

Meeting to
Transform



Collaborative Solutions in Patient-Centric Care.

CROHN'S & COLITIS CONGRESS™

A Partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association

Treating the Refractory IBD Patient and the Rising Bar for Patient Outcomes



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Disclosures for Peter Higgins

- Research Funding
 - CCF
 - NIH
 - BCBS of Michigan
 - AbbVie
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 - Arena
 - Ascentage Pharma
 - Buhlmann
 - Eli Lilly
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 - Janssen
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 - Medimmune
 - Nestle
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 - RedX Pharma
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 - Lycera
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 - UCB
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 - NIH
 - CCF



Agenda

- The Refractory Patient
 - Rule out mimics
 - Options for treating Refractory Inflammation due to IBD
 - Approach to Complicated structural bowel damage with Abscess
- The Rising Bar in IBD Treatment
 - Clinical remission
 - Endoscopic / Biologic remission
 - Histologic Remission
 - Biologic PLUS Quality of Life Remission



The Refractory IBD Patient



IBD Mimics to Consider

- Infection: TB, Yersinia, CMV, HSV, Histoplasmosis
- Ischemia
- Idiopathic Myointimal Hyperplasia of the Mesenteric Veins
- Neoplasm: refractory strictures or fistulas
 - Kaposi's sarcoma, lymphoma/leukemia, adeno Ca, squamous Ca
- Structural issues: Meckel's diverticulum
- Drugs: NSAIDs, Olmesartan, Checkpoint inhibitors
- Celiac disease (+/- IBD)
- Autoimmune enteritis, eosinophilic enteritis, Behcet's
- Endometriosis
- Solitary Rectal Ulcer Syndrome (SRUS)
- Segmental Colitis Associated with Diverticulosis (SCAD)

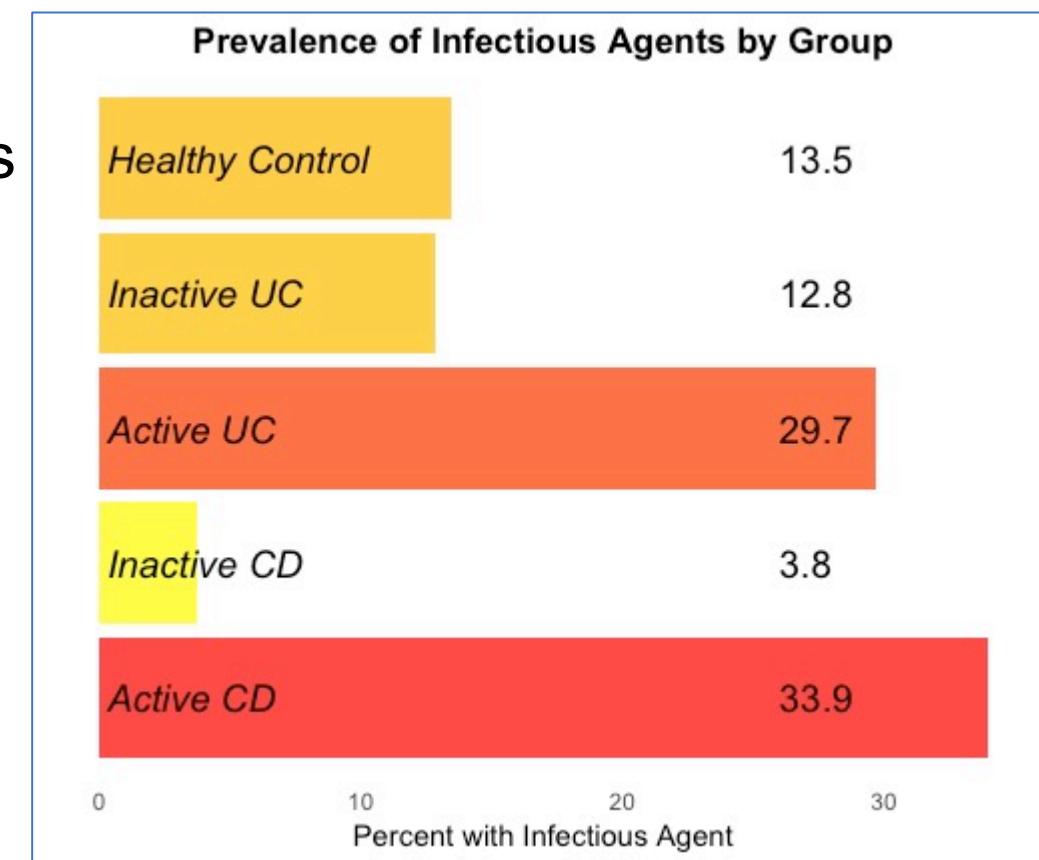




Rule Out Infection

- Consider
 - TB, Yersinia, CMV, HSV, Histoplasmosis
 - GI tract infections
 - PCR panels
 - Norovirus
 - E. coli
 - Salmonella
 - Campylobacter
- Infection can initiate a flare – you may need to treat infection, then the flare

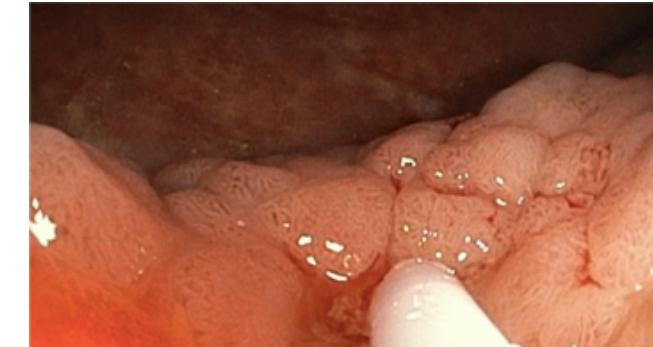
Poster 086, #CCCongress





Don't Miss a Cancer

- Calprotectin and CRP often elevated
- Be suspicious of refractory strictures (especially colonic)
 - Can be adenocarcinoma
- Be suspicious of a firm refractory perianal fistula
 - Can be adenocarcinoma or squamous cell carcinoma
- Less common:
 - Intestinal lymphoma/leukemia
 - Melanoma
 - Kaposi's sarcoma



Colonic adenocarcinoma

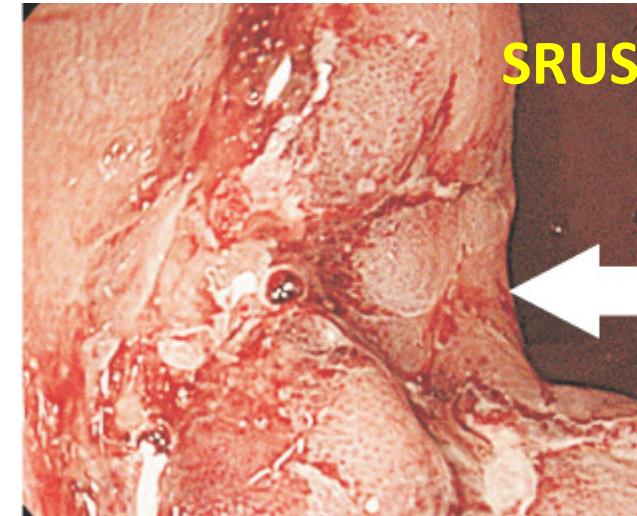


Intestinal B cell lymphoma



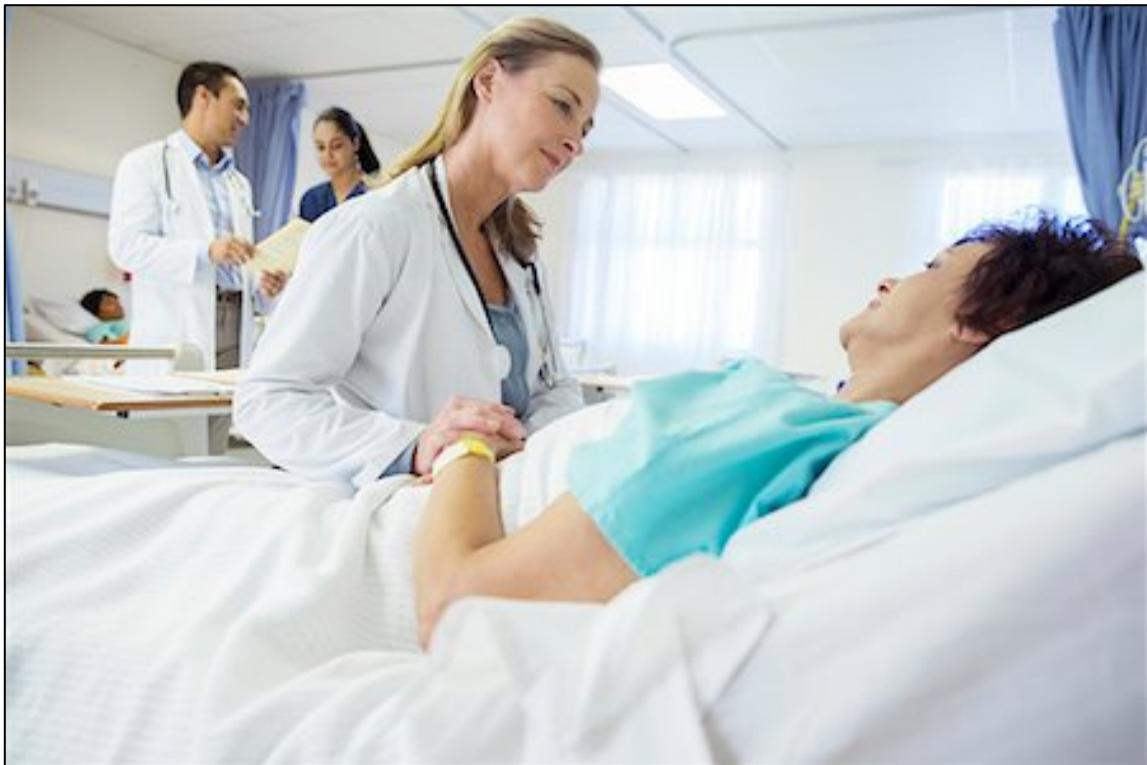
Confusing Structural Problems

- Meckel's diverticulum – small bowel obstructions
- SCAD
 - Segmental colitis associated with diverticulitis
- SRUS
 - Solitary Rectal Ulcer Syndrome
 - Bleeding with constipation
- Endometriosis
 - Pain, obstruction
 - Mostly rectosigmoid





The Refractory IBD Patient: Laura's (fictional) Case



- Laura is a 30 y/o female with UC that has responded to 5-ASA for 2 years.
- Her current flare is not responding to 4.8 g 5-ASA + 4 g bid 5-ASA enemas + one day of 60 mg IV solumedrol.
- 11 bloody BM with mucus,
45 second urgency,
LLQ cramping before bowel movements in the last 24 hr.



Laura Worsens

- Infectious testing is negative
 - 72 hours of solumedrol – now 8 bloody BM daily
 - CRP was 74, improved to 52 mg/L
 - Travis Index positive, 85% PPV for colectomy
 - Rescue therapy – choices
 - Cyclosporine induction – bridge to thiopurines or Vedolizumab
 - IFX induction – generally use 10 mg/kg, 2nd dose 72 hours after first dose if CRP still > 5 mg/L
 - Starts IFX. CRP to 18 mg/L after 72h, 2nd dose reduces to 3 mg/L
 - Aza 2.5 mg/kg added, next dose IFX in 2, then 6 weeks. Remission.



Travis, et al. Gut. 1996;38(6):905-10.

<http://www.med.umich.edu/ibd/docs/severeucprotocol.pdf>



Future Options for Refractory Inflammation

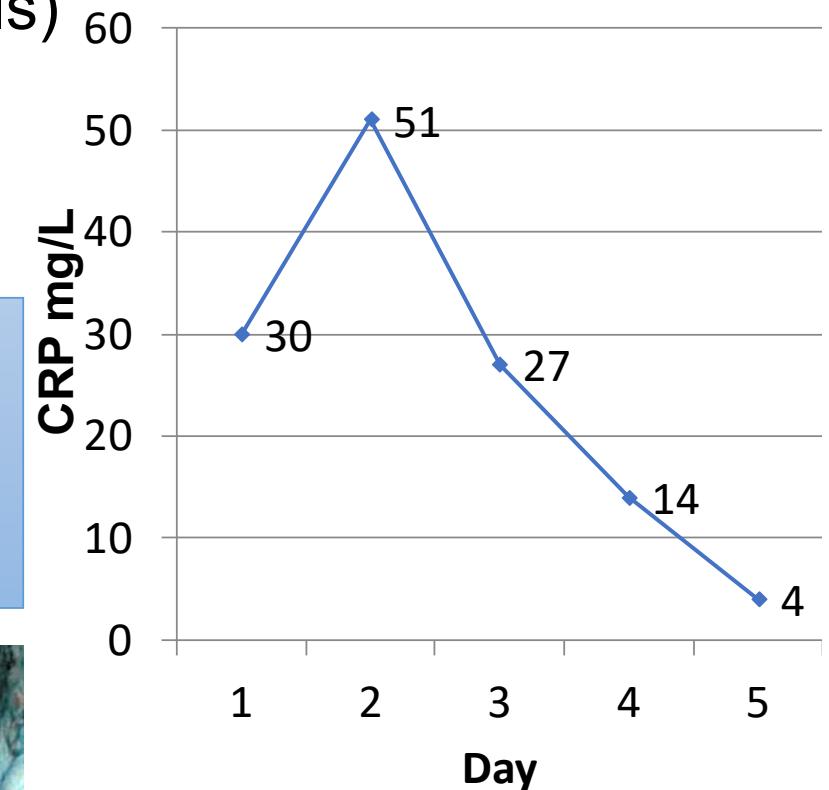
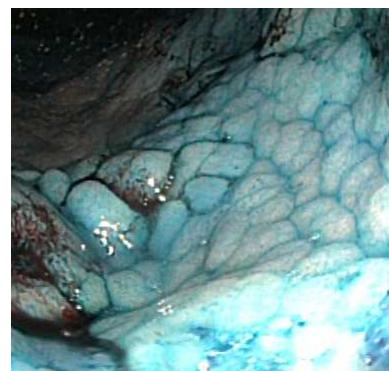
- New therapies with new MoAs (now in clinical trials)
- Combination therapies?
- Intensified Induction?

52 y/o male with pancolitis, failing IFX/Aza/prednisone 40 mg daily
Admitted to hospital for IV steroids, likely colectomy
Added 10 mg tid tofacitinib to IV steroids x 9 doses
Continued on IFX, tapered oral steroids x 8 weeks
Swapped Aza for tofacitinib 10 mg bid after insurance approval

Mucosa Healed



Dysplasia Revealed





The Refractory IBD Patient – Complicated Crohn's

- Could this represent Structural Damage? Anthony's (fictional) case



- Anthony is a 28 year old male with a 13-year history of ileocolonic Crohn's disease.
- He had an ileocecal resection in 2008, and an ileal resection in 2012.
- He did well on infliximab from 2008-2012 (surgery for stricture), then adalimumab from 2013-2017.
- Now having RLQ pain, fevers, fatigue, 4-5 loose stools daily, and CRP 38 mg/L, ESR 84.
- Infection is evaluated with C diff toxin test and PCR panel. All negative.
- Adalimumab trough level is 10.9 mg/mL, no ABA
- Fecal calprotectin 473 mcg/g of stool



The Refractory IBD Patient – Complicated Crohn's

- The Good News for Anthony



- No evidence of infection.
- Clear inflammation – both systemic and in the GI tract
- Adequate levels of adalimumab, and no anti-biologic antibody.
- Start intravenous steroids
- MR Enterography ordered



The Refractory IBD Patient – Complicated Crohn's

- The Bad News for Anthony



- After 3 days, CRP still 22 mg/ L
- Still having pain, loose stools
- MR Enterography result
 - Is there a stricture?
 - Could there be a fistula, or an abscess?

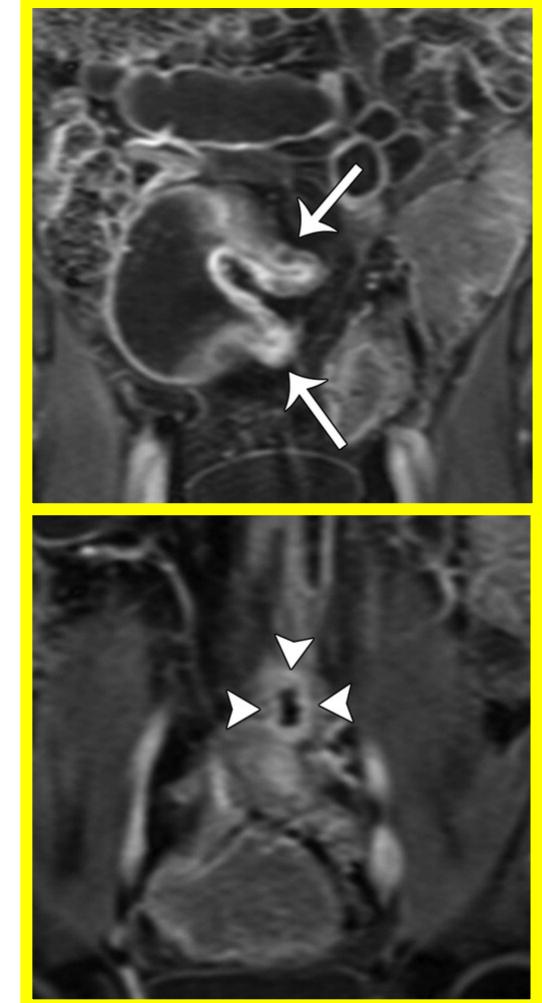


The Refractory IBD Patient – Complicated CD

- The Bad News for Anthony



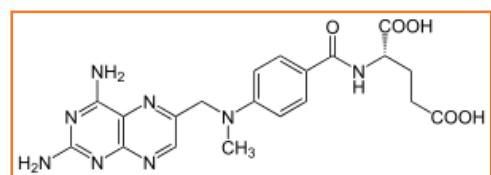
- Inflamed, narrowed segments of distal ileum with upstream dilation
- Adjacent small abscess



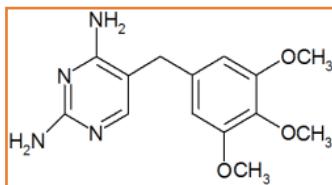


Therapeutic Choices

- Infection, Stricture, and Inflammation – Which to Treat?



Methotrexate



Trimethoprim

- Start with infection – broad spectrum IV antibiotics for gut flora (piperacillin/tazobactam in this case)
- Drain pus if possible – difficult transcutaneous access near vessels – able to aspirate 2 cc, test sensitivity to antibiotics
- Treating inflammation
 - In the presence of abscess, avoid systemic steroids and anti-TNFs (“abscess fertilizers”)
 - Can use methotrexate in short term without worsening abscess
 - Cousin of trimethoprim

Infection → Inflammation → Structural Damage



Therapeutic Choices

- Infection, Stricture, and Inflammation – Which to Treat?



- Gradually improves on Pip/Tazo x 10 days, MTX 25 mg weekly
- Ultrasound at week 2 shows near-resolution of abscess, complete resolution by week 4.
- CRP falls to 8 mg/L by week 4
- ESR falls slowly to 25 by week 8
- Repeat MRE at week 12 – still 8 cm strictured segment, lumen of 2-3 mm, dilation to 3.8 cm, residual enhancement in upstream 25 cm
- Has lost 4 kg, Alb 3.1
- Time for Decisions...



Therapeutic Choices

- Operate now or later?



- Operate now
 - Not on steroids, small wt loss, Albumin low but not <3. Will resect 35 cm.
- Operate later
 - Control inflammation first
 - Improve nutrition, albumin, muscle mass
 - May be able to resect less intestine in 6 months
- Which would you do?
- Starts ustekinumab at 6 mg/kg, schedules surgery for week 28 (midpoint between doses q 8 weeks)



Therapeutic Choices

- Operate later? “Neo-adjuvant” ustekinumab...



- Does well on “neo-adjuvant” ustekinumab, CRP down to 2 mg/L, ESR to 12, Albumin to 3.8, regains 3 kg
- Operation at week 28 goes well
 - Continues MTX to day of surgery
 - Some adhesions near fistula
 - Able to resect only 10 cm
- No wound infection
- Able to continue ustekinumab at week 32 without missing a dose.



The Refractory IBD Patient

- Be sure it is IBD, many mimics exist
 - Consider infection, malignancy, bowel damage, drugs
- Treat infection → inflammation → structural damage
- Objectively measure inflammation
- Treat inflammation until resolved, or step up therapy in a timely fashion



Delay in Control of
Inflammation →
Structural Bowel Damage



Endoscopic
Remission



Histologic
Remission



The Rising Bar for IBD Therapy

Re-Defining Remission Upward



Clinical Remission

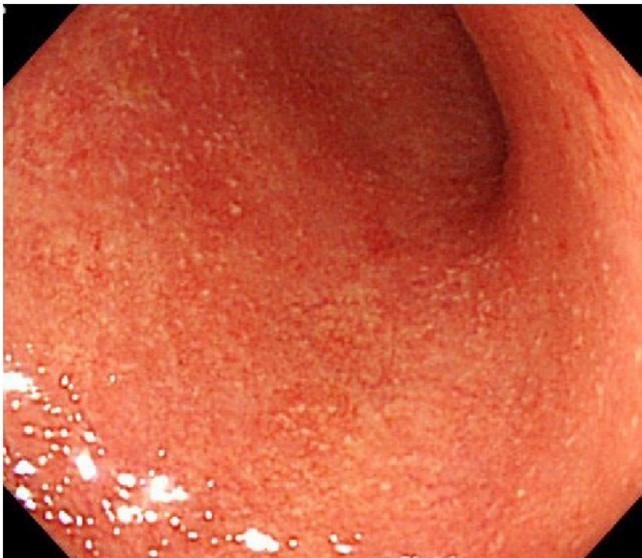


- This is good.
- The patient feels well ***right now***.
- However:
 - Some patients adapt to, and come to accept:
 - Smoldering inflammation
 - Restrictive diets to reduce Sx
 - Tolerating symptoms
- How ***good*** is this clinical remission?





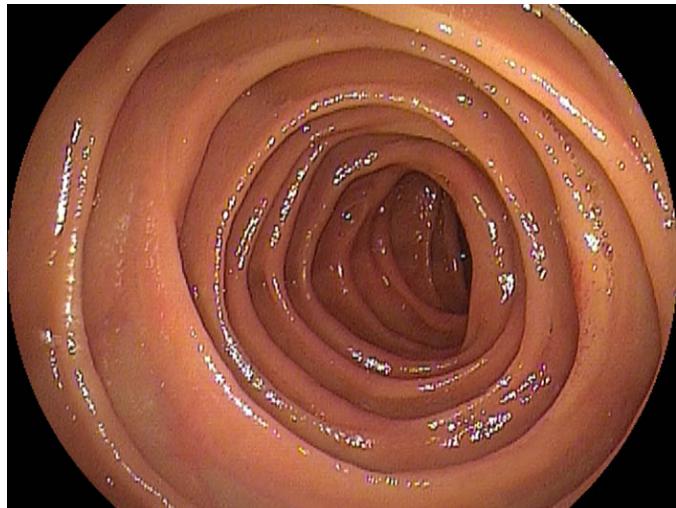
Clinical Remission



- If there is smoldering inflammation, there is increased risk of:
 - Future flare
 - Future steroids and hospitalizations
 - Bowel damage and future surgeries
- Clinical remission is good now, but clinical remission ≠ a good future



Biologic Remission by Endoscopy



- The patient's intestines (as far as you can reach) look good.
- This is predictive of good outcomes in the next year.
- Endoscopy is imperfect
 - You can not easily reach all of GI tract.
 - You can't do endoscopy very often.
 - You have to assume that what you see is representative.
 - Sometimes (~26%) this assumption is wrong.

Testing in 4 -way comparison study	Sensitivity for Active Crohn's Disease
Capsule Endoscopy	83%
CT Enterography	83%
SBFT	65%
Ileocolonoscopy	74%

Solem, CA, Gastrointest Endosc. 2008; 68: 255-66.



Biologic Remission by Imaging



- Entire gastrointestinal tract looks good.
- Predictive of good outcomes in the next year.
- Drawbacks
 - (In US) Expensive if you use MRE.
 - Requires radiation if you use CTE.
 - More difficult than blood/stool sampling.
 - Can get false positives with infection.
 - You can't do imaging very often.

Case courtesy of Dr. Dalia Ibrahim, Radiopaedia.org, rID: 30357



Endoscopic / Biologic Remission



- Biomarkers
 - Inexpensive, easy to obtain frequently
 - Not specific
 - Any infection will raise C-reactive protein (CRP)
 - Gut infections will raise fecal calprotectin (FCP)
 - Inexpensive enough to track over time
 - ~ 20% will not make CRP despite a moderate flare
 - FCP can be false negative in ~10% in small bowel CD with an intact IC valve.
 - FCP can vary (± 200) from stool to stool

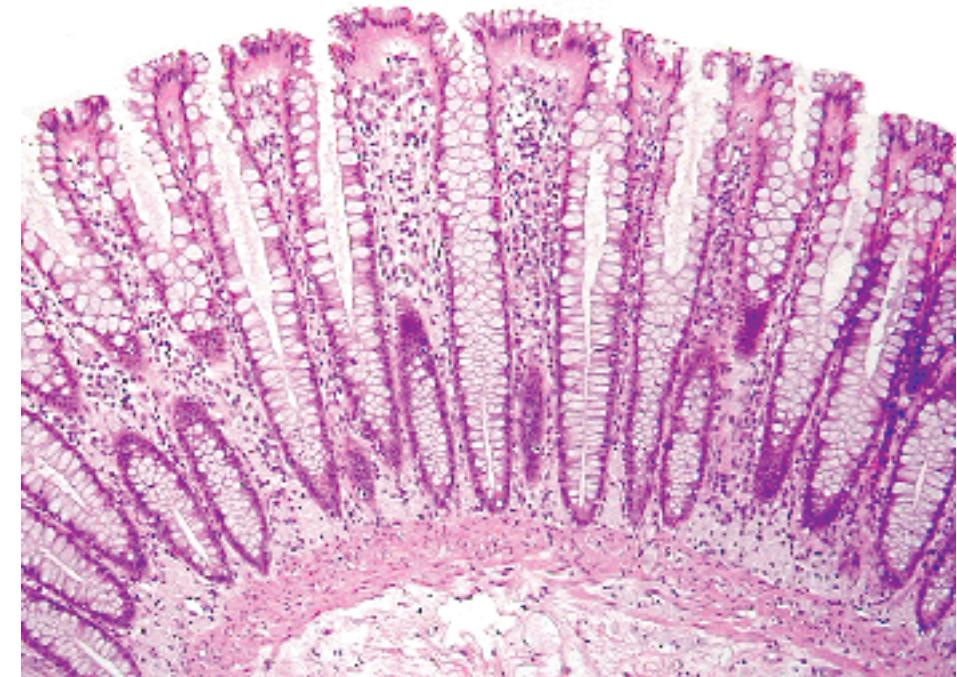
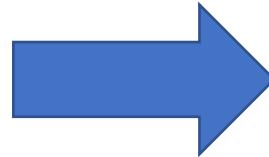
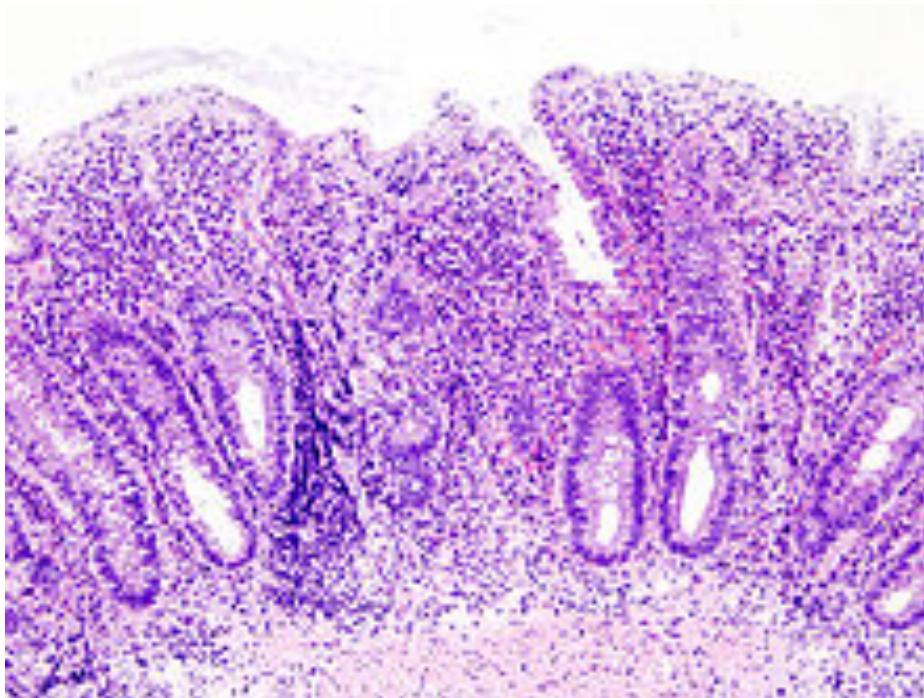
Calafat, M. Inflamm Bowel Dis. 2015;21:1072-6.



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Next Level Care: Histologic Remission





Histologic Remission

- 40% of endoscopically normal IBD colonoscopies→histologic inflammation
- Histologic remission = Inflammatory infiltrate, structural changes resolve
 - Occurring increasingly often with more effective therapies
- Associated with better long-term outcomes
 - Fewer flares, steroids, hospitalizations, colectomy
 - Reduced risk of colon cancer

Bessisow, T, AJG 2012, 107: 1684-1692.

Hefti, Dis Col Rect, 2009, 52: 193-7.

Christensen, B, CGH 2017; 15:1557-1564.

Melson, Dis Col Rect, 2010; 53:1280-86.

Rutter, Gastroenterology 2004; 126: 451-459.



The Pursuit of Objective Remission

- Patient often feels well now
- Patient (and payor) may not want the costs or risks of escalating therapy.

GI:
You have microscopic
inflammation.
You need stronger therapy
for your IBD



Patient:
But I don't feel like I **need**
stronger therapy
for my IBD



The Changing World of IBD

- For many years, we have treated IBD for symptom control
 - Patients felt much better, were thankful
 - Doctors felt good!
 - Doctors and patients lived in the now – How do you feel today?
 - But increasing evidence shows we should treat for the ***future***...

Diabetes Specialist:
You should take medicine for
your high glucose and
high blood pressure



Patient:
But I feel fine.
Why should I take medicines
when I feel fine?



The Changing World of IBD

- Future IBD treatment will be more like treating diabetes or hypertension

GI:
We should treat you today
to control inflammation
in order to prevent
complications
and surgeries
in the future



Patient:
So even though I feel fine, the
calprotectin of 520 is bad,
so I should take medicines to
prevent bad things from
happening to me in the future?



Does Treat to Target Work?

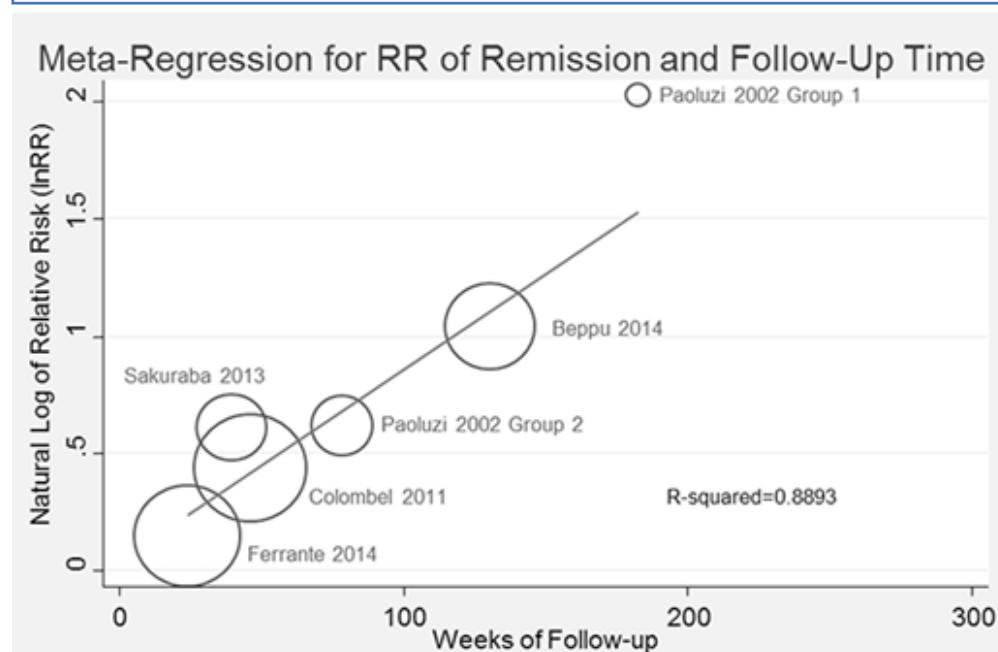
- CALM Study
- Used biomarkers to guide treat to target (T2T) escalation of adalimumab

Outcome	T2T group	CM group	p
CDEIS <4 w/out deep ulcers	46%	30%	0.010
Above plus CDAI <150, steroid free, No fistulas	37% Fewer hospitalizations	23%	0.014

Colombel, et al., Lancet 2017, 390: 2779–2789,

Does Complete MH Matter?

- Meta-regression: complete v. partial MH
- Looked at benefits vs. time of follow up.



Reinink, et al., IBD 2016 22:1859



The Tradeoffs of a Changing World

- What is the cost-benefit of treating to a biologic target?
 - Big benefits take a long time to arrive (2-4 years)
 - Is it worth the added medication cost?
 - Is it worth the added risk of side effects?





The Tradeoffs of a Changing World

- We will likely need prospective cost-effectiveness studies to convince national health authorities and health insurers before treatment to a biologic endpoint is routine.
- One particular challenge in the US:
 - Patients change health insurers on average ~ every 2.5 years
 - Current insurer suffers early costs, may not see benefits
 - US health Insurers are incentivized to treat for now, not for the future.

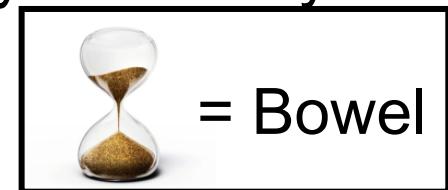
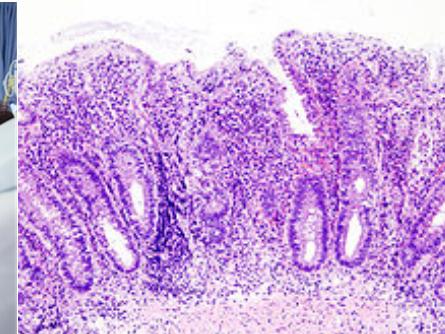
The REACT2 study
(2018, T2ET)
is one to watch.





Summary

- The Refractory IBD Patient
 - Make sure this flare is IBD
 - Treat infection → inflammation → structural damage
 - Objectively measure inflammation & step up IBD therapy in a timely fashion
- The Bar is Rising in IBD Outcomes
 - Treat inflammation for symptom improvement now
 - Treat to inflammation targets to prevent future complications
 - Frequent monitoring with biomarkers and tight control of inflammation
 - Caveat for T2T: infections and cancer can have positive FCP, CRP





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Thank You

