Brigham and Women's Hospital
Founding Member, Mass General Brigham

# Challenging GI Cases

Joshua Korzenik, MD
Director, Resnek Family Center for Primary Sclerosing Cholangitis
Founding Director, BWH Crohn's and Colitis Center
Gastroenterology, Hepatology and Endoscopy
Department of Internal Medicine
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

# Joshua Korzenik, MD

- Albert Einstein College of Medicine
- Medicine Residency @BIDMC
- GI Fellowship @Yale
- Founding Director, BWH Crohn's and Colitis Center
- Director, Resnek Family Center for PSC Research

# Disclosures

- Consultant

  Corevitas, Thetis, Promakhos, ClostraBio, Suono Bio

# Case #1

- 42 yo woman with a hx of Crohn's ileocolitis for 4 years
- Initially on steroids;
- Infliximab initiated 3 years ago.
  - On presentation had diarrhea and bilateral hip pain all of which resolved on infliximab.
- She has been  on infliximab at 5 mg/kg every 8 weeks.
- PMH: hyperlipidemia- on atorvastatin
- She comes in with complaints of joint pains.

- What questions for her?
- What would you do next?

# Complication

- Joint pain
  - Hips, knees, ankles
  - No GI symptoms
- Spreading of joint pains to include hands and wrists
- Physical exam normal;
  - arthralgias no arthritis
- What would you do to sort this out?

# Differential Diagnosis

- IBD –related arthropathy
- Non-inflammatory: Osteoarthritis
- Drug related
- Other- Lyme, viral

# Results

- Infliximab level of 4
- Calprotection < 16
- Rheumatoid factor negative
- ANA 1:1280
- Anti-dsDNA  positive

| | **ANA positivity (%)** |
|---|---|
| Infliximab | 46% |
| Adalimumab | 19% |
| Certolizumab pegol | 8% |

**Figures from ACCENT-II, CLASSIC-II and PRECiSE-II**

# Other Auto-Immune Diseases Provoked by Anti-TNF Agents

- Drug-induced lupus
- Psoriasis
- Alopecia areata/totalis
- Autoimmune hepatitis
- Sjogren's syndrome
- Demyelinating diseases
- Vasculitis
- IBD

# Classic DILE vs Anti-TNF DILE

| | **Classic DILE** | **Anti-TNF DILE** |
|---|---|---|
| M:F ratio | Equal | Female predominance |
| ANA | Universally positive | Universally positive |
| Anti-dsDNA | <1% | >90% |
| Anti Histone | >90% | 20-50% |
| Hypocomplementemia | Rare | Frequent |

# What next for autoimmune reaction?

- Reaction most often fully resolves
- If severe arthralgias- short term steroids
- Next therapy:  can usually wait
- If more severe: Not an anti-TNF
- If psoriasis- ustekinumab/risankizumab
  - The p40/p19 medications can be less effective for joints
- Upadacitinib is a good alternative for joints

# Case #2

- 62 yo man with a hx of occasional reflux
- c/o of more severe symptoms of burning over past 4 months
- No weight loss, 12 LB weight gain over past year
- Minor cough
- Medications:
  - omeprazole 20 mg twice a day
  - Amlodipine 10 mg daily
- What next?

# What questions to ask?

- PPI
  - How many doses are you missing per week?
  - When are you taking them?
  - Are you taking them before food?
  - How long?
    - 8 weeks for erosive
    - 4 weeks for non-erosive

# What next?

- About 20-25% will still have symptoms
- Rationale to switch to another PPI
  - Rapid metabolizer?
  - Most likely- omeprazole or esomeprazole
  - Switch to rabeprazole

- Additional
  - Famotidine for breakthrough at night
  - ? Check a pH probe

# Are you missing something?

- Gastric emptying delay?
- Partial small bowel obstruction?
- Visceral hypersensitivity?
- Bile reflux?

# Nocturnal Acid Breakthrough

- As much as 75% will have ongoing symptoms despite twice a day PPI
- Famotidine 20 mg qhs

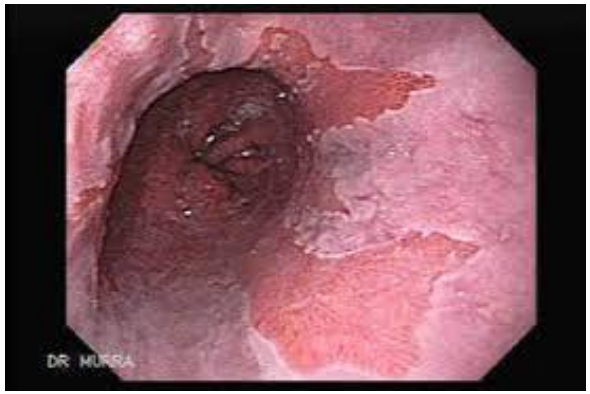
# Additional approaches

- Lifestyle measures
  - Tobacco use, coffee, chocolate, mint, fatty meals, elevate head of bed
- Bile salt reflux
  - Sucralfate
- Anti-reflux measures
  - Baclofen 5-10 mg 2 x/day before meals
- Still not improving

Mermelstein et al. Clin Exp Gastroenterol. 2018

# Further Testing

- EGD
  - Barrett's esophagus
- Bravo capsule
  - Acid reflux
- Alternative acid suppression:



# Vonoprazan

- potassium-competitive acid blocker (P-CAB)
- Advantages vs PPI
  - Faster onset of action
  - Does not require acid activation
  - Is not food dependent
  - More predictable acid suppression over 24 hours
  - Effective in CYP2C19 rapid metabolizers
    - 10mg/20 mg once a day *(Voqezna)*

# Case #3

- 74 yo woman c/o diarrhea increasing over past 2 years
  - acutely worse over past month
- 5-7 loose stools a day;
- Antibiotics for tooth extraction 8 weeks earlier
- Normal screening colonoscopy  year earlier
- No weight loss
- +tobacco 1 pack per day
- Meds:
  - HCTZ 25 mg daily
  - Levothyroxine 125 mcg daily
  - Rosuvastin 10 mg daily
  - Omeprazole 20 mg daily
  - Ibuprofen 400 mg twice a day about 5 days a week
- PE: unremarkable

# What differential?

- *C difficile*
- Inflammatory
- Medication
- Functional- IBS
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk
- Inflammatory
- Medication
- Functional- IBS
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk
- Inflammatory
  - ESR, CRP, calprotectin
- Medication
- Functional- IBS
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk
- Inflammatory
  - ESR, CRP, calprotectin
- Medication
  - Omeprazole
- Functional- IBS
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk
- Inflammatory
  - ESR, CRP, calprotectin
- Medication
  - Omeprazole
- Functional- IBS
  - Bacterial overgrowth/ SIBO
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk: C difficile neg
- Inflammatory
  - ESR, CRP, calprotectin
- Medication
  - Omeprazole
- Functional- IBS
  - Bacterial overgrowth/ SIBO
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk: C difficile neg
- Inflammatory
  - ESR, CRP, calprotectin: ESR 14; CRP 1.8
  - Calprotectin- < 27
- Medication
  - Omeprazole
- Functional- IBS
  - Bacterial overgrowth/ SIBO
- Diet
- Other

# What differential?

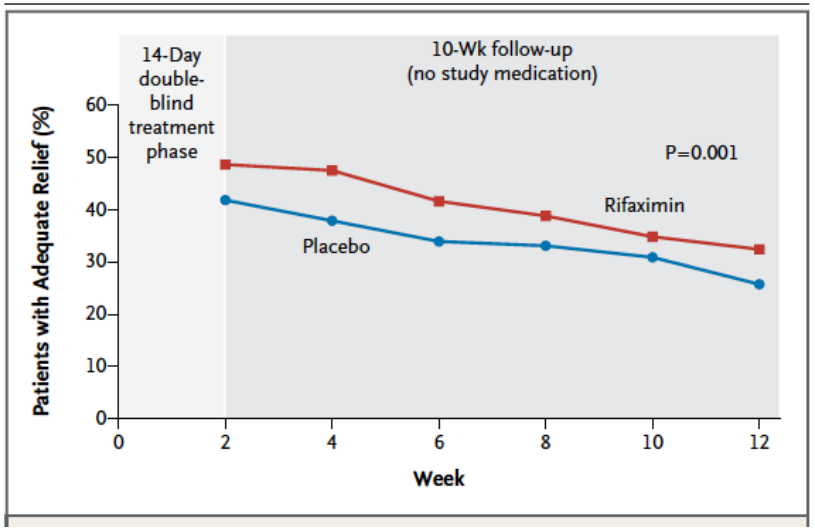
- C difficile-
  - antibiotic and PPI risk: C difficile neg
- Inflammatory
  - ESR, CRP, calprotectin: ESR 14; CRP 1.8
  - Calprotectin- < 15.6
- Medication
  - Omeprazole: trial switching to lansoprazole
- Functional- IBS
  - Bacterial overgrowth/ SIBO
- Diet
- Other

# What differential?

- C difficile-
  - antibiotic and PPI risk: C difficile neg
- Inflammatory
  - ESR, CRP, calprotectin: ESR 14; CRP 1.8
  - Calprotectin- < 15.6
- Medication
  - Omeprazole: trial switching to lansoprazole
- Functional- IBS
  - Bacterial overgrowth/ SIBO: positive
- Diet
- Other

# SIBO: Rifaximin in IBS

- Hypothesis that symptoms of IBS may result from abnormal fermentation assoc with small intestinal bowel overgrowth (SIBO)
- Prevalence by lactulose breath test of 65 % to 84% in IBS patients
- Rifaximin relieved global symptoms up to 10 weeks after discontinuation of therapy (Pimentel et al)
- Improve gas/bloating at lower dose




Combined results: 1260 patients randomized in 2 parallel studies to rifaximin 550 mg tid for 2 weeks with 10 week follow-up

NEJM, 2011

# Diet and IBS

- Exclusion of gas-producing foods
  - Underlying visceral hyperalgesia
  - Exclusion of foods that increase gas production:
    - beans, cruciferous vegetables (broccoli, cauliflower, cabbage), celery, carrots, raisins, bananas, prunes

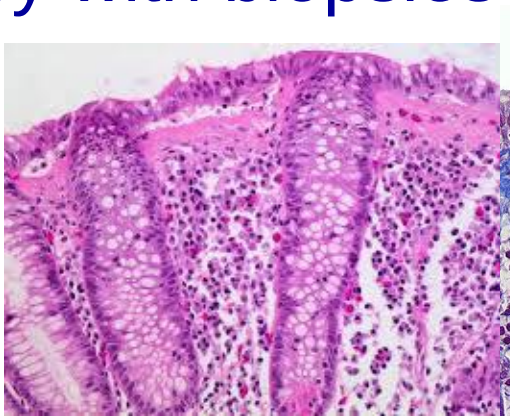
# Diet and IBS

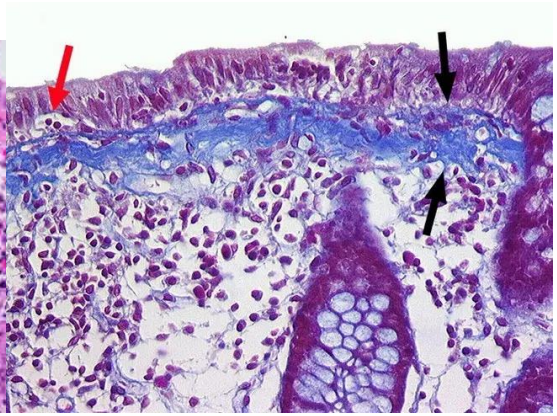
- Carbohydrate malabsorption – “FODMAP’s”
  - **F**ermentable
  - **O**ligosaccharides
  - **D**isaccharides
  - **M**onosaccharides
  - **A**nd
  - **P**olyols
- May lead to Sx of IBS, increased intestinal permeability and possibly inflammation

- **O**ligosaccharides
  - Fructans (wheat, onions, artichokes)
  - Galactans (legumes, cabbage, and brussel sprouts)
- **D**isaccharides
  - Lactose (dairy)
- **M**onosaccharides
  - Fructose (honey, watermelon, high fructose corn syrup)
- **P**olyols (sugar alcohols)
  - Sorbitol (chewing gum)
  - Xylitol
  - Mannitol

- Some studies restricting FODMAP's have suggested benefit
- Consider trial of low FODMAP's diet

- No improvement
  - What now?!
- Second opinion:
  - Screening colonoscopy negative
  - No biopsies taken
  - Repeat colonoscopy with biopsies
- Collagenous colitis





# Microscopic Colitis

- Collagenous (1976) and Lymphocytic Colitis (1989)
  - Chronic watery diarrhea
  - Normal endoscopic appearance (or nearly normal)
  - Normal radiologic studies
- Histologic evidence of chronic inflammation
  - Collagenous colitis: increased subepithelial collagen deposition
  - Lymphocytic colitis: differs from IBD, infectious colitis

Distinct entities vs spectrum of single disorder ?

# Epidemiology

- “Middle-age” onset
- 6th to 7th decade
  - 25% before age of 25
  - Described in children
- Female preponderance ?
  - Review of all published cases of microscopic colitis: no gender difference
- Risk factors:
  - Smoking
  - NSAIDs
  - Genetic link: few familial cases

# Response To Therapy

| | Lymphocytic N = 170[1] | Lymphocytic N = 199[2] | Collagenous N = 163[3] |
|---|---|---|---|
| antidiarrheal | 73% | 70% | 71% |
| bismuth | 73% | | |
| sulfasalazine | 42% | 21% | 34% |
| mesalamine | 45% | 50% | 50% |
| Bile binders | 42% | 57% | 59% |
| Steroids /budesonide | 65% | 88% | 82% |
| AZA/6-MP | 20% | | |
| methotrexate | | | 84%[4] |

1) Pardi et al, Am J Gastro, 2002;14:2829-33; 2) Oleson et al, Gut 2004;53:536-541 3) Bohr et al, Gut 1996; 39, 846-851 4) Riddell, J Gastro Hep, 2007

# Case #4

- 27 yo man with a 1 yr hx of left-sided UC
- At diagnosis:
  - prednisone and then mesalamine initiated.
- Did well for 8 months
- No other medications
- Worsening urgency and bloody diarrhea-
  - 12+ stools/day
- PE: normal
- Labs: wbc 8.7 hct 44  CRP 1.7

# Next steps?

- Differential diagnosis:
  - Infection
  - C difficile
- Other?
- Check a calprotectin
  - 1724 calpro
- Start steroids
  - Prednisone 40 mg daily
  - With 2000iu vit D3 and calcium

# Therapeutic Choices

**UC**

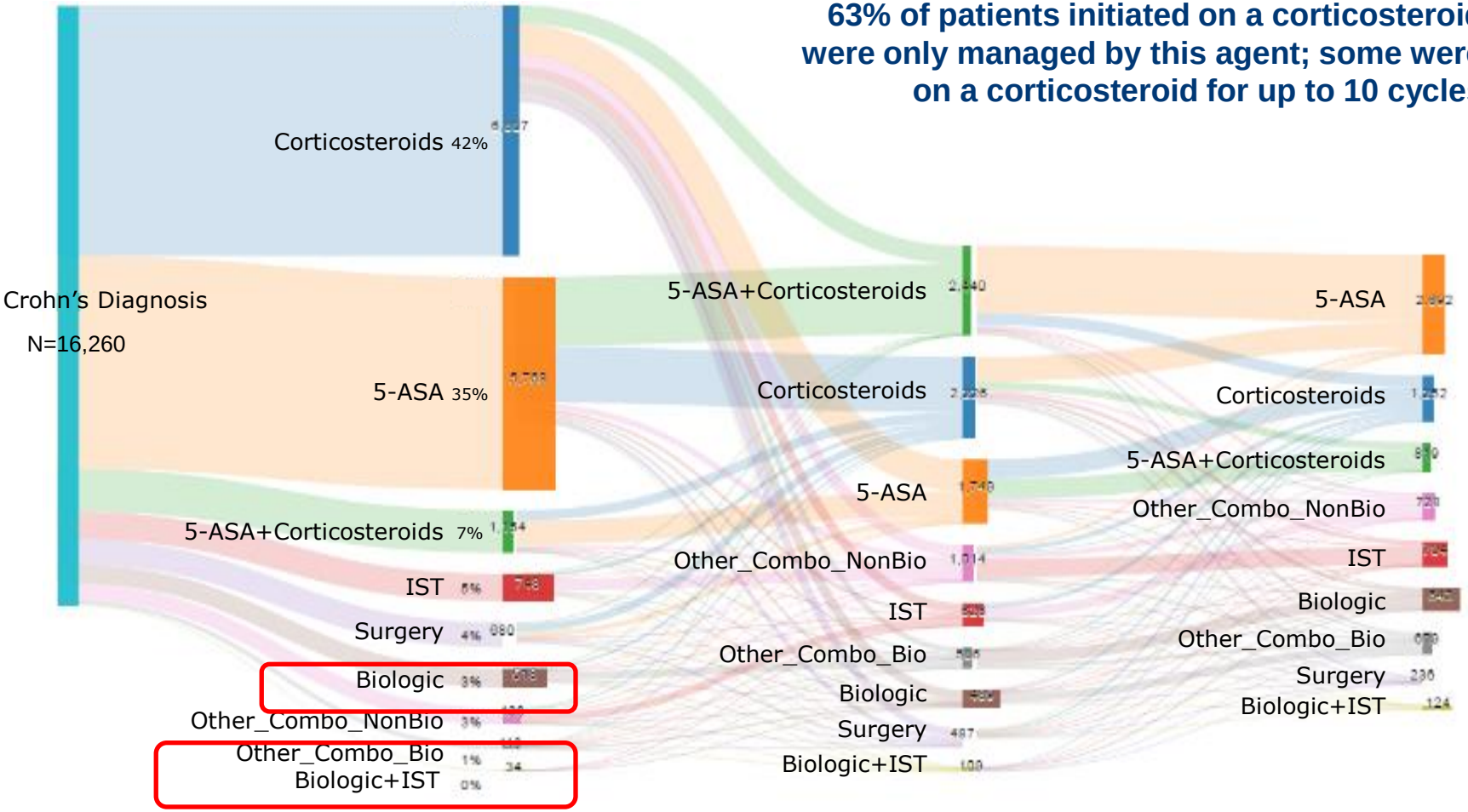
- TNFi
- vedolizumab
- ustekinumab
- risankizumab
- guselkimab
- tofacitinib
- upadacitinib
- 6-MP/aza
- ~~steroids~~

**CD**

- TNFi
- vedolizumab
- ustekinumab
- risankizumab
- 6-MP/aza
- MTX
- ~~steroids~~

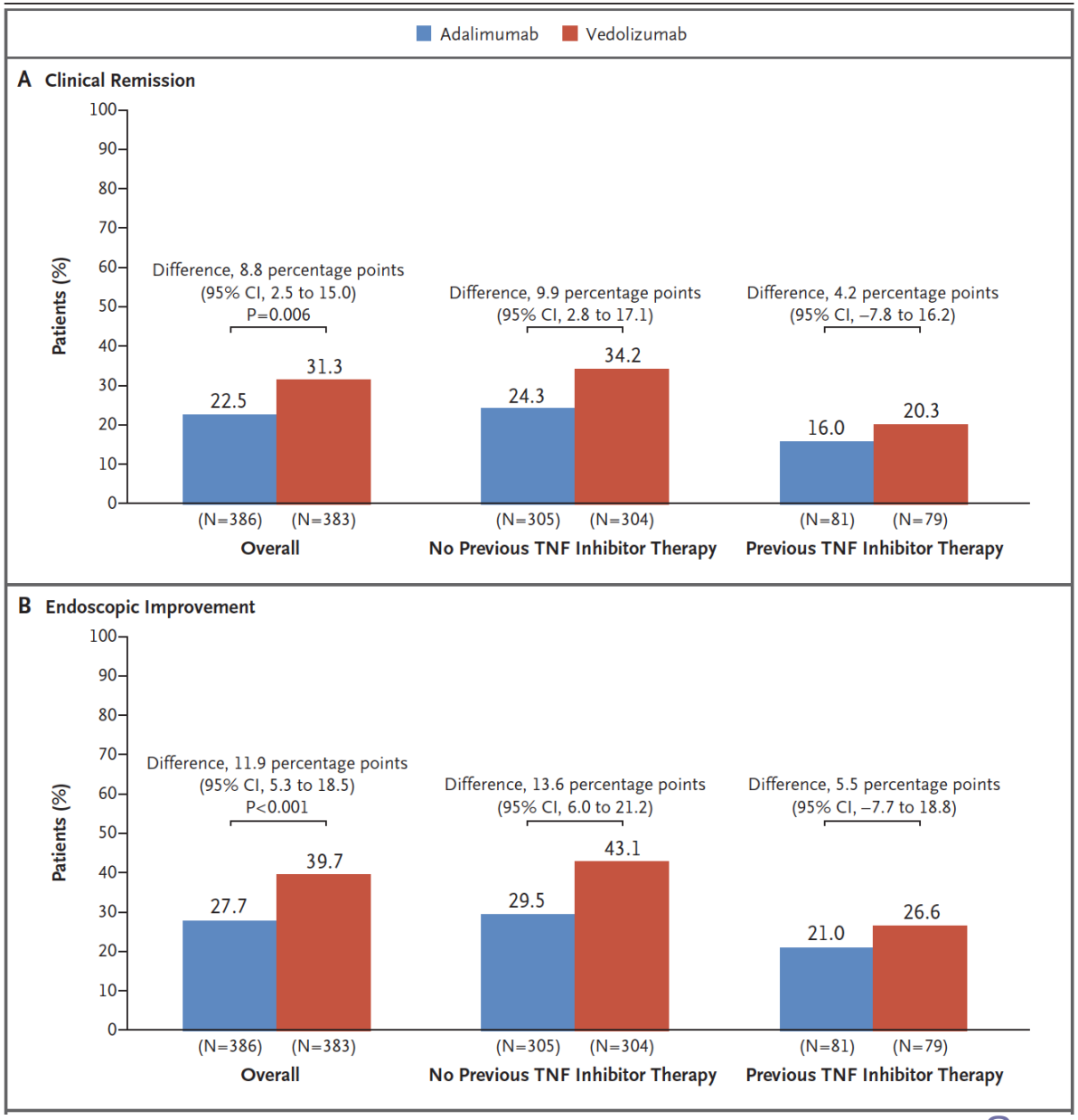
# Selection of therapy in US is not guided by best data

**63% of patients initiated on a corticosteroid were only managed by this agent; some were on a corticosteroid for up to 10 cycles**




Siegel CA, et al. ECCO, Barcelona, February 2017

# VARSITY: VEDOLIZUMAB VS ADALIMUMAB FOR UC




Sands, NEJM, 201

# What next?

- Improves partially
  - Still 8x/day
- Discontinue mesalamine
  - Much improved
- Reluctant to go on to a biologic
  - Tries curcumin
  - Transient improvement
- Much worse
  - Hospitalized

# Inpatient

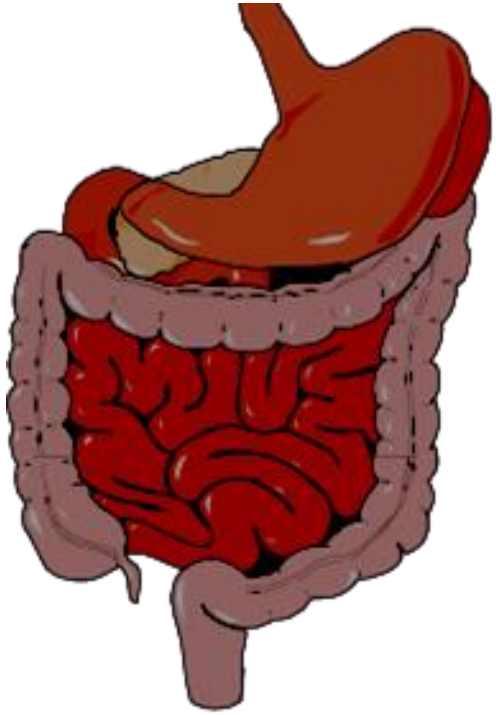
- Refuses steroids
- Trial upadacitinib
  - Rapid response
  - Monitor lipids, CPK, CBC, LFT

# Case #5

- 44 yo woman with a 7 year history of constipation
- Had a colonoscopy 3 years ago;
- Osteoarthritis, hx breast cancer 8 years ago with successful treatment, MI – 6 years ago
- Meds:
  - ibuprofen 600 mg 2-3 times daily
  - Atorvastatin
  - Metoprolol
  - Aspirin
  - Methylcellulose fiber
- PE: normal

# Causes of Secondary Constipation[1,2]

**Medications**
- Antacids
- Opioids
- NSAIDs
- Antihypertensives
- Anticholinergics
- Iron salts
- Calcium channel blockers
- Others



**Medical causes**
- Neurologic conditions
- Metabolic disorders
- End-stage renal disease[1]
- Painful perianal disease
  - Hemorrhoids
  - Anal fissures

**Constipation further compromises QOL for these patients**

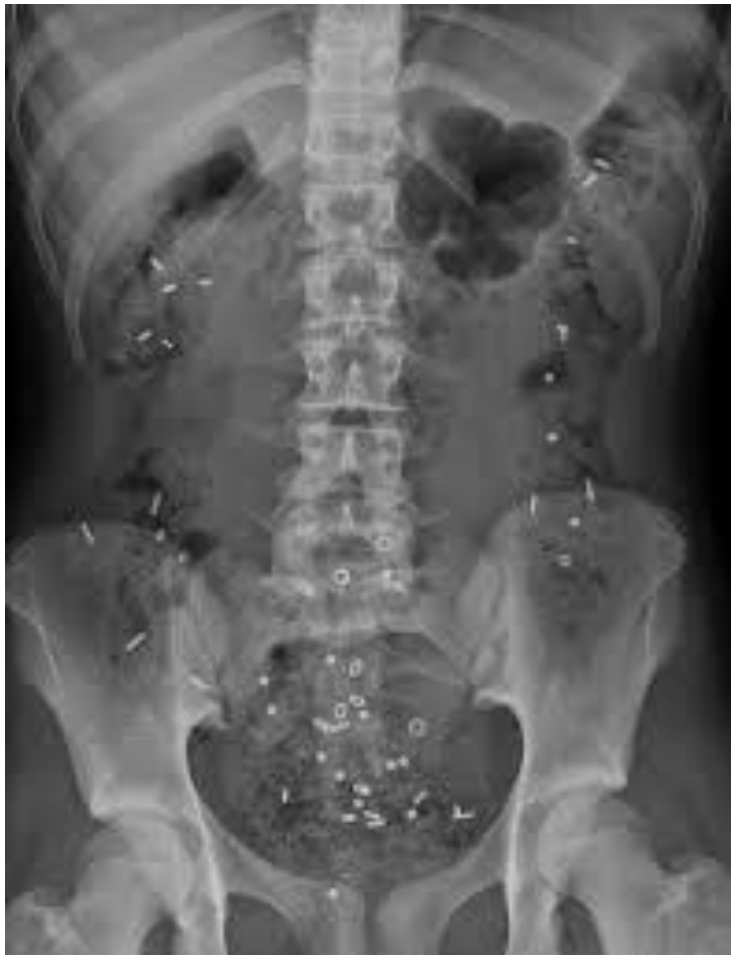
# Diagnostic Assessment of Chronic Constipation

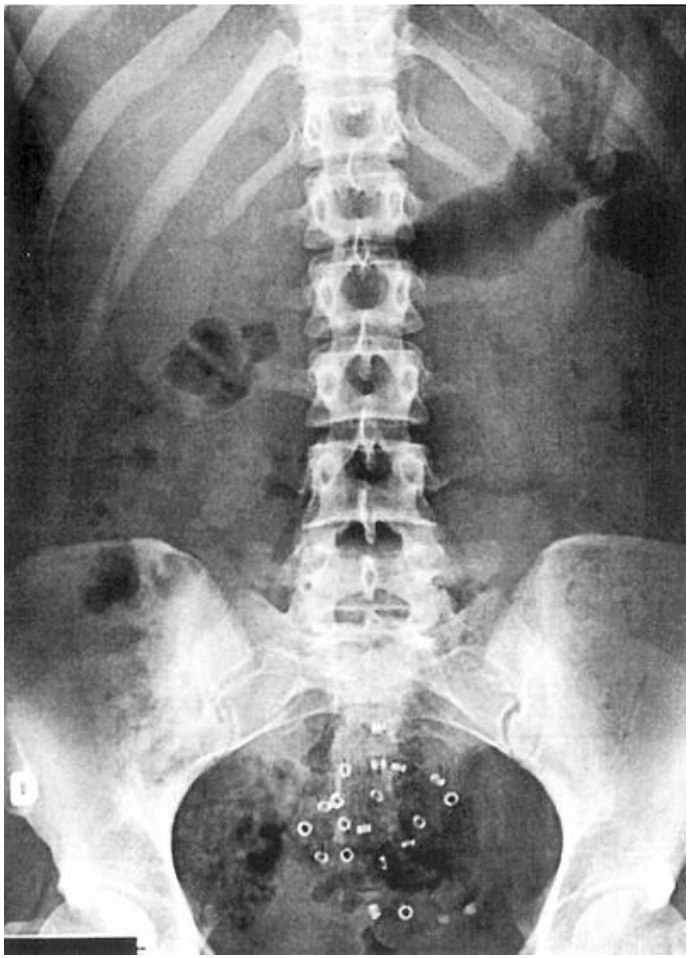
| Routine workup | |
|---|---|
| Patient history | Nature of symptoms, duration and characteristics, laxative use, family history of bowel disturbance, assessment of emotional distress or affective disorders |
| Physical examination | Abdominal examination, anorectal and perianal examination, assessment of neurologic function |
| Laboratory tests | Glucose, electrolytes including calcium, thyroid function tests |
| Rule out obstruction | Sigmoidoscopy, colonoscopy |
| Specialized testing as needed | Barium enema, colonic transit time, anorectal manometry, balloon expulsion, and barium defecography |

# Evaluation

- Labs: calcium, thyroid, electrolytes, CMP all normal
- Given PEG 3350 (Miralax) with modest response
- Linaclotide tried with mild benefit?
- What next:
  - Repeat colonoscopy?
  - CT scan?
  - Sitz marker study?
  - Medication?

# Sitz marker





# Anorectal manometry

- Unable to expel balloon
- Pelvic floor dysfunction
- Pelvic floor physical therapy

Hedrick, Constipation and Pelvic Outlet Obstruction, 2013

# References


- 1) Subramanian S, Yajnik V, Sands BE, Cullen G, Korzenik JR. Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent. *Inflamm Bowel Dis. 2011;17(1):99-104.*
- 2) Mermelstein J, Chait Mermelstein A, Chait MM. Proton pump inhibitor-refractory gastroesophageal reflux disease: challenges and solutions. *Clin Exp Gastroenterol. 2018;11:119-134.*
- *3)* Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med. 2011;364(1):22-32.*
- *4)* Olesen M, Eriksson S, Bohr J, Järnerot G, Tysk C. Lymphocytic colitis: a retrospective clinical study of 199 Swedish patients. *Gut. 2004;53(4):536-541.*
- *5)* Hedrick TL, Friel CM. Constipation and pelvic outlet obstruction. *Gastroenterol Clin North Am. 2013;42(4):863-876.*