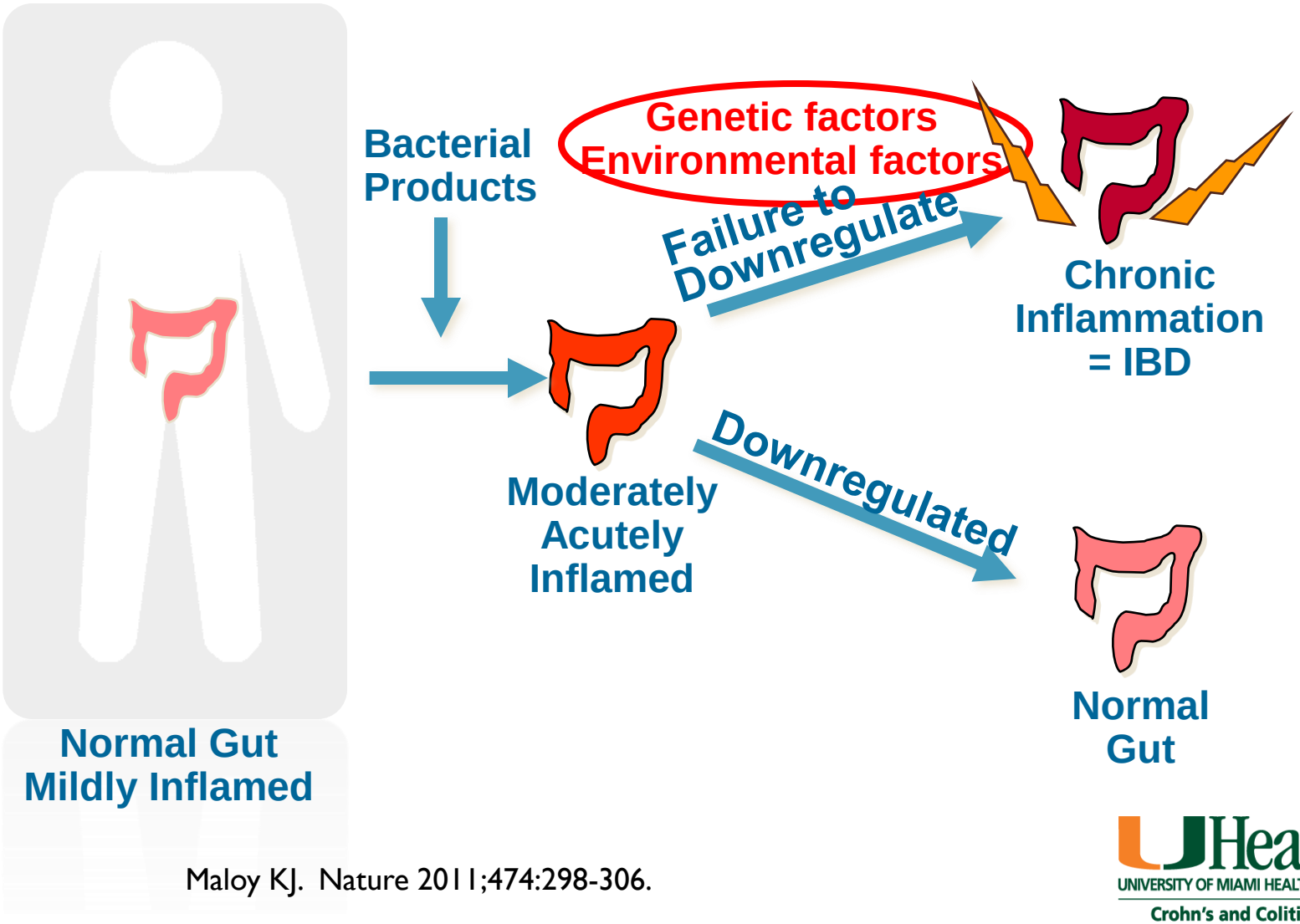
Immune Dysregulation



Maloy KJ. Nature 2011;474:298-306.

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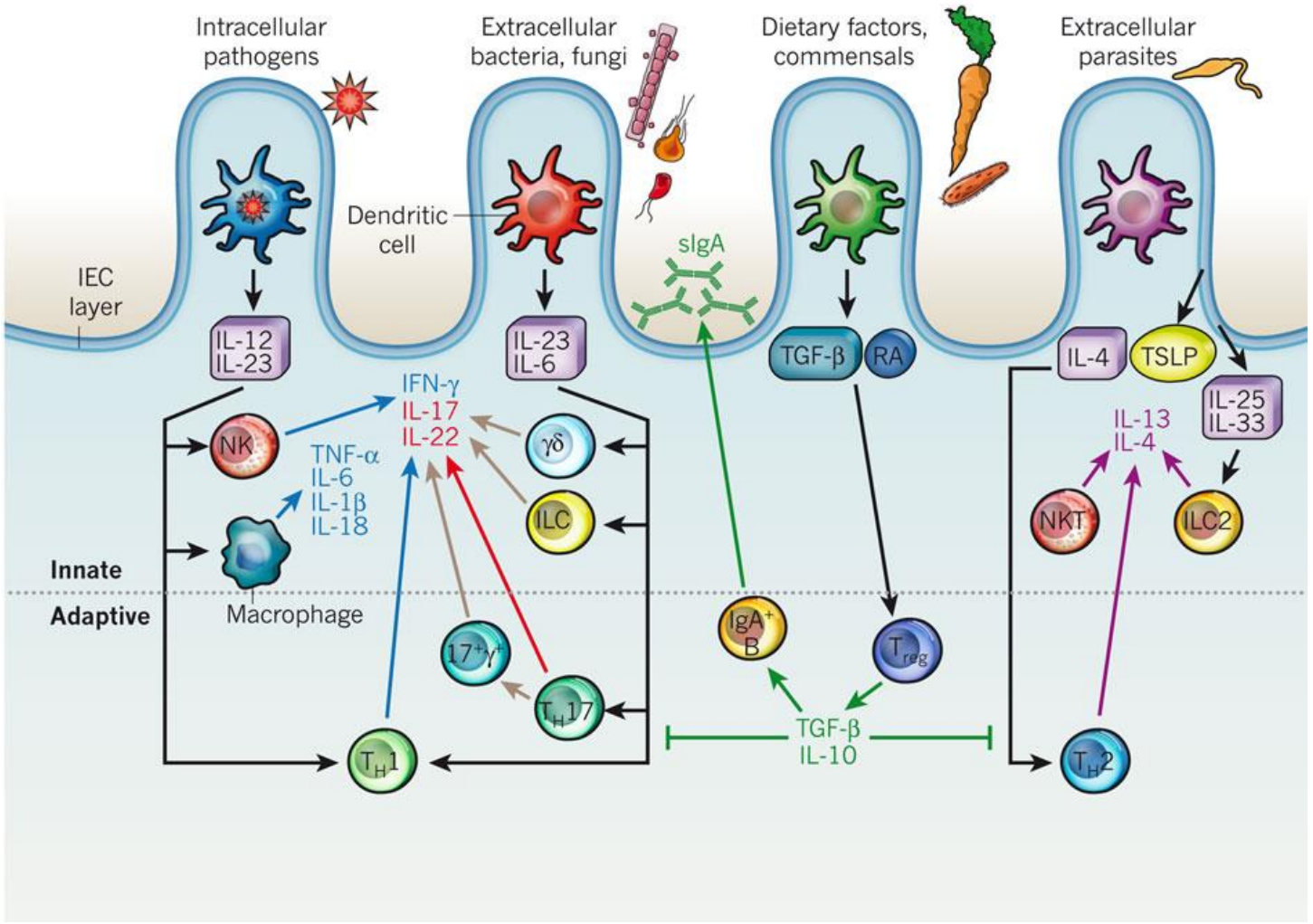

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Symptoms of IBD

- Diarrhea
- Abdominal pain and tenderness
- Loss of appetite and weight
- Fever
- Fatigue
- Rectal bleeding
- Stunted growth in children
- Perianal disease (CD)

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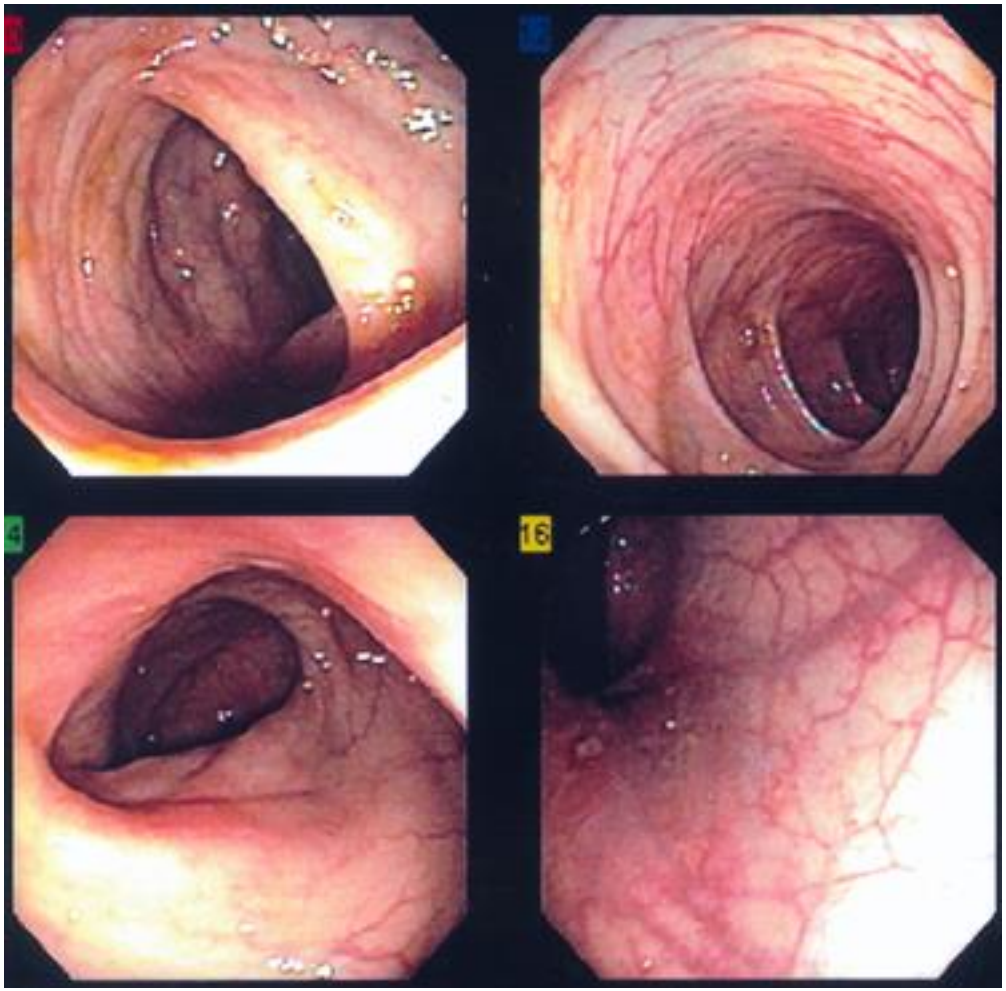
Normal colon



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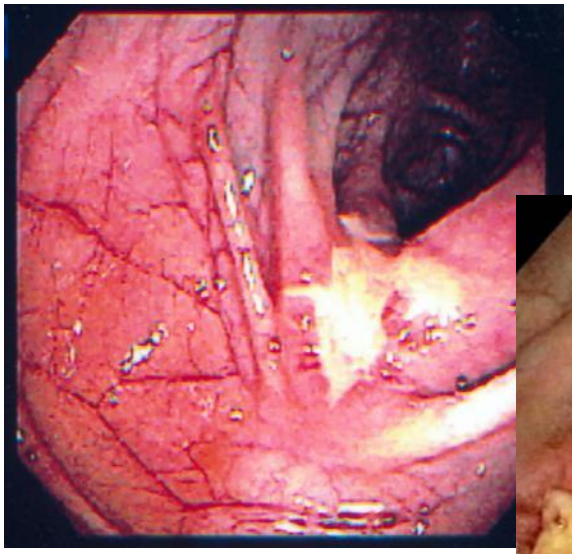
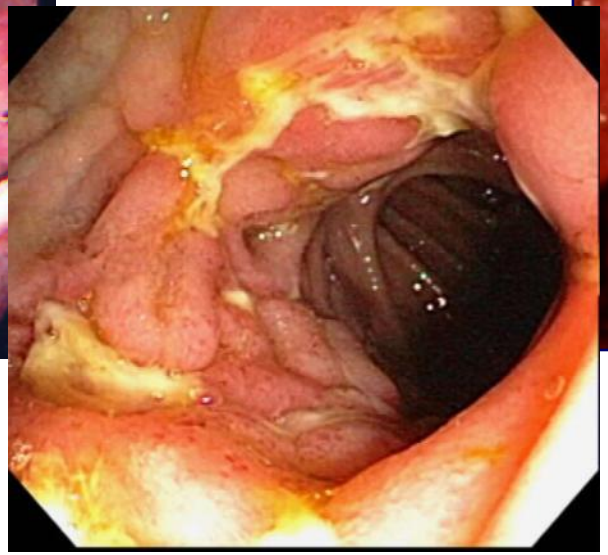
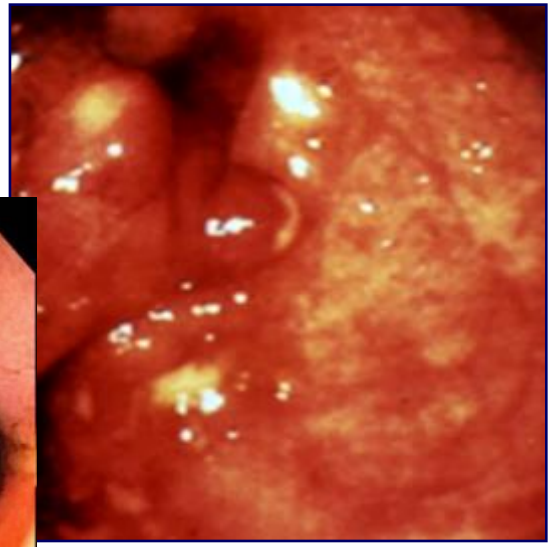
Crohn Disease
Endoscopic Appearance



Discrete Ulcer



Cobblestoning



Stricture
(Narrowing)

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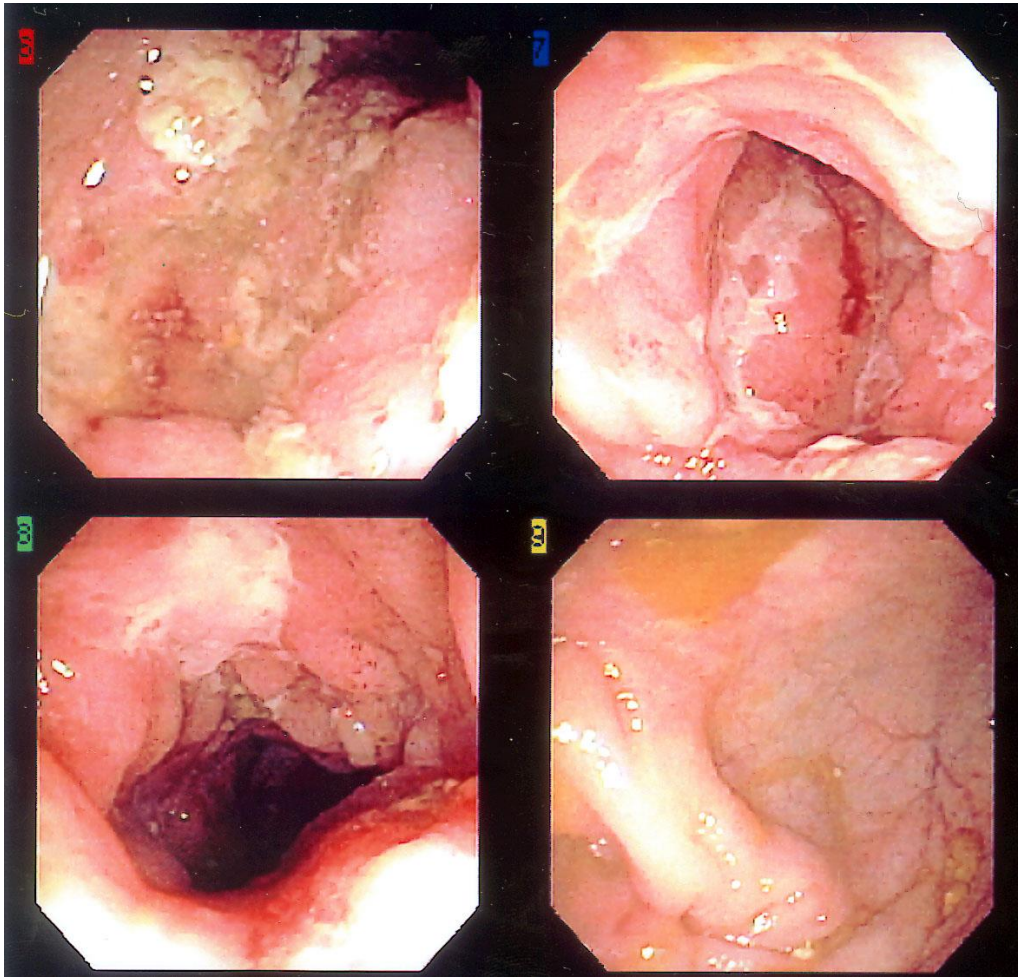
Crohn disease ileitis



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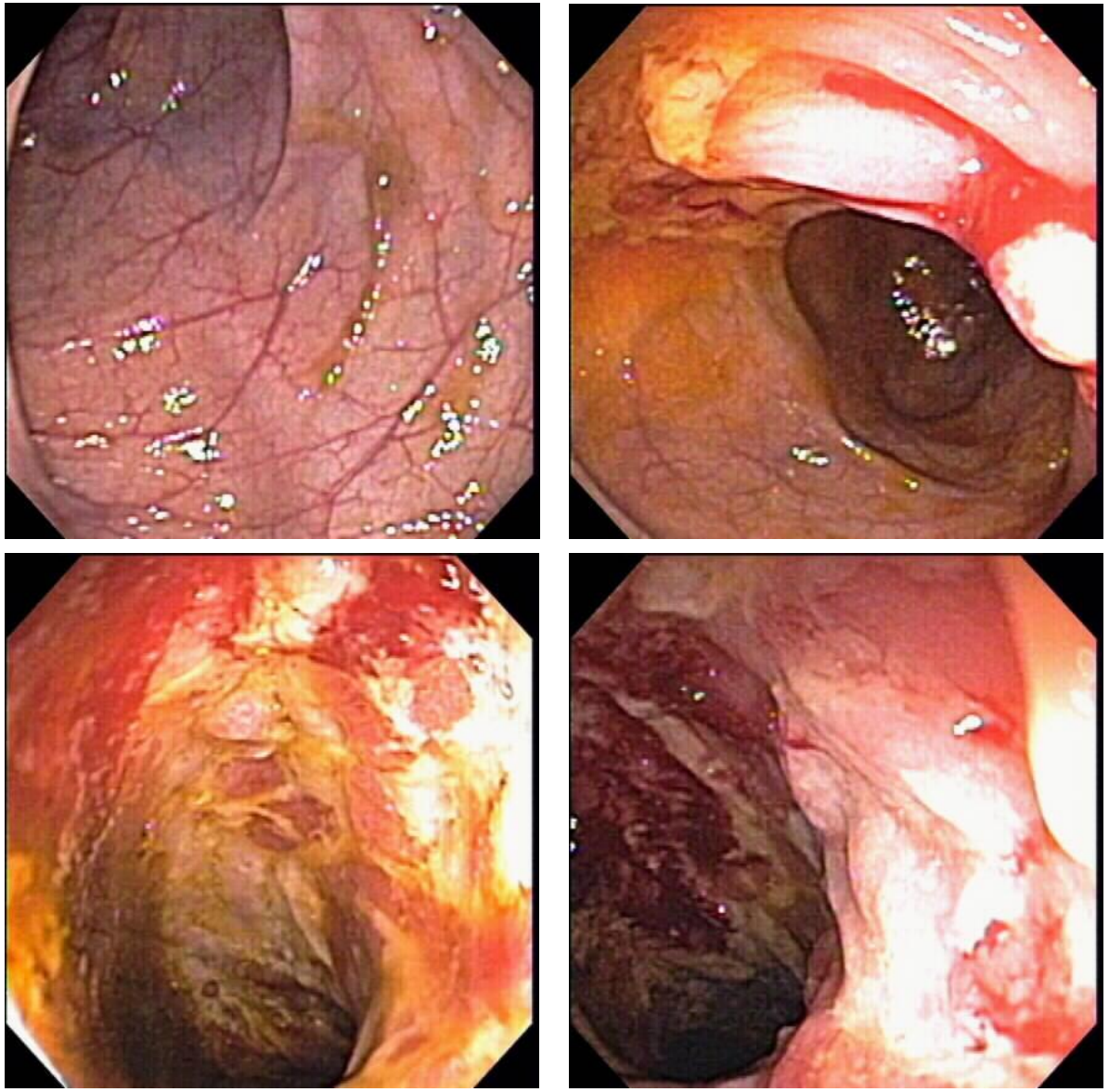
Crohn disease colitis



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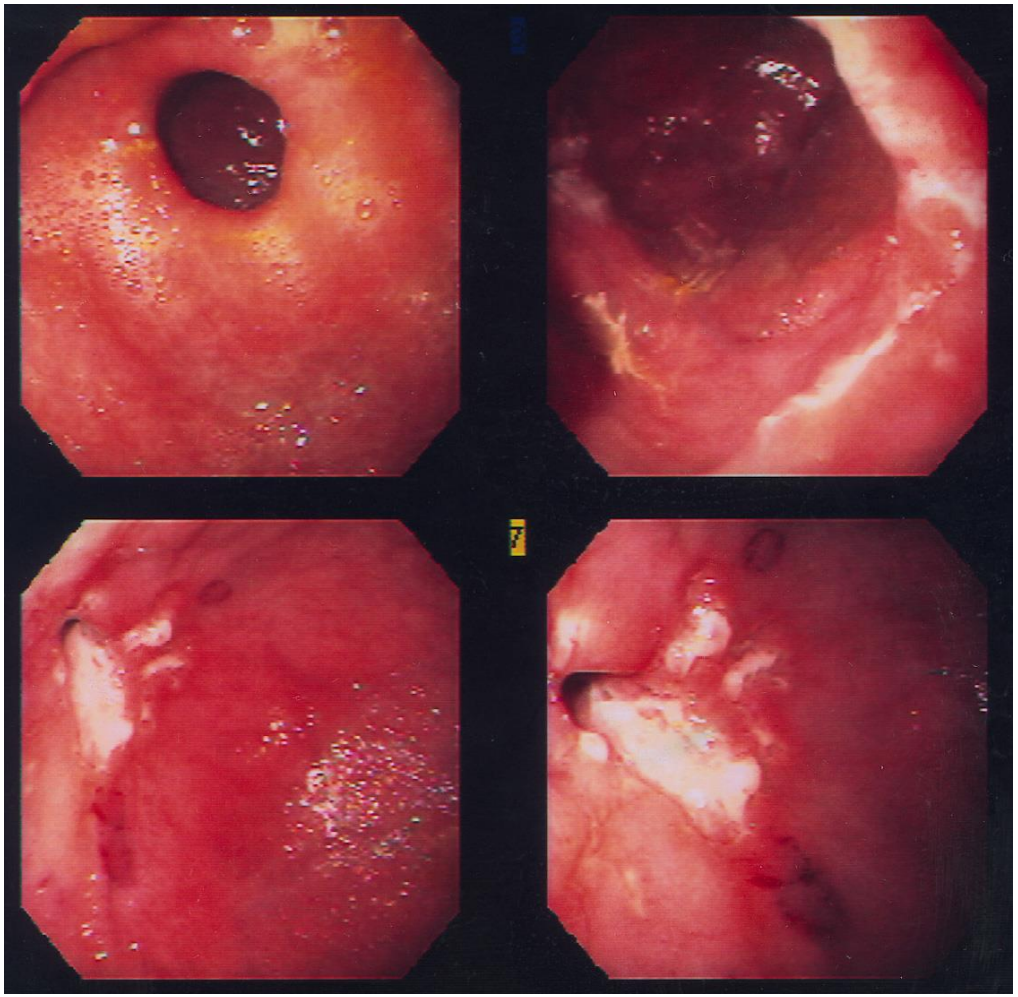
Upper tract Crohn disease



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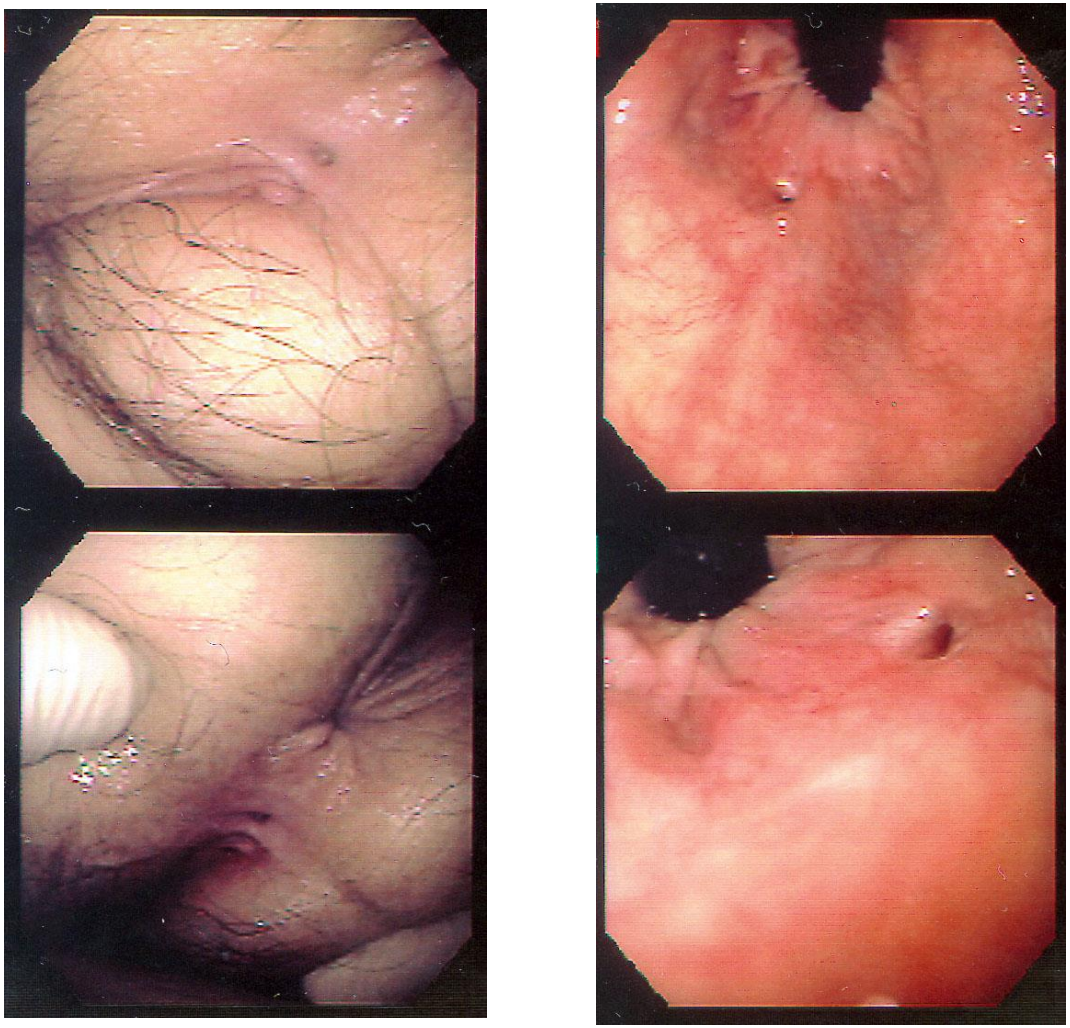
Perianal fistula



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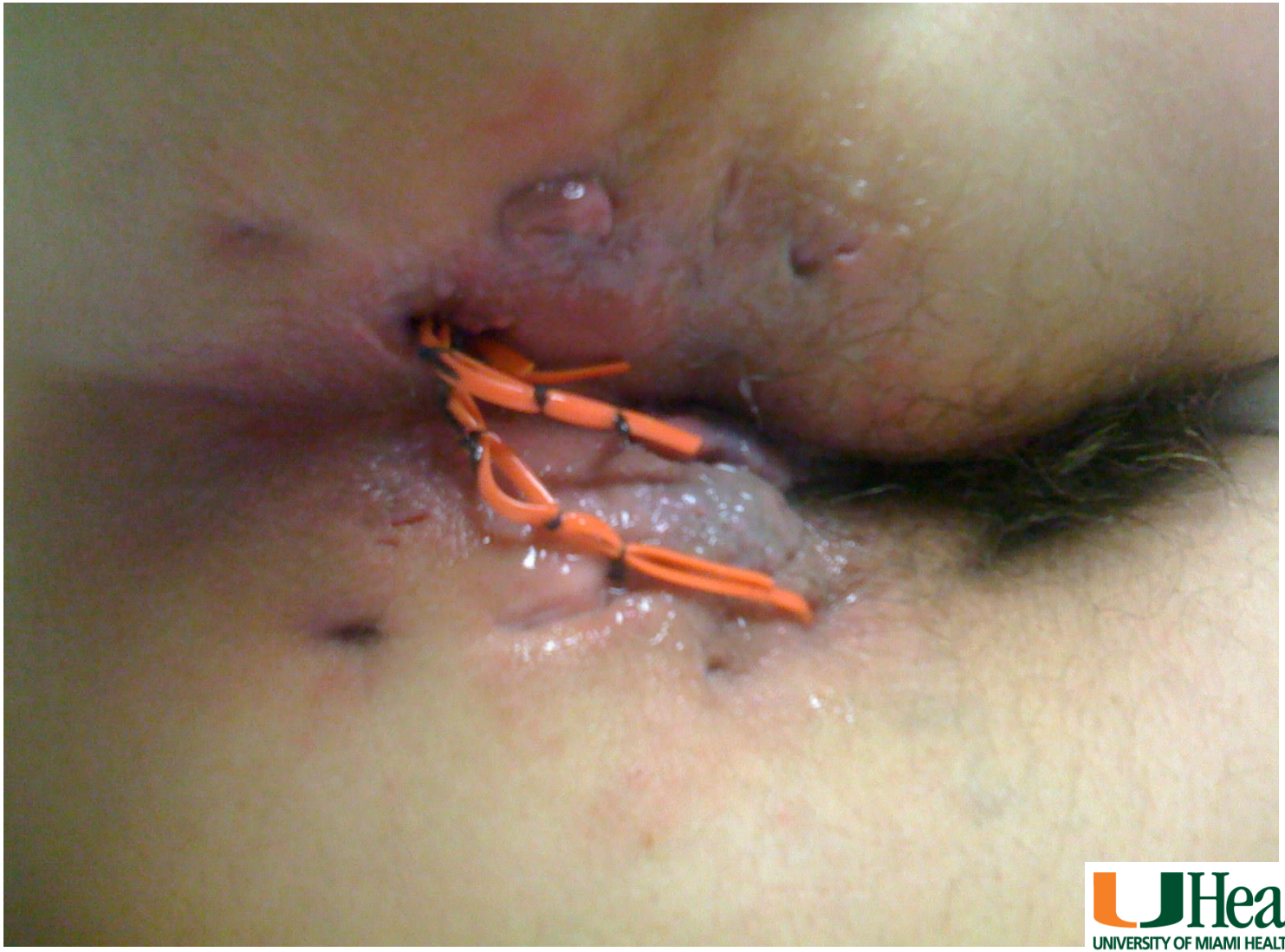
Perianal fistulae



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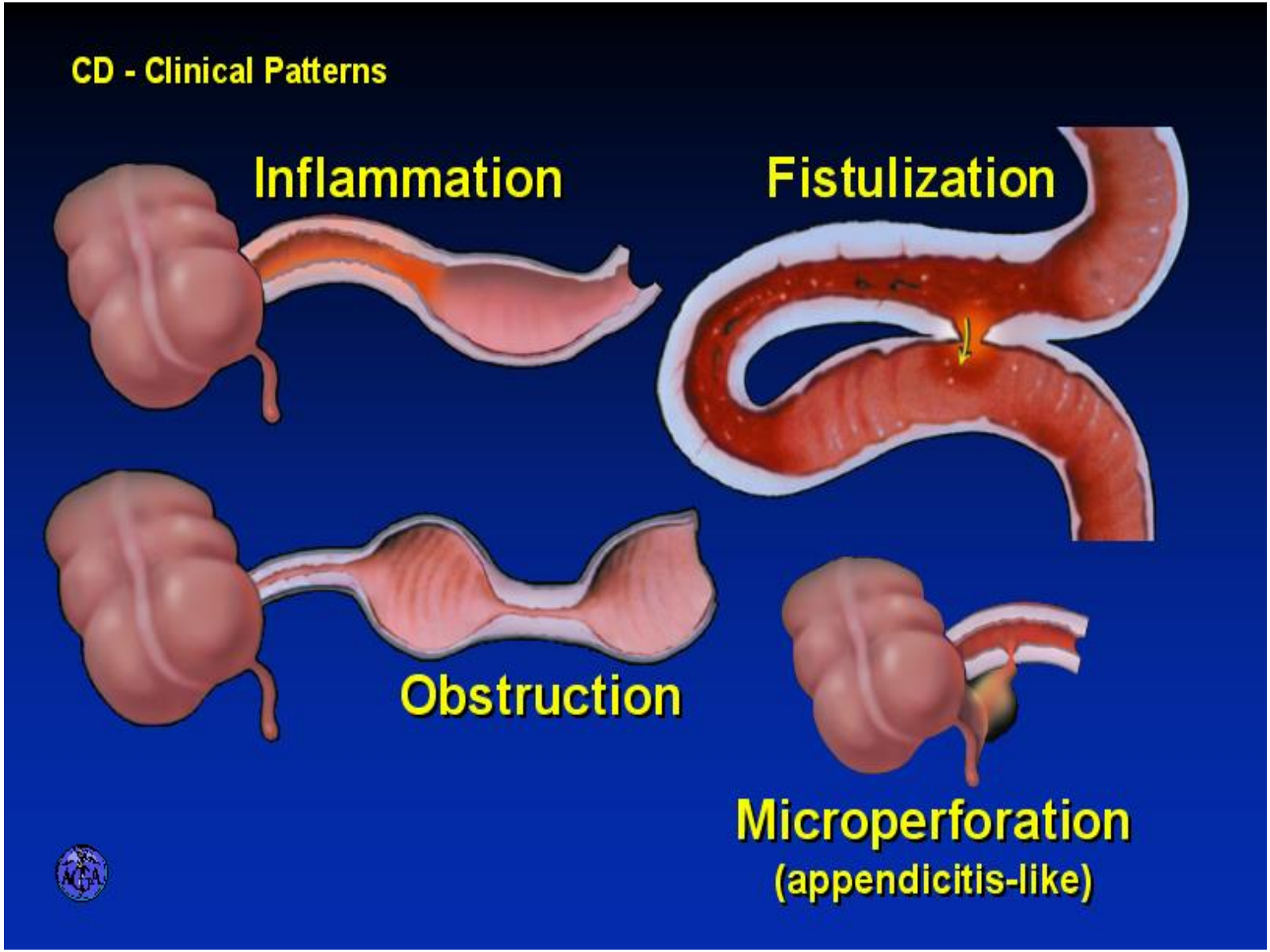

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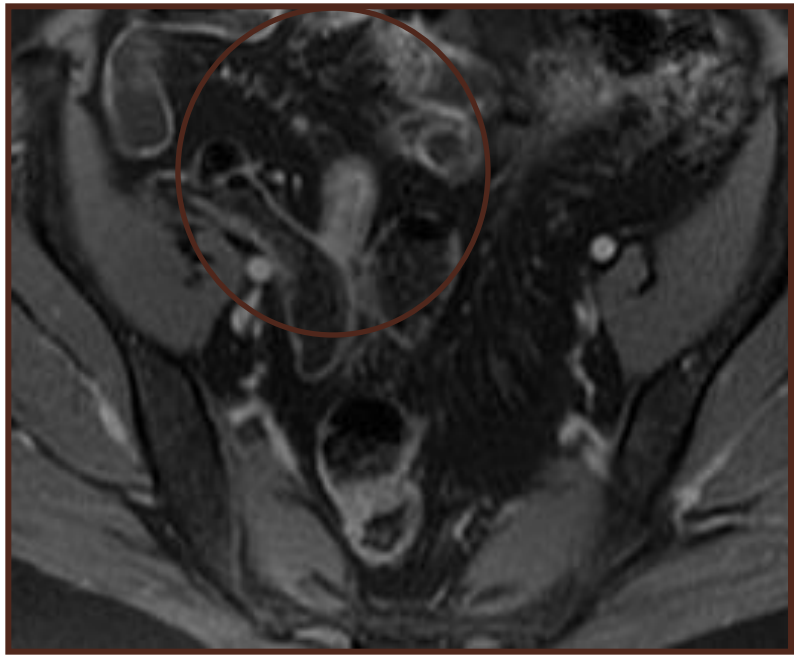
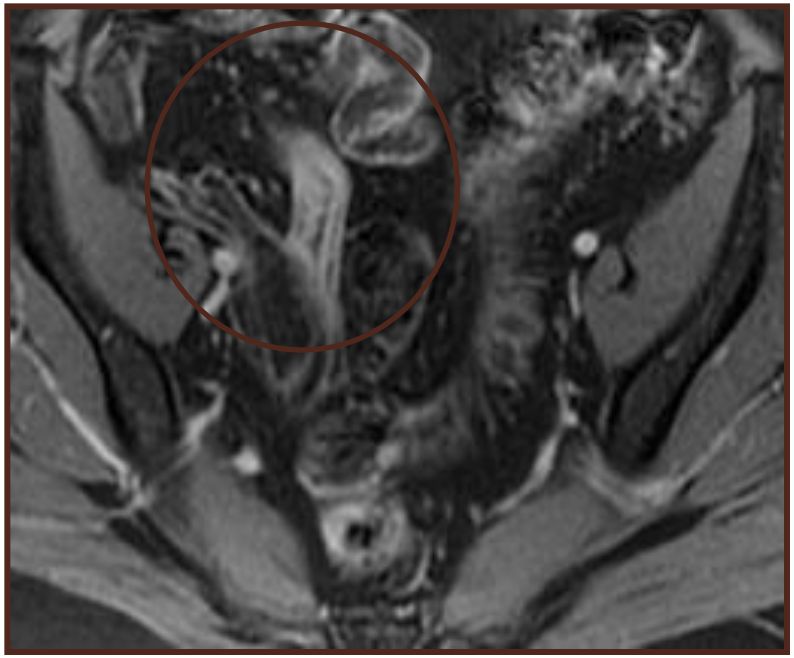
Contrast Enhancement





- Ileal wall thickening and hyperenhancement in a patient with known Crohn disease
- Symptoms of flare
- Ileocolonoscopy and SBFT were normal

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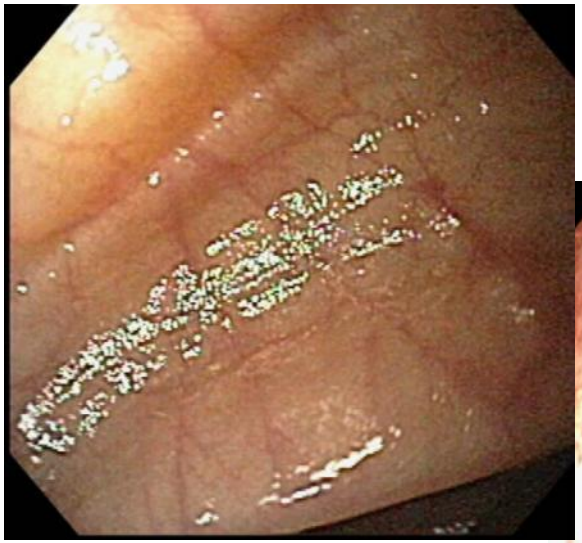
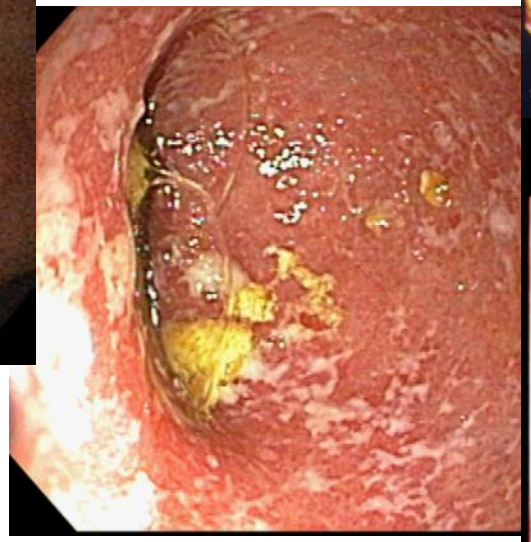
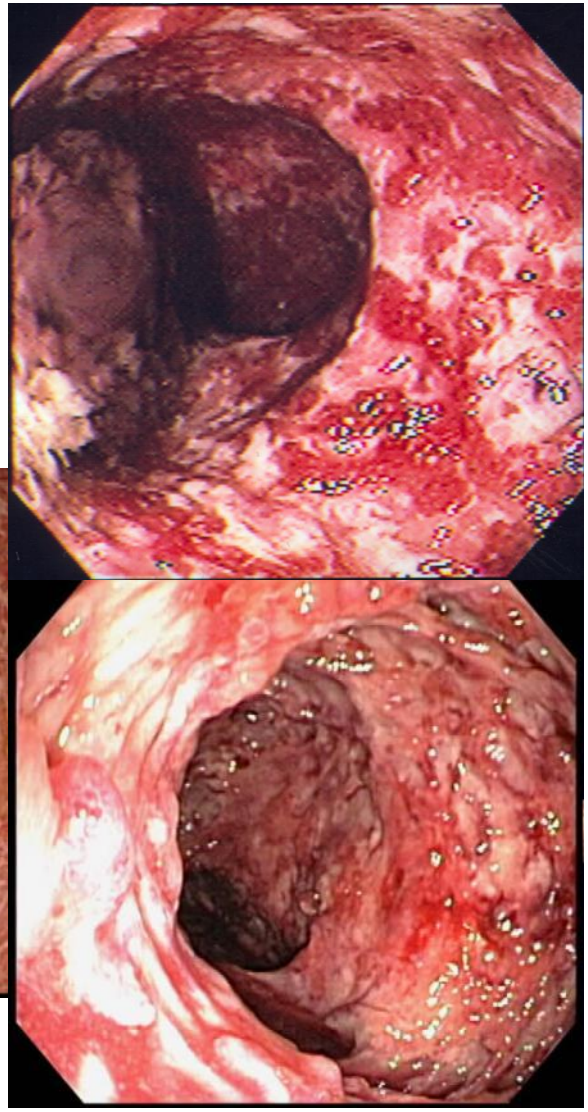
Ulcerative Colitis



Normal Colon



Mild-moderate UC



Severe UC

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Determining Severity of UC: ACG Practice Guidelines

FULMINANT

>10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distension, transfusion requirement, colonic dilation on X-ray

>6 bloody stools/day + fever, tachycardia, anemia, or ↑ ESR

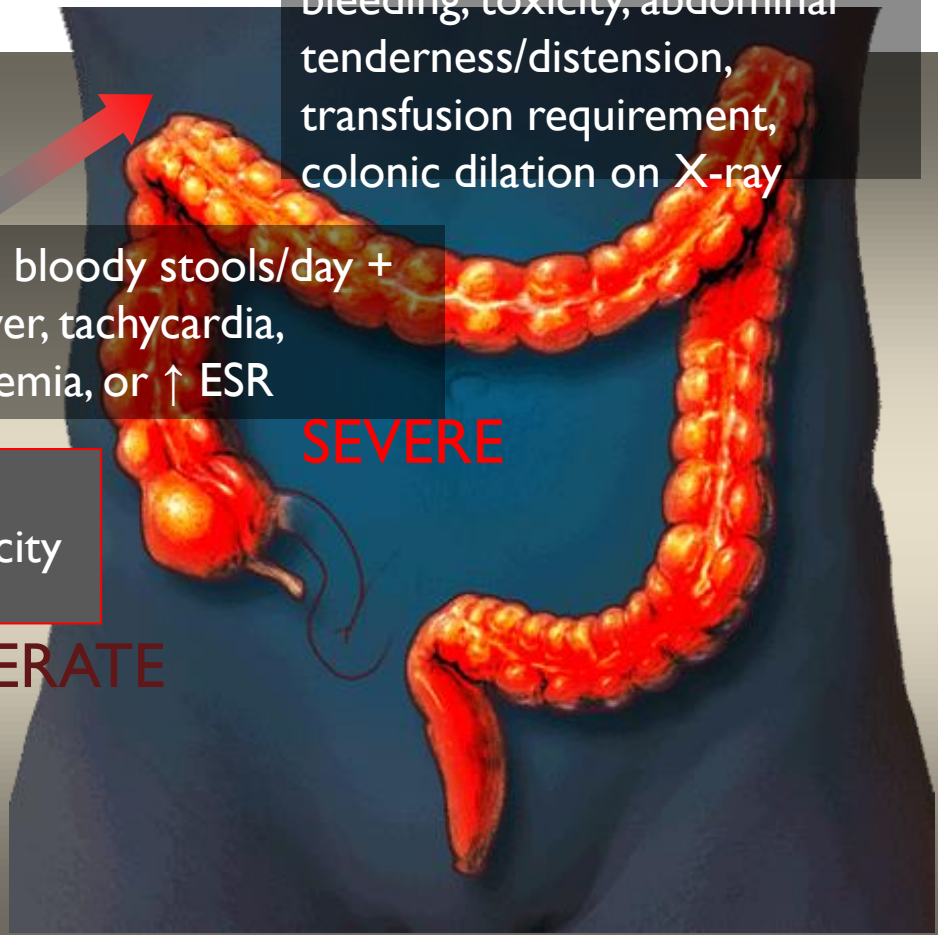
SEVERE

≥ 4 stools/day
Minimal signs of toxicity

MODERATE

<4 stools/day ± blood
Normal ESR
No signs of toxicity

MILD



Kornbluth A. Am J Gastroenterol. 2004;99:1371-85.

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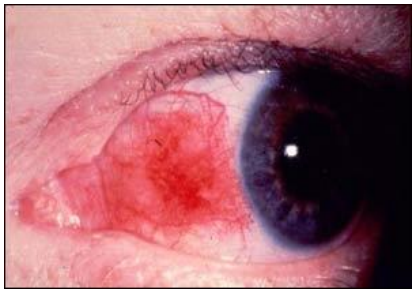
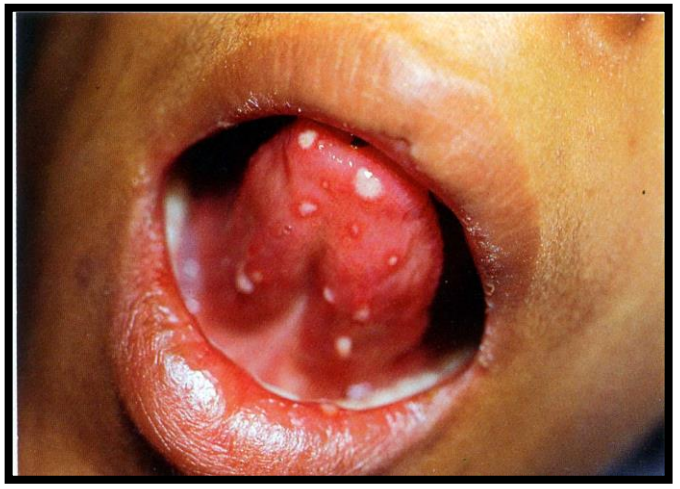
Extra-intestinal Manifestations of IBD





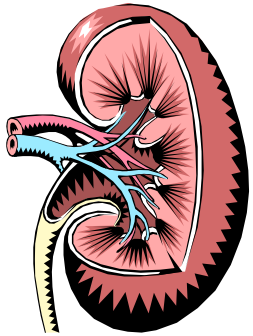
Skin

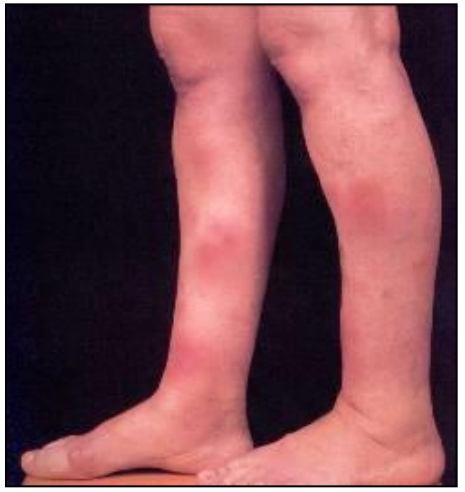
Eye

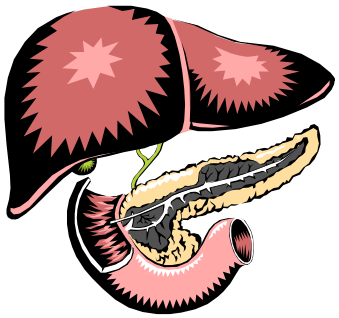
Bones and Joints

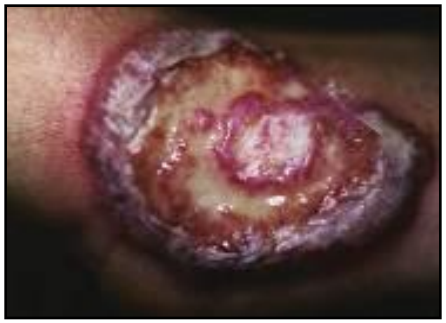
Kidney

Liver/Gall Bladder









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The initial presentation

- Ulcerative colitis versus infection
  - Travel/exposure history and chronicity
  - Stool studies
    - infection
    - inflammation
  - Serologies/inflammatory markers
  - Lower endoscopy with biopsies
- Crohn disease versus appendicitis or infection
  - CT/MR enterography
  - Colonoscopy
  - Stool studies
    - infection
    - inflammation
  - Serologies/inflammatory markers

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Reasons for hospitalization in an established IBD patient

- Severe disease refractory to outpatient medical therapy
- Complications of the disease
- Complications of the treatment

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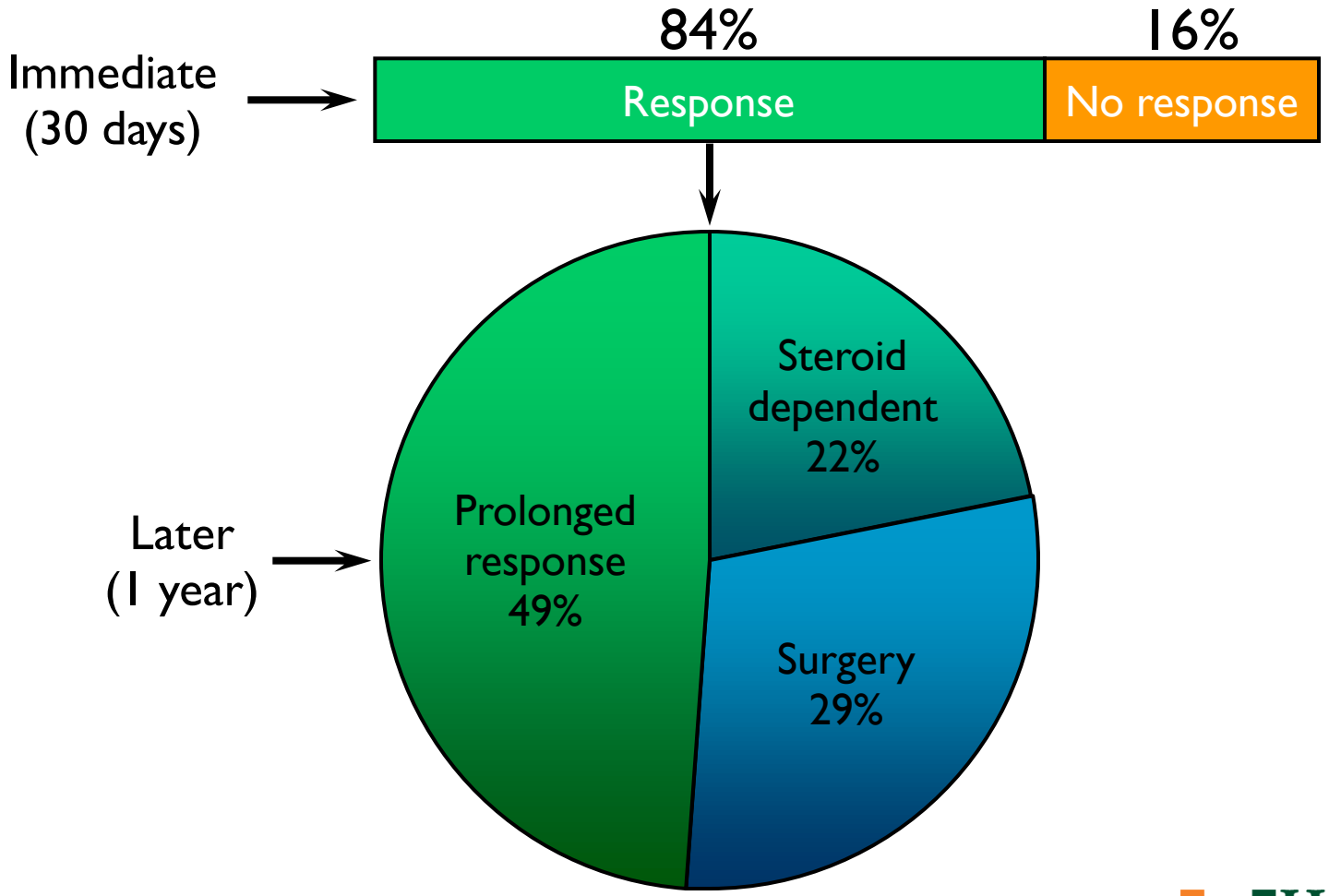
Corticosteroids (in ASUC)



Faubion WA. Gastroenterology 2001;121:255-60.

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Are there predictors of IV steroid failure?

- Failure at day 3 dependent on:
  - Mean number of BMs:
    - 4-6 — 1 point
    - 7-9 — 2 points
    - >9 — 4 points
  - Albumin < 3.0 g/dL — 1 point
  - Colonic dilation — 4 points
- 85% failure rate if score > 4
- CRP on day 3 of admission
  - colectomy vs. non-colectomy, 56.6 vs 32.7; p=0.04
- Severe lesions on endoscopy (large mucosal abrasion, extensive deep ulceration, "well-like ulceration") independently predict colectomy

Ho GT. Aliment Pharmacol Ther 2004;19:1079-87.

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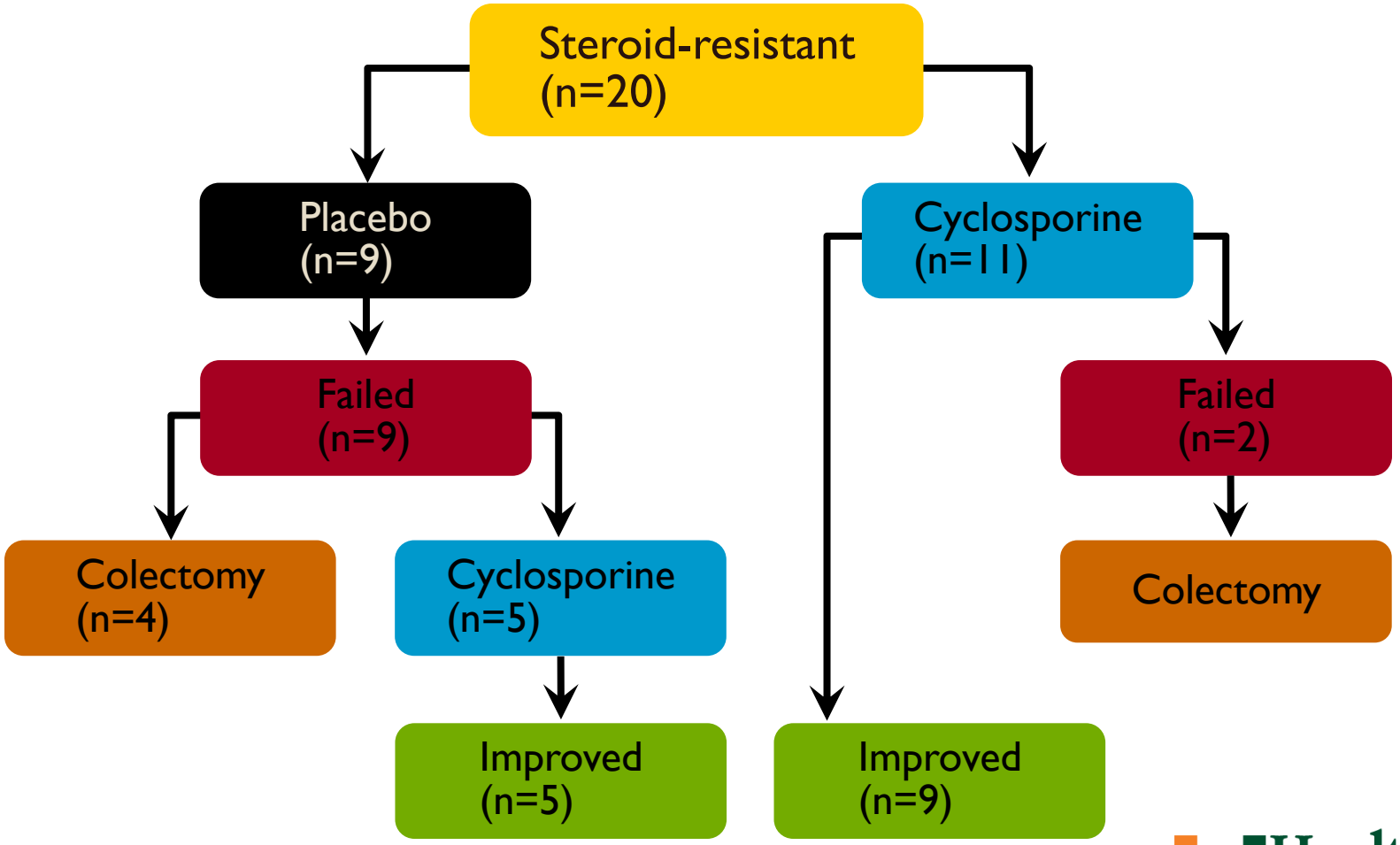
Cyclosporine A (in ASUC)



Lichtiger S. N Engl J Med 1994;330:1841.

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Infliximab for Moderate to Severe UC: ACT 1/2

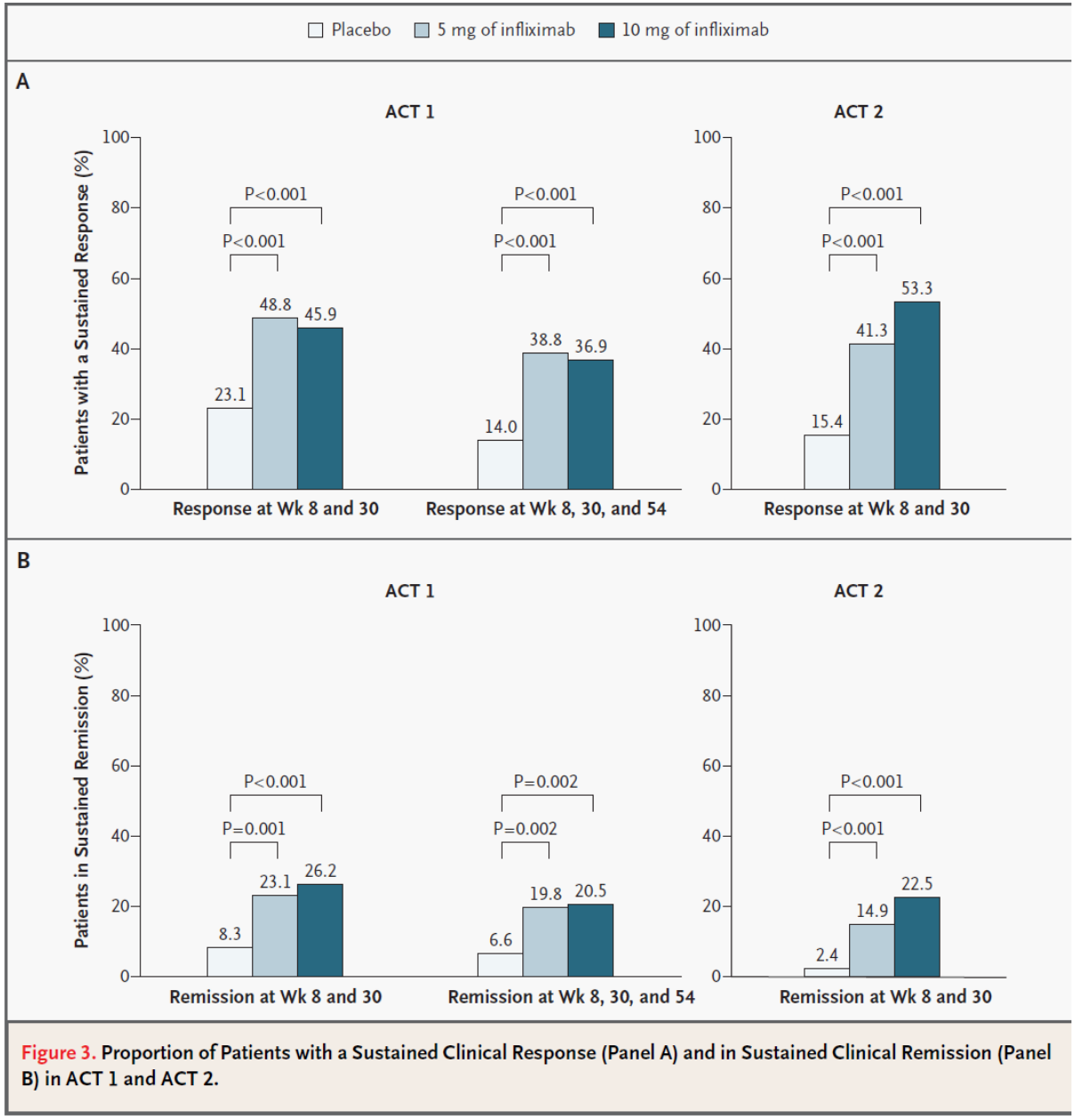

Figure 3. Proportion of Patients with a Sustained Clinical Response (Panel A) and in Sustained Clinical Remission (Panel B) in ACT 1 and ACT 2.

Rutgeerts P. N Engl J Med 2005;353:2462-76.

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Infliximab for Severe UC

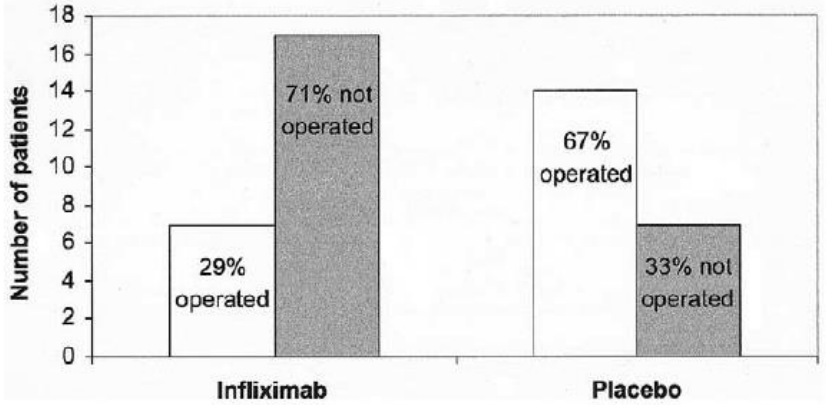

Figure 1. Proportion of surgical/nonsurgical patients in the infliximab and placebo groups.

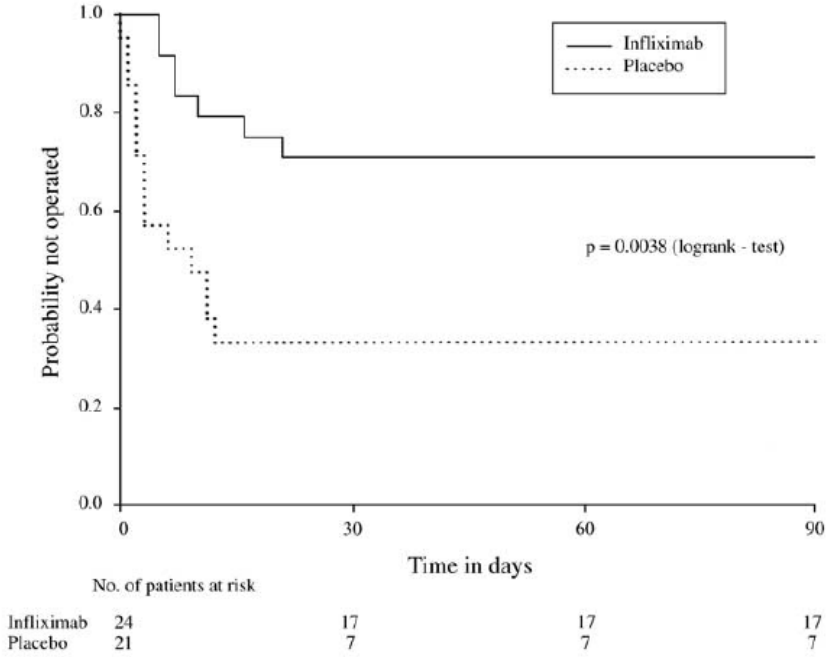

Figure 2. Proportion of surgical patients and time to operation in the infliximab and placebo groups.

- Colectomy in:
  - 29% infliximab patients
  - 67% placebo patients (p=0.017)
- Colectomy in fulminant patients
  - 69% (9/13) placebo
  - 47% (7/15) infliximab (p=0.3)

Järnerot G. Gastroenterology 2005;128:1805-11.

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CYSIF trial

Summary

Background Ciclosporin and infliximab are potential rescue treatments to avoid colectomy in patients with acute severe ulcerative colitis refractory to intravenous corticosteroids. We compared the efficacy and safety of these drugs for this indication.

Methods In this parallel, open-label, randomised controlled trial, patients were aged at least 18 years, had an acute severe flare of ulcerative colitis defined by a Lichtiger score greater than 10 points, and had been given an unsuccessful course of high-dose intravenous steroids. None of the patients had previously received ciclosporin or infliximab. Between June 1, 2007, and Aug 31, 2010, patients at 27 European centres were randomly assigned (via computer-derived permutation tables; 1:1) to receive either intravenous ciclosporin (2 mg/kg per day for 1 week, followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14, and 42). In both groups, azathioprine was started at day 7 in patients with a clinical response. Neither patients nor investigators were masked to study treatment. The primary efficacy outcome was treatment failure defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy, or death. Analysis was by intention to treat. This trial is registered with EudraCT (2006-005299-42) and ClinicalTrials.gov (NCT00542152).

Findings 115 patients were randomly assigned; 58 patients were allocated to receive ciclosporin and 57 to receive infliximab. Treatment failure occurred in 35 (60%) patients given ciclosporin and 31 (54%) given infliximab (absolute risk difference 6%; 95% CI −7 to 19; p=0·52). Nine (16%) patients in the ciclosporin group and 14 (25%) in the infliximab group had severe adverse events.

Interpretation Ciclosporin was not more effective than infliximab in patients with acute severe ulcerative colitis refractory to intravenous steroids. In clinical practice, treatment choice should be guided by physician and centre experience.

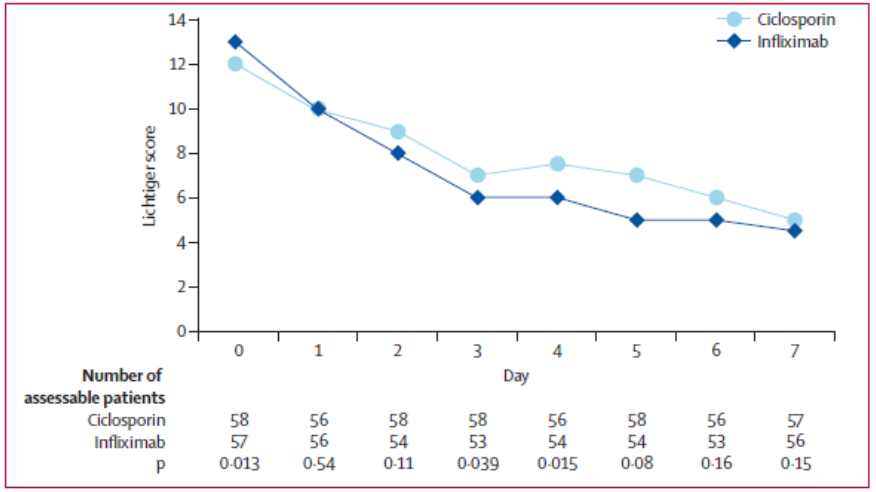

Figure 2: **Lichtiger scores from day 0 to day 7, by treatment**

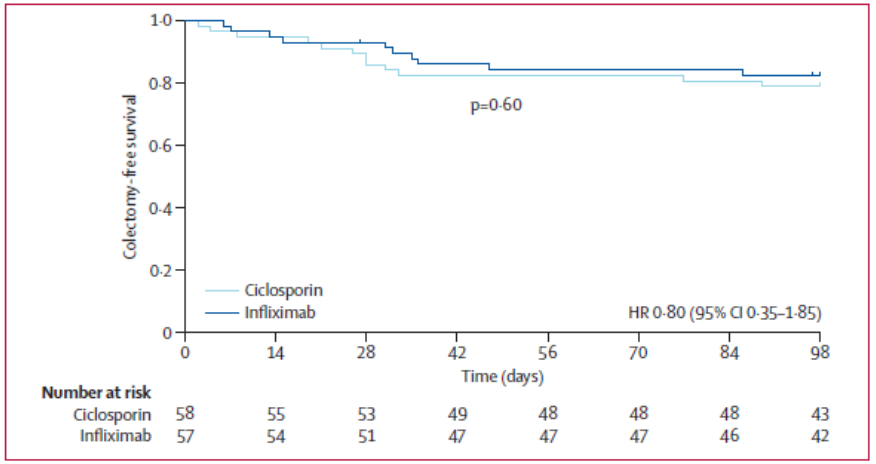

Figure 3: **Kaplan-Meier curves for colectomy-free survival**
In the infliximab group, nine patients in whom treatment was unsuccessful had rescue therapy before day 98: four were switched to ciclosporin (two colectomies), three received extra (ie, not on days 0, 14, or 42) infliximab infusions of 5 mg/kg (one colectomy), and two received scheduled infliximab infusions of 10 mg/kg (ie, a double dose on day 14 or 42; one colectomy). In the ciclosporin group, six patients in whom treatment was unsuccessful had rescue therapy before day 98: five received infliximab, including four infusions of 5 mg/kg (two colectomies) and one of 10 mg/kg (one colectomy) and we increased one patient's steroid dose (no colectomy). HR=hazard ratio.

Laharie D. Lancet 2012;380:1909-15.

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CONSTRUCT trial

Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial

John G Williams, M Fasih Alam, Laith Alrubaiy, Ian Arnott, Clare Clement, David Cohen, John N Gordon, A Barney Hawthorne, Mike Hilton, Hayley A Hutchings, Aida U Jawhari, Mirella Longo, John Mansfield, Jayne M Morgan, Frances Rapport, Anne C Seagrove, Shaji Sebastian, Ian Shaw, Simon P L Travis, Alan Watkins, for the CONSTRUCT investigators

Summary

Background Infliximab and ciclosporin are of similar efficacy in treating acute severe ulcerative colitis, but there has been no comparative evaluation of their relative clinical effectiveness and cost-effectiveness.

Methods In this mixed methods, open-label, pragmatic randomised trial, we recruited consenting patients aged 18 years or older at 52 district general and teaching hospitals in England, Scotland, and Wales who had been admitted, unscheduled, with severe ulcerative colitis and failed to respond to intravenous hydrocortisone within about 5 days. Patients were randomly allocated (1:1) to receive either infliximab (5 mg/kg intravenous infusion given over 2 h at baseline, and again at 2 weeks and 6 weeks after the first infusion) or ciclosporin (2 mg/kg per day by continuous infusion for up to 7 days, followed by twice-daily tablets delivering 5·5 mg/kg per day for 12 weeks). Randomisation used a web-based password-protected site, with a dynamic algorithm to generate allocations on request, thus protecting against investigator preference or other subversion, while ensuring that each trial group was balanced by centre, which was the only stratification used. Local investigators and participants were aware of the treatment allocated, but the chief investigator and analysts were masked. Analysis was by treatment allocated. The primary outcome was quality-adjusted survival—ie, the area under the curve (AUC) of scores from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ) completed by participants at baseline, 3 months, and 6 months, then every 6 months from 1 year to 3 years. This trial is registered with the ISRCTN Registry, number ISRCTN22663589.

Findings Between June 17, 2010, and Feb 26, 2013, 270 patients were recruited. 135 patients were allocated to the infliximab group and 135 to the ciclosporin group. 121 (90%) patients in each group were included in the analysis of the primary outcome. There was no significant difference between groups in quality-adjusted survival (mean AUC 564·0 [SD 241·9] in the infliximab group *vs* 587·0 [226·2] in the ciclosporin group; mean adjusted difference 7·9 [95% CI −22·0 to 37·8]; p=0·603). Likewise, there were no significant differences between groups in the secondary outcomes of CUCQ scores, EQ-5D, or SF-6D scores; frequency of colectomy (55 [41%] of 135 patients in the infliximab group *vs* 65 [48%] of 135 patients in the ciclosporin group; p=0·223); or mean time to colectomy (811 [95% CI 707–912] days in the infliximab group *vs* 744 [638–850] days in the ciclosporin group; p=0·251). There were no differences in serious adverse reactions (16 reactions in 14 participants receiving infliximab *vs* ten in nine patients receiving ciclosporin); serious adverse events (21 in 16 patients *vs* 25 in 17 patients); or deaths (three in the infliximab group *vs* none in the ciclosporin group).

Interpretation There was no significant difference between ciclosporin and infliximab in clinical effectiveness.

Willams JG. Lancet Gastro Hep 2016;1:15-24.

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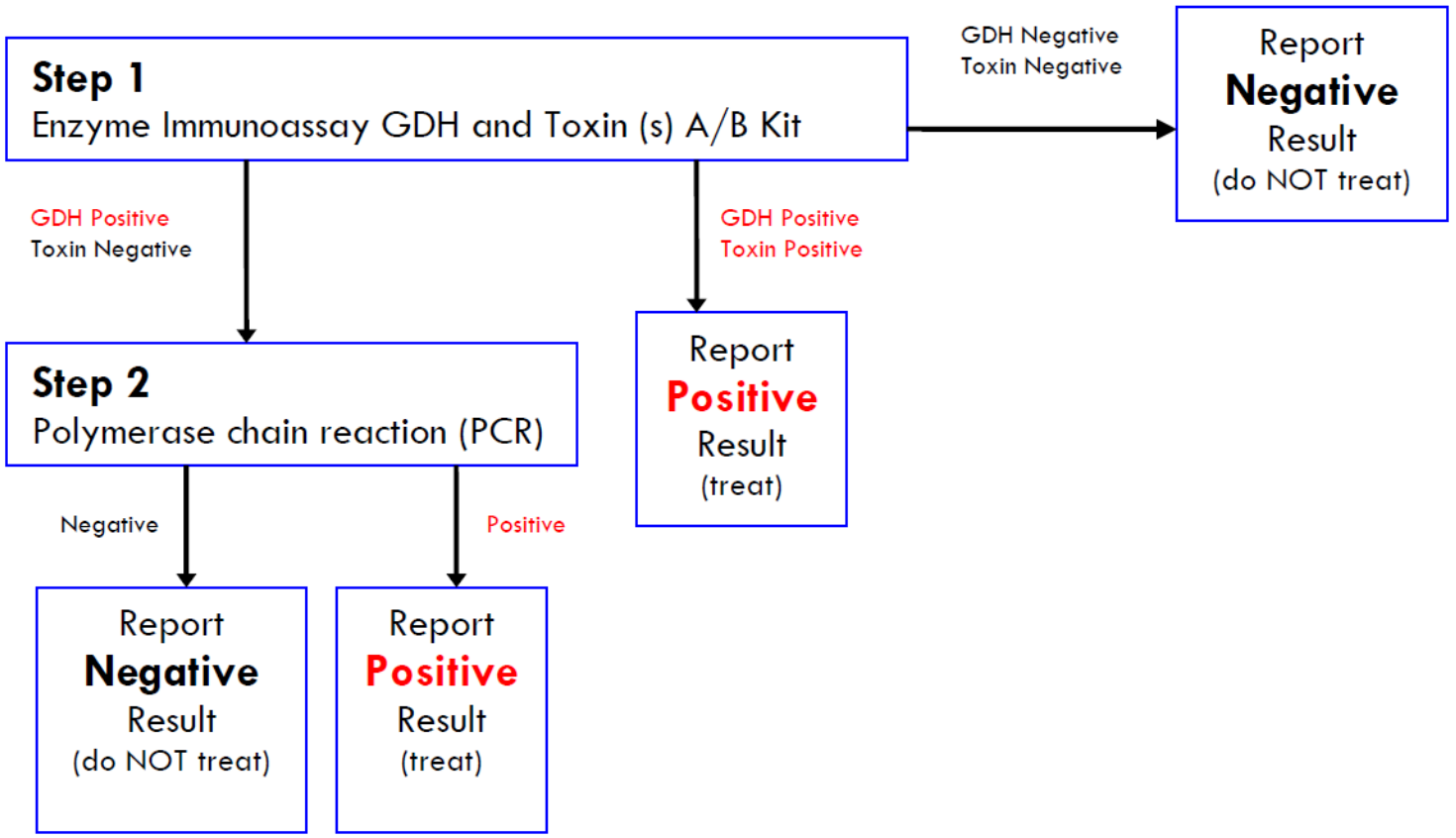
C diff testing



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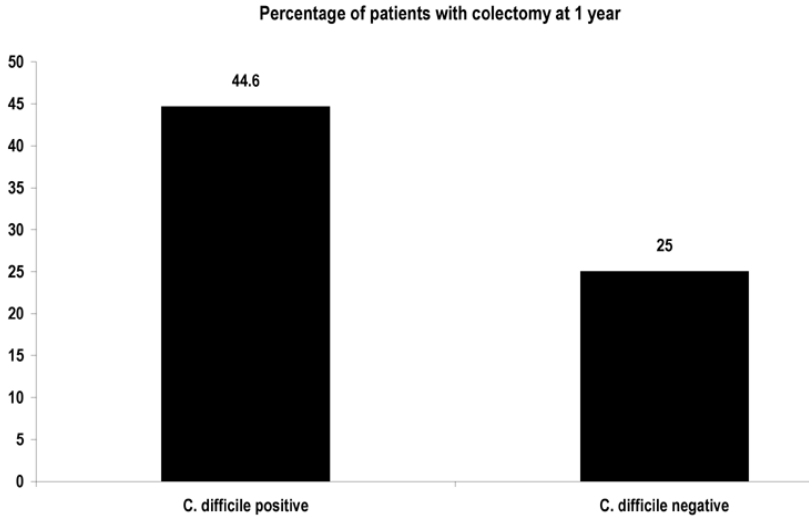
If a patient has C. diff, outcomes are worse



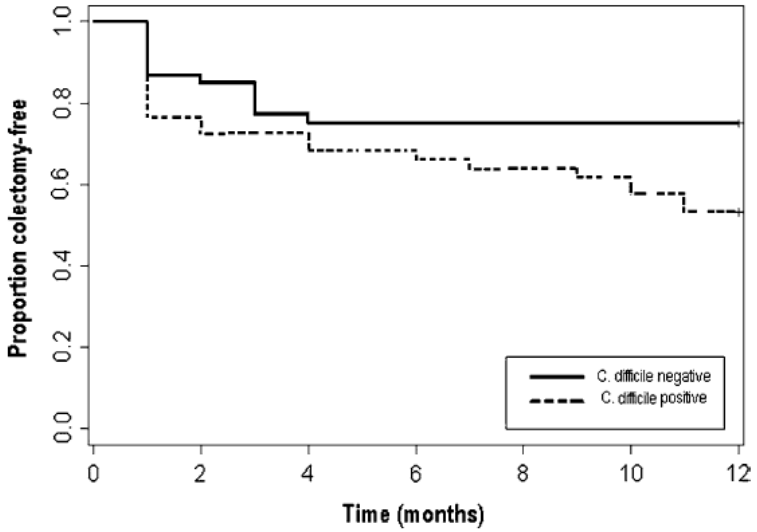


Fig. 4 Kaplan–Meier curve for colectomy-free survival at 1 year

Jodorkovsky D. Dig Dis Sci 2010;55:415-20.

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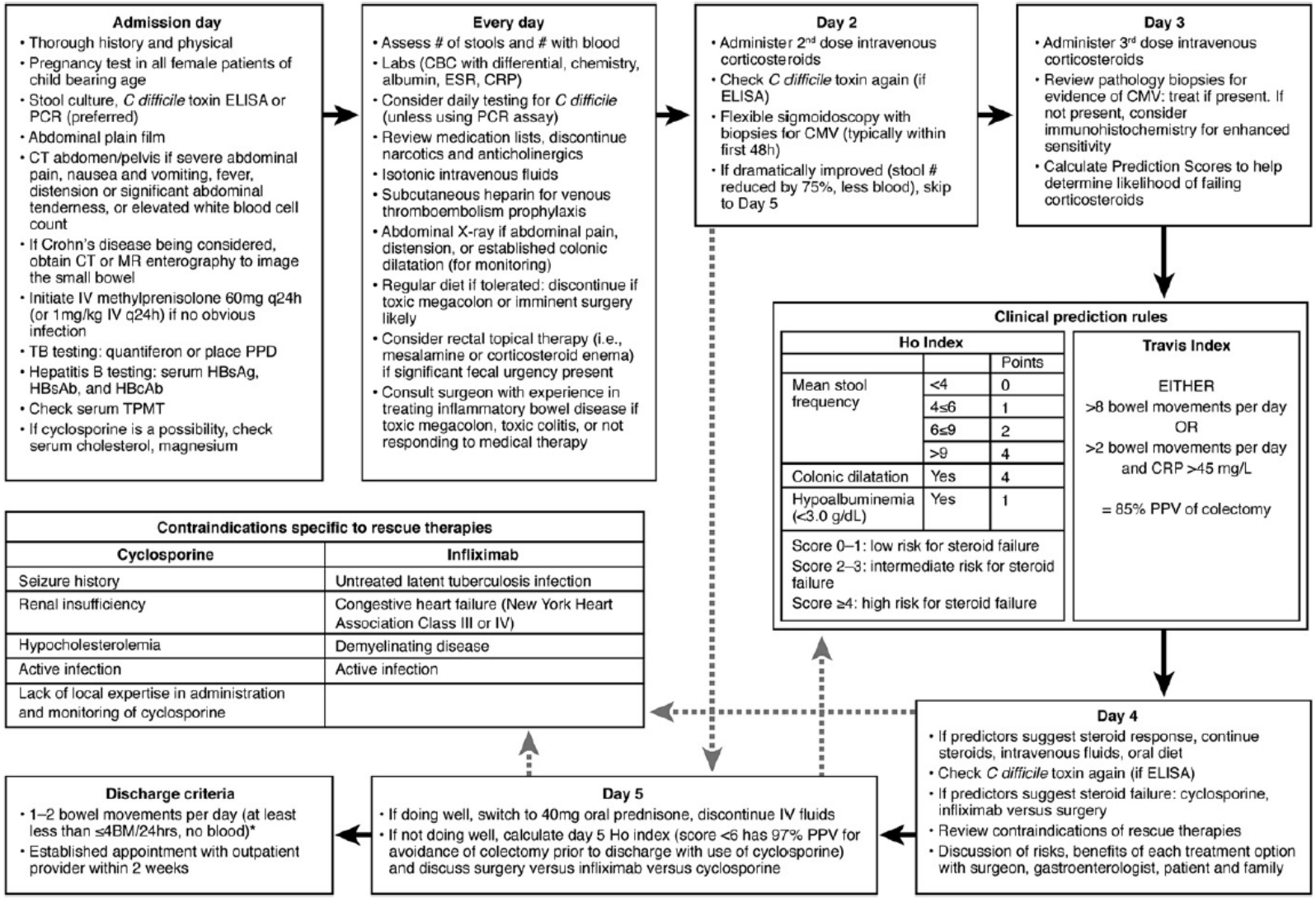

Figure 1. Proposed algorithm for managing ulcerative colitis in the hospital.[13,15,63] *Exact number of acceptable bowel movements varies patient to patient but needs to be while tolerating a full diet and manageable for that patient.

Pola S. Clinical Gastroenterol Hepatol 2012;10:1315–25.

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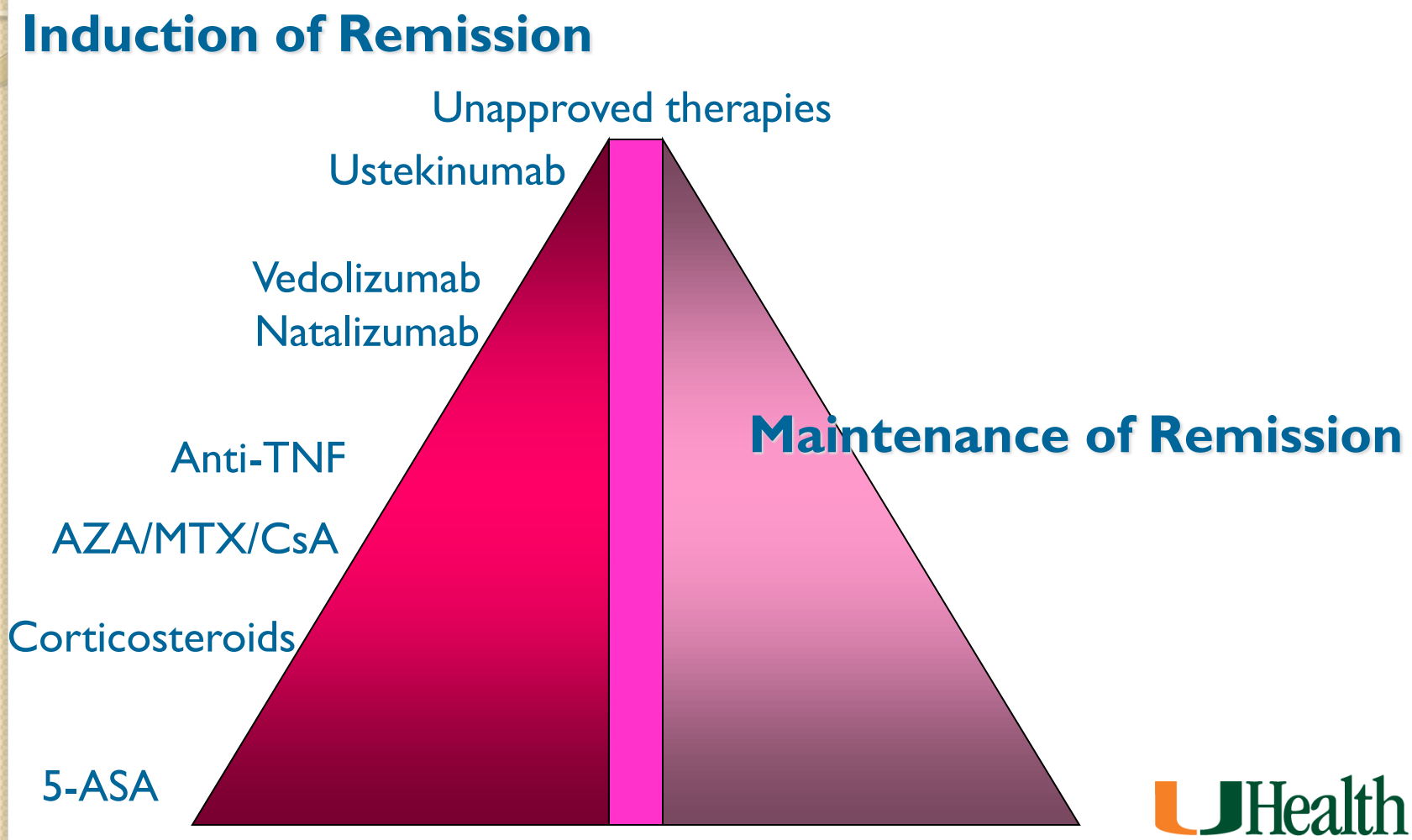
Therapeutic Pyramid in IBD: changing in the era of personalized medicine



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Outpatient Medical Therapy in IBD

- Should we be aggressive?
  - Treat early or late?
  - Step-up or Top-down?
  - Mono- or dual therapy?

- Weighing risks and benefits
  - Risks of treatment
  - Benefits of treatment
  - Risks of NO treatment
    - worse disease, cancer

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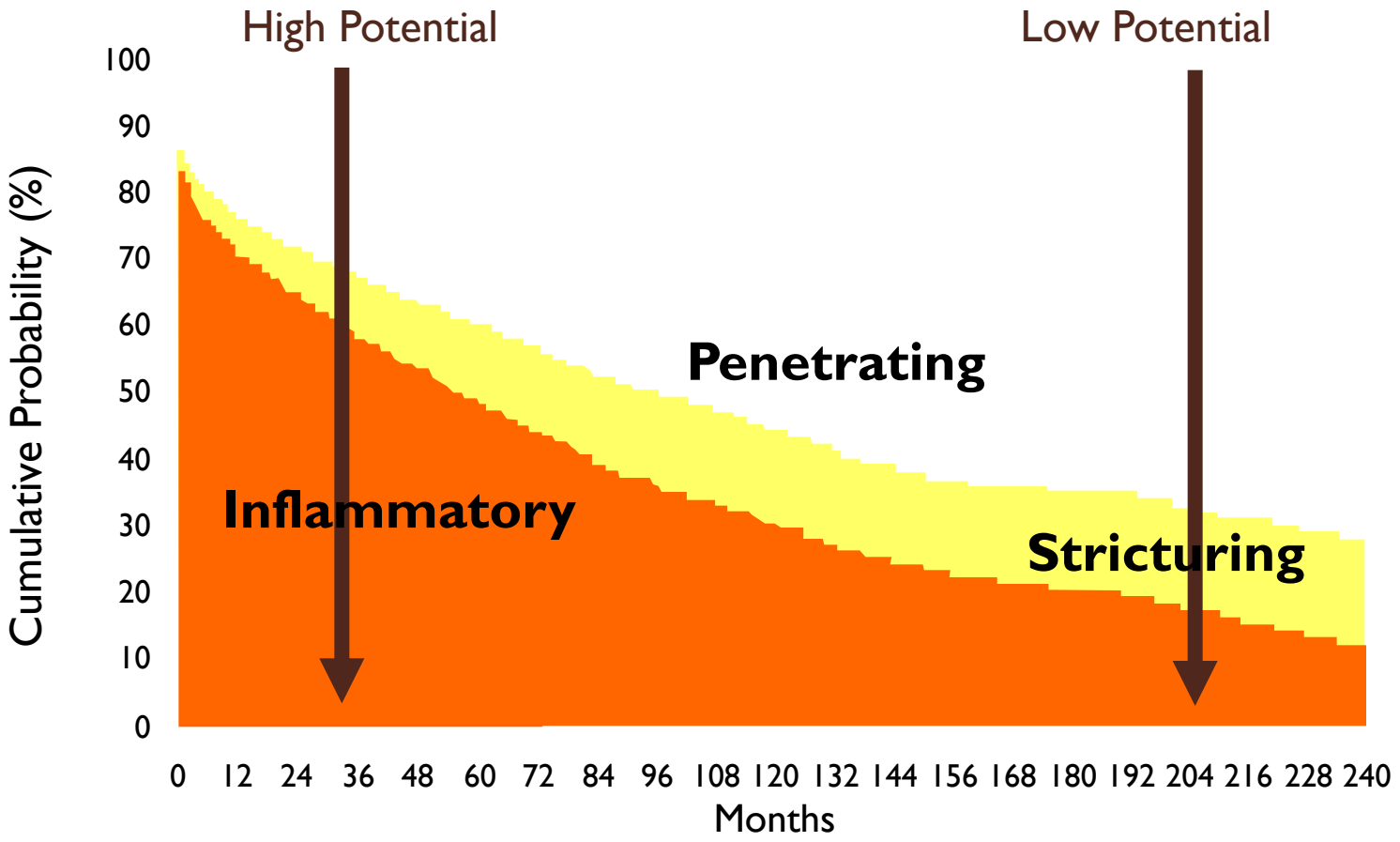
Treat Early or Late?



Patients at risk:

N =	2002	552	229	95	37

Cosnes J. Inflamm Bowel Dis 2002;8:244-50.

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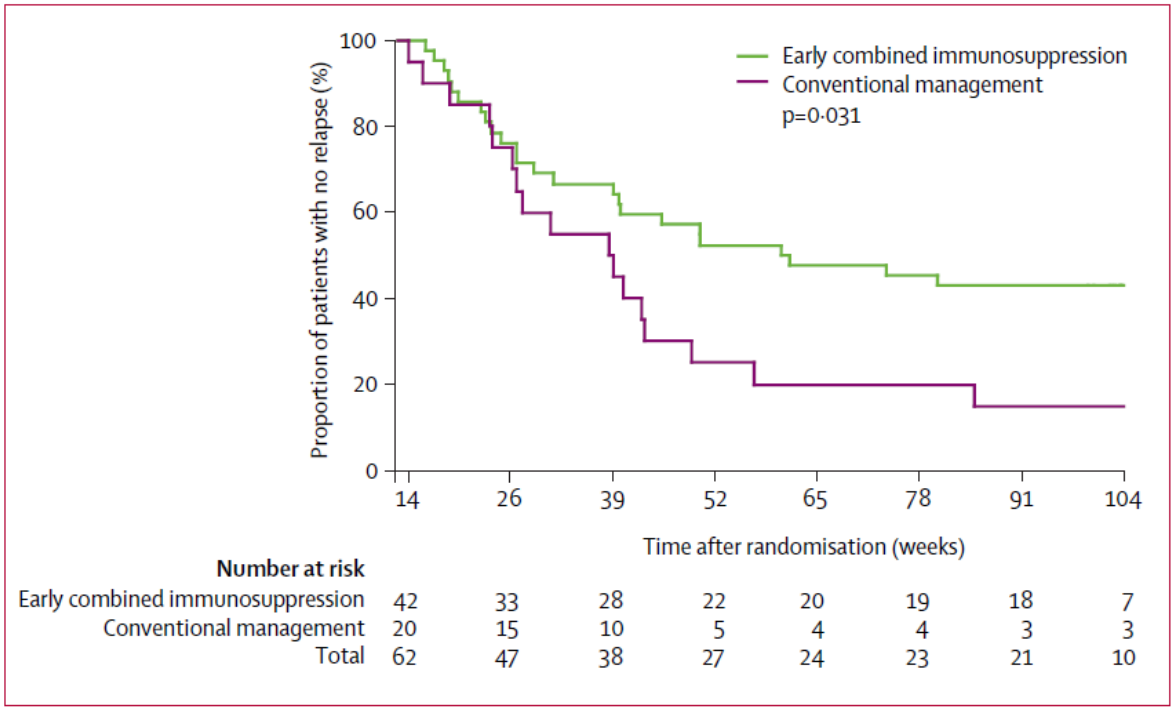
Step up versus top down approach



Number at risk								
Early combined immunosuppression	42	33	28	22	20	19	18	7
Conventional management	20	15	10	5	4	4	3	3
Total	62	47	38	27	24	23	21	10

Figure 3: **Proportion of patients who did not relapse**
Kaplan-Meier estimates of the time to relapse after successful induction treatment at week 14. Relapse was defined by a score of greater than 200 on the Crohn's Disease Activity Index, need for a bowel resection, or the need to add additional treatment according to assigned regimen. The p value was calculated by the log-rank test.

CDAI >200, naïve to steroids, immunomodulators, and biologics

D'Haens G. Lancet 2008; 371: 660-7.

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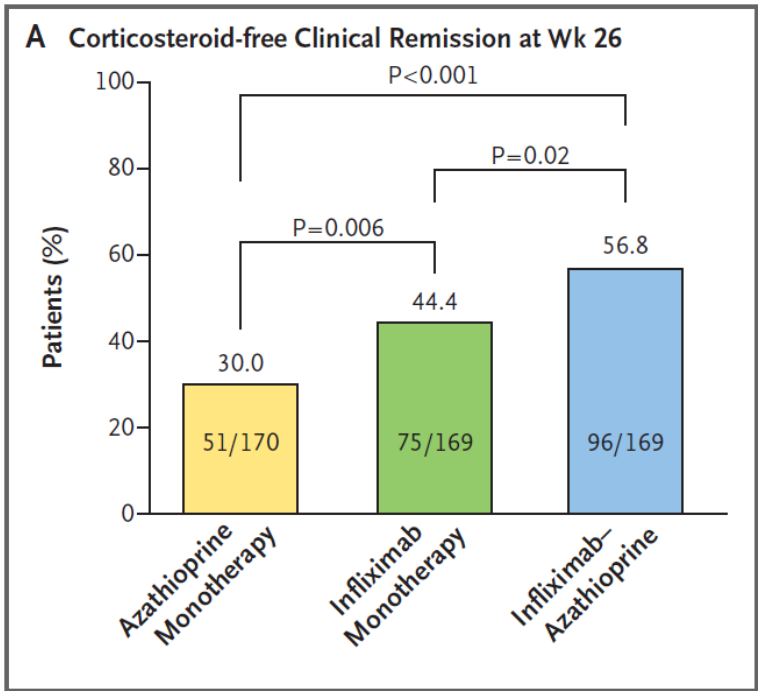
Mono- or dual therapy?



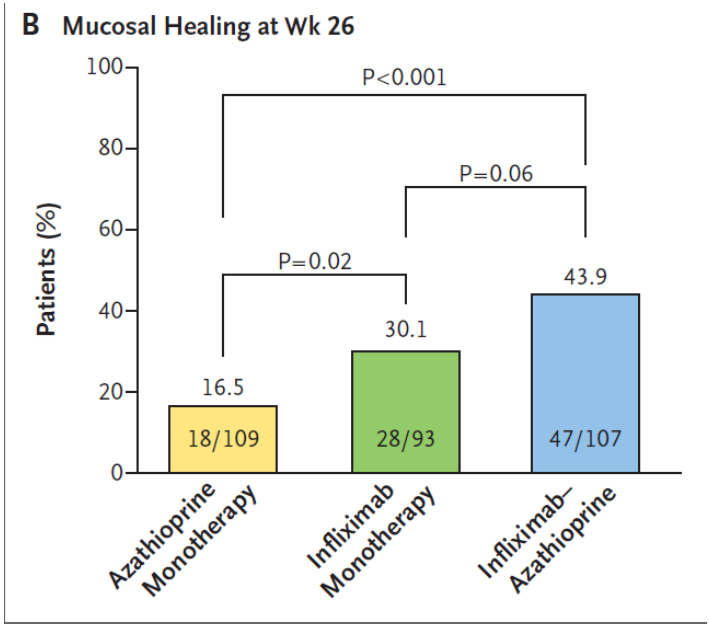


Figure 2. Patients with Corticosteroid-free Clinical Remission (Panel A) and Mucosal Healing (Panel B) at Week 26.

- CDAI 220-450, naïve to immunomodulators and biologics
- Similar findings in UC (SUCCESS trial)
- COMMIT (MTX) → negative study but high response

Sandborn WJ. New Engl J Med 2010;362(15):1383-95.
Panaccione R. Gastroenterol 2014;146:392-400.
Feagan BG. Gastroenterol 2014;146(3):681-8.

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Medical Therapy in IBD

- So the data suggest that we should:
  - Treat early
  - Treat aggressively
  - Treat with combined therapy

Symptom remission

→ Steroid-free symptom remission

→ Mucosal healing

→ Deep (histologic) remission

Are we asking for problems?

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Anti-TNF side effects

- TREAT registry of infliximab
  - Increased infection → much of that comes from steroids, narcotics, and disease severity
  - No increase in mortality
- Meta-analysis of 10 IBD trials with infliximab +/- AZA
  - No increase in infection, mortality, or malignancy
    - AZA-treated UC patients → more infections
    - AZA-treated CD patients → more malignancy

Lichtenstein G. Am J Gastroenterol 2012;107:1051-63.

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What about the risk of NOT treating?

- Fewer CD surgeries in Hungary independently associated with earlier and greater AZA use

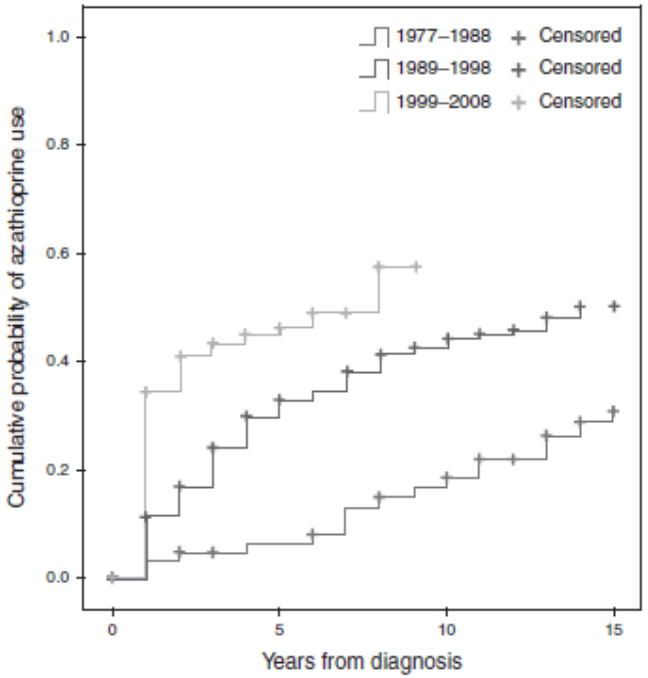

Figure 1. Azathioprine use according to the year of diagnosis in patients with Crohn's disease. $P_{LogRank}<0.001$, $P_{Breslow}<0.001$.

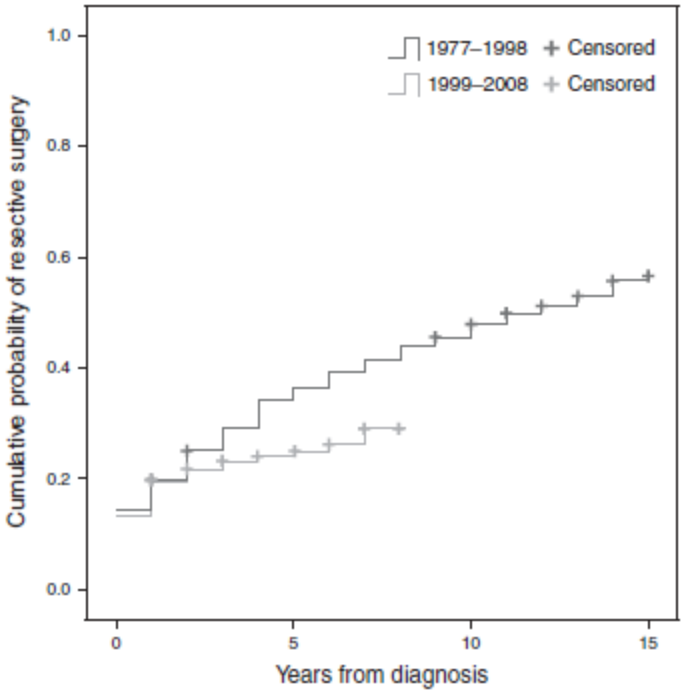

Figure 2. Cumulative probability of resective surgery according to the year of diagnosis. $P_{Logrank}=0.022$, $P_{Breslow}=0.07$.

Lakatos PL. Am J Gastroenterol 2012;107:579-88.

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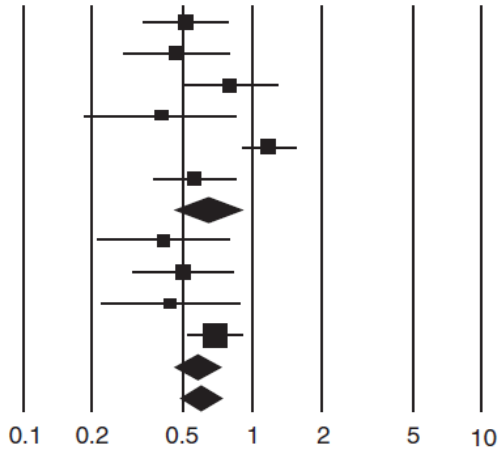
What about the risks of NOT treating?

- Thiopurines reduce need for 1st resection in Crohn disease by 40%
  - Meta-analysis of 17 studies, >20,000 patients
  - HR: 0.59 (95 % CI 0.48 – 0.73)

Group by	Study name	Hazard ratio	Lower limit	Upper limit
Study population				
1.00	Vernier-Massouille	0.51	0.33	0.78
1.00	Ramadas	0.47	0.27	0.80
1.00	Schaefer	0.80	0.50	1.29
1.00	Lakatos	0.40	0.19	0.86
1.00	Nguyen	1.18	0.90	1.55
1.00	Chatu	0.56	0.37	0.85
1.00	Pooled (population)	0.64	0.44	0.93
2.00	Picco	0.41	0.21	0.81
2.00	Peyrin-Biroulet	0.50	0.30	0.83
2.00	Gao	0.44	0.22	0.88
2.00	Camus	0.69	0.52	0.91
2.00	Pooled (hospital based)	0.57	0.45	0.73
Overall	Pooled (combined)	0.59	0.48	0.73



1= population-based study
2= hospital ortertiary referral-based studies

Chatu S. Am J Gastroenterol 2014;109:23-34.

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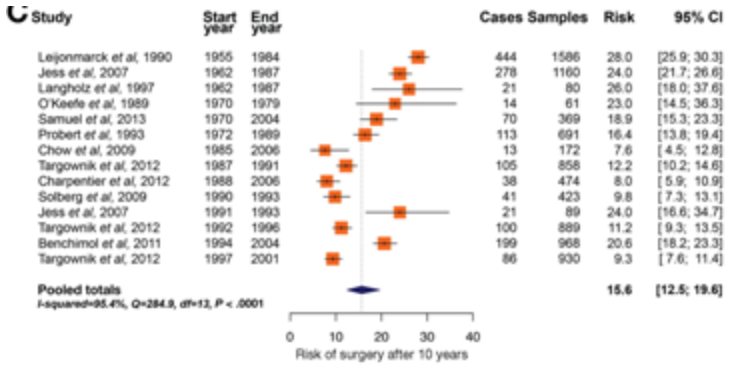
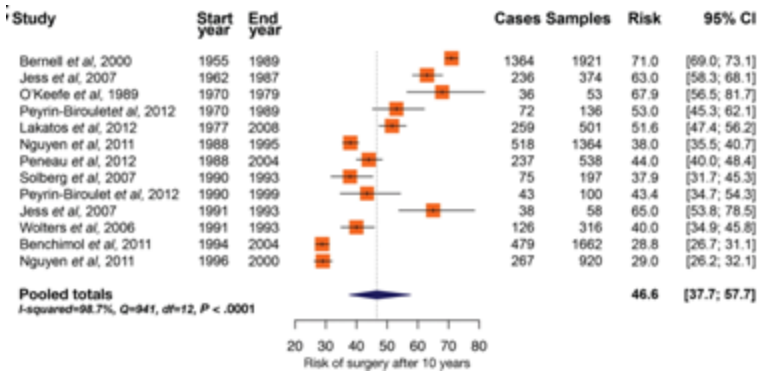
What about the risk of NOT treating?

- Rate of IBD surgeries decreasing in last 6 decades
  - Meta-analysis of 30 studies
  - Due to better/more aggressive therapy?





Frolkis AD. Gastroenterology 2013;145(5):996-1006.

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What about the risk of NOT treating?

- Decreased cancer risk by aggressively treating IBD (ulcerative colitis)
  - Danish cohort
  - 178 million patient years
  - In recent years, relative risk of colorectal cancer in UC has disappeared
    - due to more aggressive therapy?
- This decrease not seen in Kaiser study
  - But probably selected for longer duration and greater severity

Jess T. Gastroenterology 2012;143(2):375-81.
Herrington LJ. Gastroenterology 2012:143(2):382-9.

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What about the risk of NOT treating?

- Greater risk of hospitalizations and surgeries than lymphoma

Table 1. Comparing risk of lymphoma with immunomodulator therapy vs. risk of complications due to disease progression

	Azathioprine/6-mercaptopurine	Anti-TNF
Number needed to treat to cause one additional lymphoma per year with therapy	4,357 (age 20–29) 355 (age >65) (ref. 38)	2380 (ref. 56)
Number needed to cause one additional relapse per year by stopping therapy	3 (ref. 58)	
Number needed to cause one additional hospitalization per year with episodic therapy		7 (ref. 59)
Number needed to cause one additional abdominal surgery per year with episodic therapy		14 (ref. 59)

TNF, tumor necrosis factor.
Numbers adapted from referenced articles.

Bewtra M. Am J Gastroenterol 2012;107: 964-70.

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Risk vs reward

- IBD patients are willing to accept higher risks of lymphoma and infection in exchange for longer duration of disease remission

Bewtra M. Am J Gastroenterol 2015;110:1675-81.

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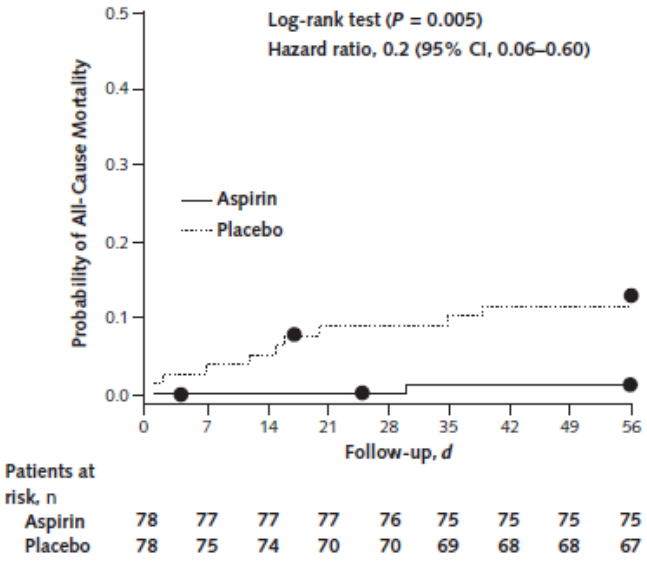
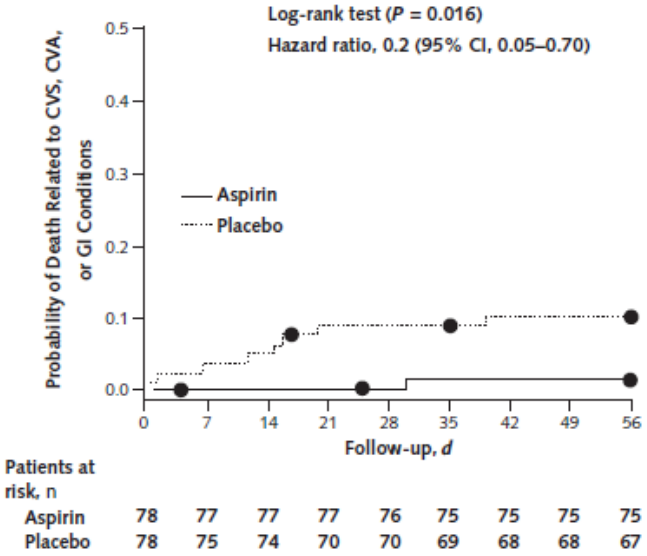
The ris ting

- We live ir se society
  - Better t ing it safe" than "going fc matical odds
- Sports
  - Baseball:
  - Basketba
  - Football:
  - Hockey:
- GI
  - Holding s at endosco
- Hippocra
  - Has bec

Figure 3. Kaplan–Meier estimates of the incidence of mortality within 8 weeks.





Moskowitz and Wertheim. *Scorecasting*. NY:Random House, 2011.
Sung JJ. Ann Int Med 2010;152(1):1-9.

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JGIM
Journal of General Internal Medicine

Sins of Omission

Getting Too Little Medical Care May be the Greatest Threat to Patient Safety

CONCLUSIONS: While preventing iatrogenic injury resulting from medical errors is a critically important part of quality improvement, we found that the overwhelming majority of substantive medical errors identifiable from the medical record were related to people getting too little medical care, especially for those with chronic medical conditions.

Hayward RA. J Gen Intern Med 2005;20(8):686-91.

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Surgery in IBD

Ulcerative Colitis

- Remove entire colon/rectum
  - Refractory disease
  - Colon cancer
- Options
  - Total proctocolectomy (TPC) with ileostomy
  - TPC and ileal pouch-anal anastomosis (IPAA) → 2 vs 3 stage

Crohn Disease

- Surgery does not cure
- Disease recurs after resection
- Resection of inflamed segments to treat complications (stricture, abscess, fistula) or refractory disease

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Managing Nutrition in IBD

- Malnutrition can occur in IBD
  - Decreased intake of food
    - symptoms
    - overzealous restriction
  - Decreased assimilation of nutrients
    - active disease in small intestine
  - Increased need for calories/protein (catabolic)
- Benefit from professional nutritional assessment
- Tailor diet to individual needs & preferences
- No clear "IBD diet"
- Micronutrient/macronutrient supplements

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Prevention in IBD

- Vaccinations
  - no LIVE vaccines if on an anti-TNF agent
    - intranasal influenza, MMR, yellow fever, zoster
  - otherwise routine vaccinations encouraged
    - influenza, pneumococcal, HPV
    - best uptake of vaccine BEFORE immunosuppression
- Blood Pressure monitoring → general recs
  - more so if on corticosteroids or cyclosporine
- Tobacco cessation
  - for all Crohn disease
  - for all UC once disease is controlled
    - cardiovascular and oncologic risks >> UC benefit

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Prevention in IBD

- Bone health
  - vitamin D levels
  - bone densitometry (DEXA)
    - especially if prolonged corticosteroids
- Vitamin B12 (+/- methylmalonic acid)
  - especially if ileal disease/resection, small bowel dysmotility/overgrowth
- Iron
  - unless mild probably better to replace IV (hepcidin)
- Eye Exams
  - annually
  - closer attention if on corticosteroids or concern for episcleritis/uveitis (extraintestinal manifestations)

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Prevention in IBD

- Malignancy screening
  - prostate and breast → same as general recs
  - non-melanoma skin → higher with thiopurine use
  - melanoma → higher with anti-TNF use
  - cervical and anal → increased risk
    - Pap smears, HPV, ?anal Pap smear
  - colon → depends on duration, extent, and control of disease
    - routine colonoscopies
- Depression
  - strong psychosocial effects of disease

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Prevention in IBD

- Risks of immunosuppression
  - infection → **highest** with steroids
  - non-Hodgkin's lymphoma → slight increased risk
    - very low risk of hepatosplenic T-cell lymphoma (mostly thiopurine + anti-TNF in teenage males)
  - bone marrow suppression
  - liver toxicity

    thiopurines
  - reactivation of hepatitis B
  - reactivation of tuberculosis

    anti-TNFs
  - liver, lung, marrow, fetus → methotrexate
  - progressive multifocal leukoencephalopathy (PML)
    - natalizumab risk based on JC virus status and duration of treatment
  - acne, mood swings, sleep disturbance, weight gain, cataracts, osteoporosis, diabetes, poor wound healing, etc → MINIMIZE STEROIDS!!

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THANK YOU

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