Diseases of the Colon: IBS & IBD

Primary Care Internal Medicine
2015

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Case #1

- **48 yo woman with a hx of fibromyalgia has been having non-bloody diarrhea alternating with constipation for 9 months. She has had a 6 lb. weight loss. Your initial recommendation is:**

a) A trial of a lactose free diet

b) A trial of prednisone

c) Increase in fiber

d) A colonoscopy

Principles of Care

- Pathophysiology not well understood
- Positive diagnosis
- Symptomatic treatment
- Several distinct subgroups of disease
- More specific therapies available for subgroups
  - Constipation predominant
    - Lubiprostone
    - Linoclotide
  - Bacterial overgrowth
  - Bile salt diarrhea

IBS Definition- Rome III Criteria

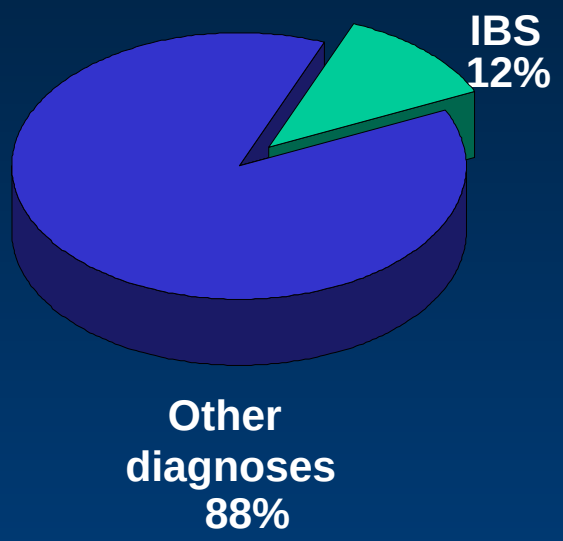
- Absence of structural or metabolic abnormalities to explain symptoms:
- Recurrent **abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with *two or more* of the following:
    - relief with defecation and/or
    - association with change in frequency of stool and/or
    - association with change in form (appearance) of stool

IBS Definition- Supportive Symptoms Diarrhea-Predominant

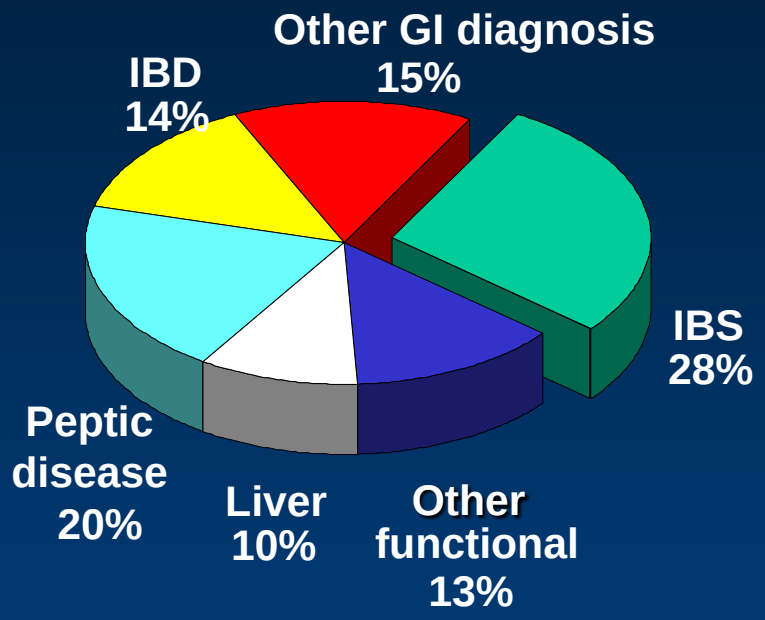
- more than 3 bowel movement per day
- loose (mushy) or watery stools
- urgency (having to rush to have a bowel movement)
- passing mucus (white material during bowel movement)
- abdominal fullness, bloating, or swelling

IBS Health Care Burden

Primary Care



Gastroenterology practice



- Most common diagnosis made by gastroenterologists
- Estimated $8 billion direct medical costs, $25 indirect costs annually in US
- 9 to 22% of US population afflicted but only 25% seek medical attention

Mitchell & Drossman, 1987

IBS Social Impact

- Impact on social function similar to depression
- Absenteeism (school or work) nearly twice the healthy population:
  - (32 days vs. 18 days)
- Mean number of visits a PCP in previous 12 months for non-GI issues:
  - 3.88 vs 1.7

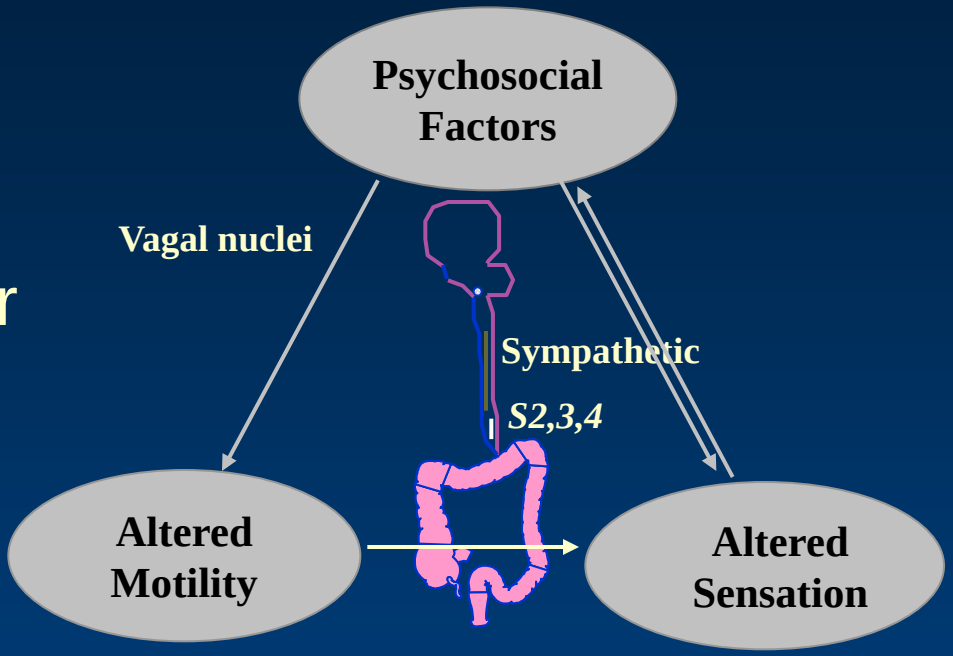
Lembo, Practical Gastro, 2007

IBS-Epidemiology

- Those that seek care are more likely to have behavioral or psychiatric problems
  - have an increased risk for other functional disorders- non-cardiac chest pain, fibromyalgia, interstitial cystitis
  - higher prevalence of physical, emotional, sexual abuse in IBS patient population
    - not causal, felt to be an associaiton
- female to male: 3 to 1 ratio

Irritable Bowel Syndrome

- Biopsychosocial Disorder
  - Psychosocial
  - Motility
  - Sensory
  - ? Infectious
- Disturbs QOL, Social Function, Healthcare Utilization

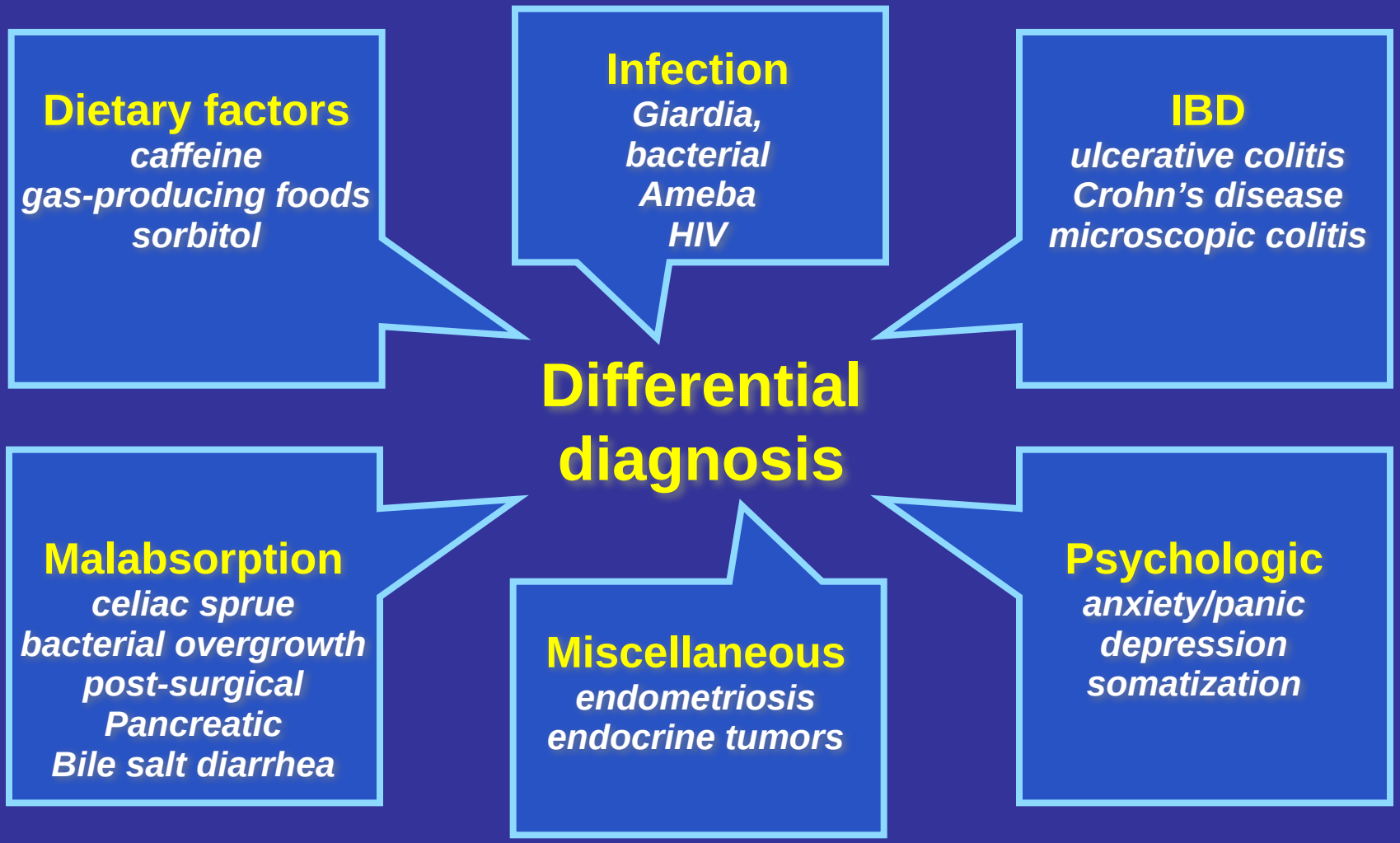


IBS: A role for microbiota?

- Illness often occurs after a GI infection
  - Antibiotic use increases risk of PI-IBS
- Role of small intestinal bacterial overgrowth (SIBO) remains controversial
  - Breath tests not fully validated
  - Studies of small bowel microbiome difficult and most have not identified a distinct change in IBS patients
- Studies of colonic microbiome have identified numerous changes in IBS but few consistent findings
  - Less *lactobacilli*
  - Less *bifidobacteria*
- Microbiome may alter gut neuromotor sensory function, gut barrier function, or brain-gut axis

Simren et al, BML, 2013

Differential Diagnosis of IBS



IBS: differential/Subtypes

- Microscopic colitis
- Bacterial overgrowth
- Dietary intolerance
- Bile salt diarrhea
- Post-infectious
- Diarrhea predominant
- Constipation predominant

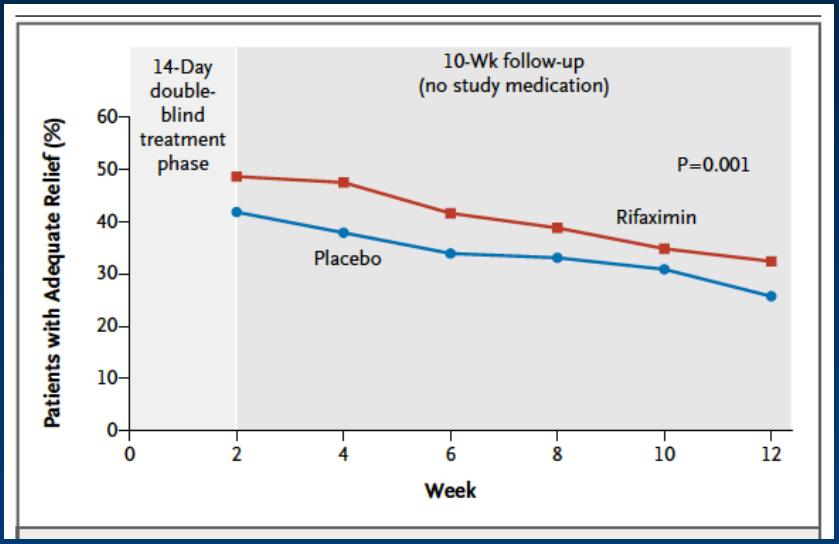
Microscopic Colitis

- 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 ?

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

Postinfectious IBS (PI IBS)

- 90 % of people recover spontaneously following a bout of enteritis
- 10 % develop PI IBS
- Overall incidence of 4% to 36% of new onset IBS after an acute enteritis.
- Symptoms can persist for years (6 years)
- Risk factors: Women, patients with anxiety, depression, severe or prolonged symptoms of gastroenteritis, absence of vomiting.
- Salmonella infection results in the highest incidence approx 10%; other pathogens include Campylobacter, E Coli, Giardia, Shigella

FODMAP Diet

- Poorly absorbed short-chain carbohydratesFermentable, Oligo-, Di, Mono-saccharides and Fermentable, Polyols
  - Mannitol, sorbitol,
  - Fructans, galactans
- Results in increased gas, bloating and discomfort
- Dietary modifications can impact symptoms

Stool Form Correlates to Intestinal Transit Time

THE BRISTOL STOOL FORM SCALE

SLOW TRANSIT

FAST TRANSIT

Type 1		Separate hard lumps, like nuts
Type 2		Sausage-like but lumpy
Type 3		Like a sausage but with cracks in the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces

Lewis SJ, Heaton KW. *Scand J Gastroenterol*. 1997;32:920-924.
Heaton KW, O'Donnell LJ. *J Clin Gastroenterol*. 1994;19:28-30.

Diarrhea

Essential Evaluation

- history, physical exam, screening labs
- stool studies:
  - occult blood,
  - fecal leukocytes-
    - Fecal calprotectin
    - Fecal lactoferrin
  - Infection ? (likely not and low yield)
    - culture
    - ova and parasites,
    - *C difficile* toxin
    - Giardia
  - 20 to 40% of acute diarrhea still remains undiagnosed

Diarrhea Evaluation

- Gastrointestinal Imaging
  - CTE or MRE (enterography) Crohn's is suspected
    - small bowel series nearly obsolete
- Colonoscopy with biopsies
  - Microscopic colitis
    - Collagenous colitis
    - Lymphocytic colitis
- Glucose/hydrogen Breath testing
  - Bacterial Overgrowth

Make a positive diagnosis[1,2]

References: 1. Paterson et al. *Can Med Assoc J*. July 1999;161:154-160. **2.** American Gastroenterological Association. *Gastroenterology*. June 1997;112:2120-2137.

What is to be done?

- Diet evaluation
  - Lactose free diet?
  - FODMAP diet?
  - Gluten free?
  - Food allergy
- Medications
  - Fiber
  - Anticholinergics
  - Low dose tricyclics

Medical Treatment

- Loperamide- antidiarrheal
  - helpful for diarrhea
  - inconclusive for abdominal pain and distention
- Psychotropic Agents- tricyclics, SSRIs
  - shows some benefit in overall symptoms and impact of psychiatric disturbance is unclear
  - TCAs: constipating SSRIs: diarrhea
  - amitryptyline high quality study showed only a trend towards global improvement, not individual symptoms

Case #2

- 21 yo man with a hx of increasing constipation over the past 6 months with minor left sided abdominal pain. No blood, weight loss. Normal labs. Has tried increasing fiber intake without success.

Your next step should be:

a) Colonoscopy

b) Abdominal CT scan

c) Abdominal MR

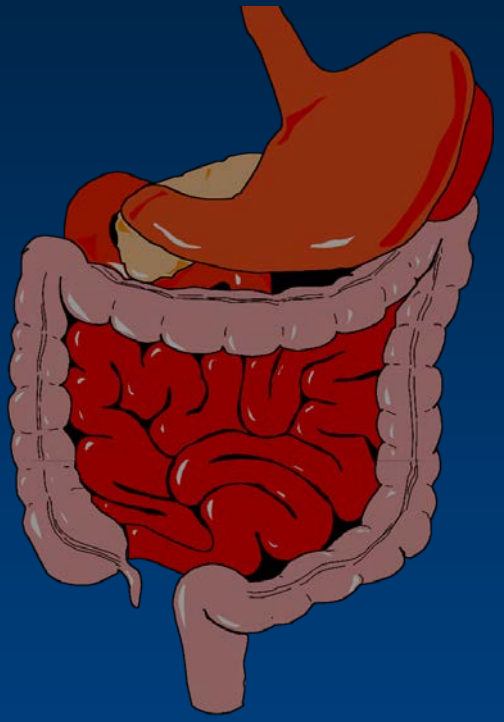
d) A trial of a medication:

   1) Lubiprostone

   2) linaclotide

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

NSAIDs = Nonsteroidal anti-inflammatory drugs; QOL = Quality of life.

1. St Peter WL, et al. *Drugs Aging*. 1998;12:441-459.
2. Wald A. *Rev Gastroenterol Disord*. 2004;4(suppl 2):S28-S33.

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

American College of Gastroenterology Chronic Constipation Task Force. *Am J Gastroenterol*. 2005;100(suppl 1):S1-S4.

Traditional Treatment Options

Lifestyle modification	Targeted mechanism	Efficacy
Increase fluid intake	Increase stool volume by augmenting luminal fluid	Limited; majority of fluid is absorbed before reaching the colon and is expelled via urine[1]
Increase exercise	Improve motility by decreasing transit time through the GI tract	Moderate; some evidence suggests this is beneficial; however, not sufficient to treat[2]
Increase dietary fiber	Increase water and bulk stool volume	Limited benefit compared with placebo[3]

1. Chung BD, et al. *J Clin Gastroenterol*. 1999;28:29-32.
2. Dukas L, et al. *Am J Gastroenterol.* 2003;98:1790-1796.
3. American College of Gastroenterology Chronic Constipation Task Force. *Am J Gastroenterol*. 2005;100(suppl 1):S1-S4.

Lubiprostone: Chloride Channels

New kid on the block:

Linaclotide (Linzess)

Guanylate cyclase-C agonist

Indication: IBS-C, chronic idiopathic constipation

57% to 63% of lubiprostone (Amitiza) treated subjects achieved spontaneous bowel movement within 24 hours

Adapted from Cuppoletti J, et al. *Am J Physiol Cell Physiol*. 2004;287:C1173-C1183.

IBS: Medical Therapy Probiotics?

- Mixed results
- Different probiotic(s)/prebiotics
- Different methodologies (28 RTCs)
  - Bifidobacterium infantis 35624
    - Several studies (n= 75[1] and n= 362[2])
      - reduced pain and composite score
- Pediatric studies
  - Ramnosis GG
    - Several studies (n= 50[3], 104, 141)
      - Decreased pain (2 studies)
      - Decreased abdominal distention (1 study)

1) O'Mahoney, Gastro, 2005. 2) Whorwell, Am J Gastro, 2006. 3)Bausserman, J Pediatr, 2005. 4) Gawronska, Aliment Pharm Ther, 2007. 5) Francavilla, Pediatrics, 2010

Current management components of IBS

- Education
- Reassurance (establish a positive diagnosis)
- Dietary modification
- Fiber
- Symptomatic treatment
- Psychological/behavioral options
- Realistic goals

Reference: Drossman. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.

When to Refer to Gastroenterologists

- Alarm symptoms: weight loss, rectal bleeding
- Symptoms not responding to initial therapeutic trial e.g. failure of constipation to respond to fiber may suggest presence of an evacuation disorder or slow transit constipation
- Patient's usual symptoms "change”
  - marked worsening of diarrhea, constipation or pain,
  - especially if associated with alarm symptoms, or abnormal screening blood tests
  - colon has not been imaged for >2 years

Take home points: IBS

- IBS is a positive diagnosis
- Be aware of red flags
- Evolving therapy:
  - Tricyclics, antibiotics, etc
- Don’t forget other causes:
  - Lactose intolerance
  - Medications
  - IBD

Case #3

- 29 yo woman with intermittent diarrhea for 3 months, fatigue and RLQ discomfort and an episode of abdominal pain with vomiting and distention.
- Next best step:
  A) Colonoscopy
  B) Abdominal CT
  C) Abdominal MRE
  D) A trial of mesalamine

Common Symptoms of Inflammatory Bowel Disease

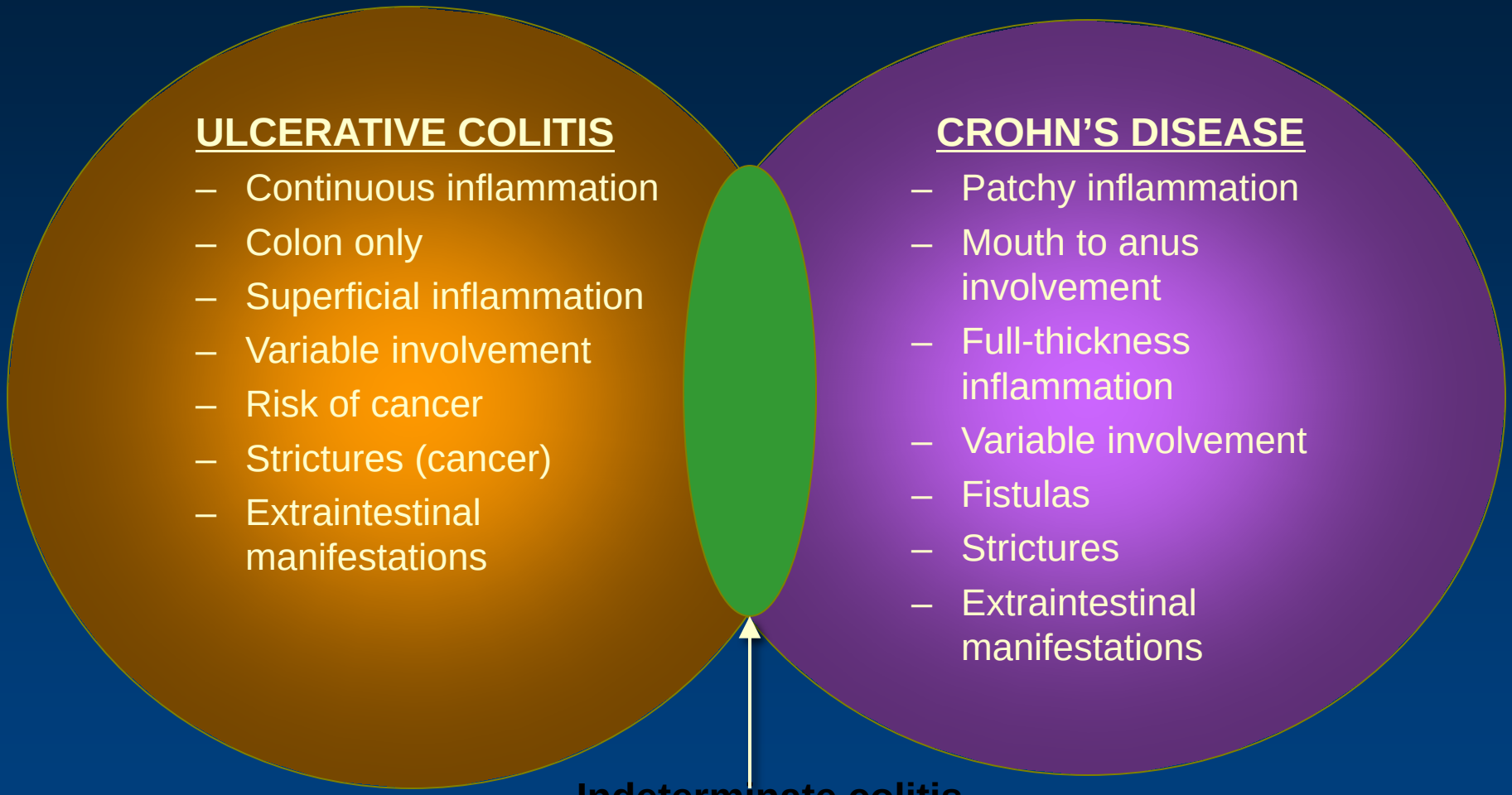
- Diarrhea
- Abdominal pain and tenderness
- Loss of appetite and weight
- Fever
- Fatigue
- Rectal bleeding and anal ulcers
- Fistulae (Crohn’s)
- Stunted growth in children

Principles of Care

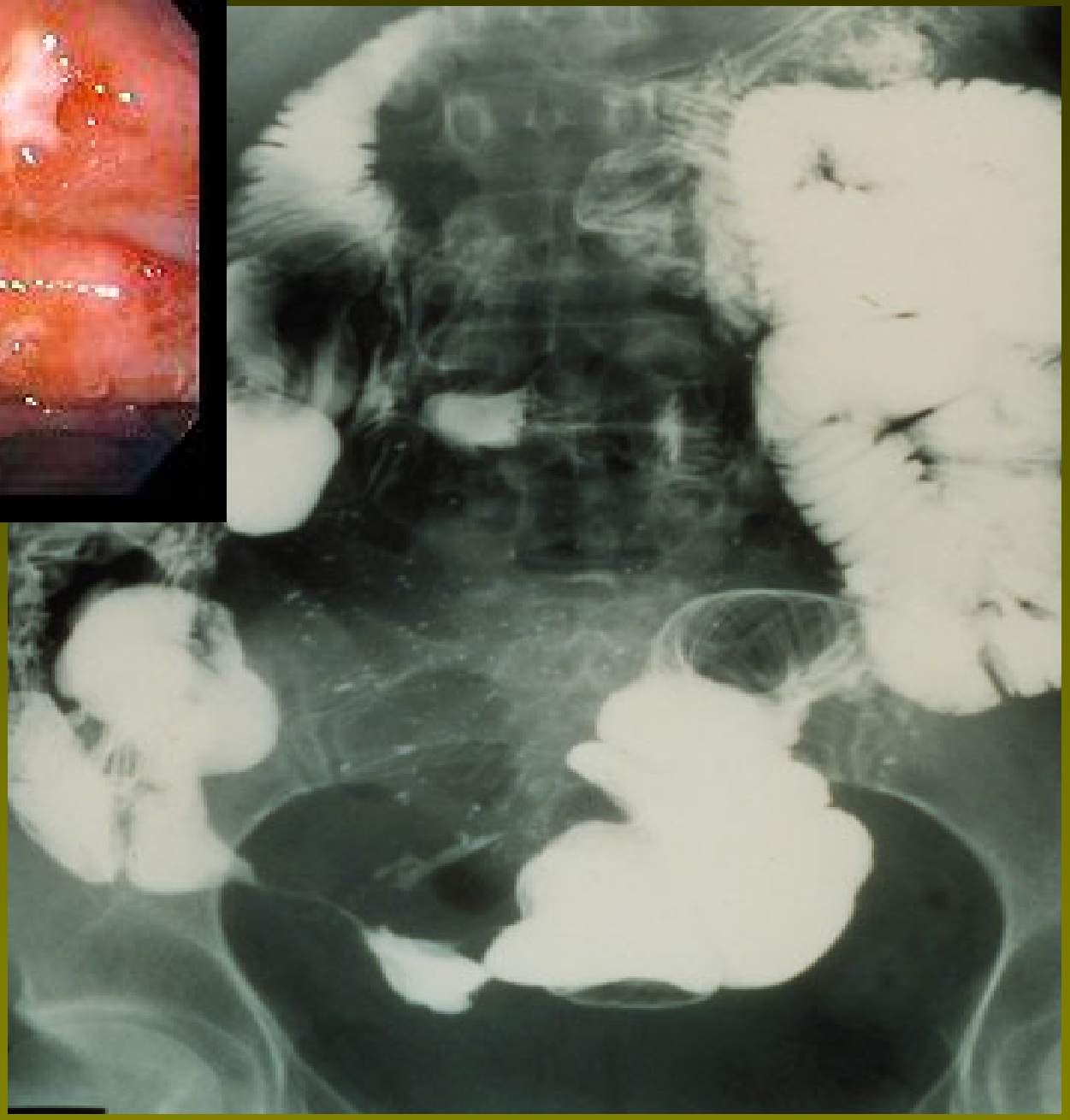
- Minimize steroid use
- Aim for mucosal healing
- Take advantage of increasing options for therapy
  - *Therapeutic drug monitoring*
- Complex care with broad set of maintenance measures
- Careful monitoring for response and adverse events

The Spectrum of IBD

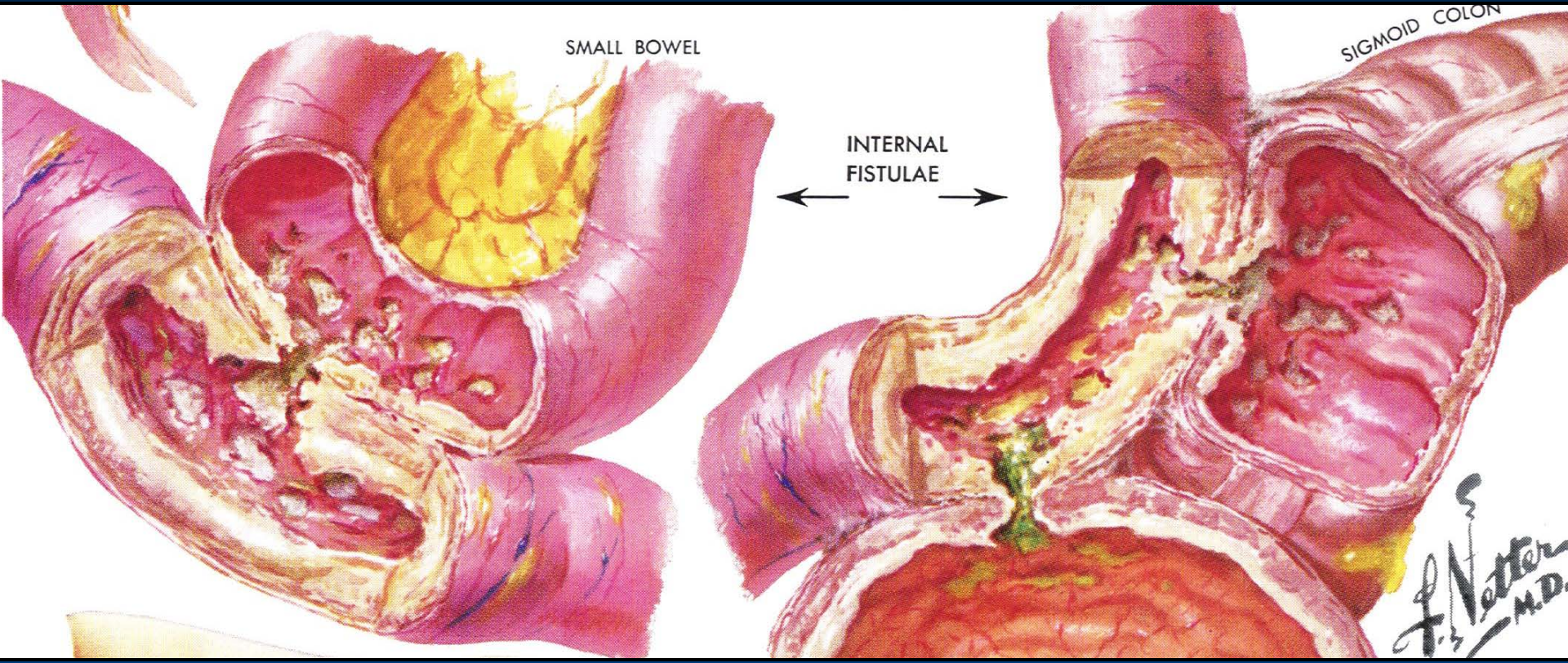
1-2 Million Americans



Ulcerative Colitis



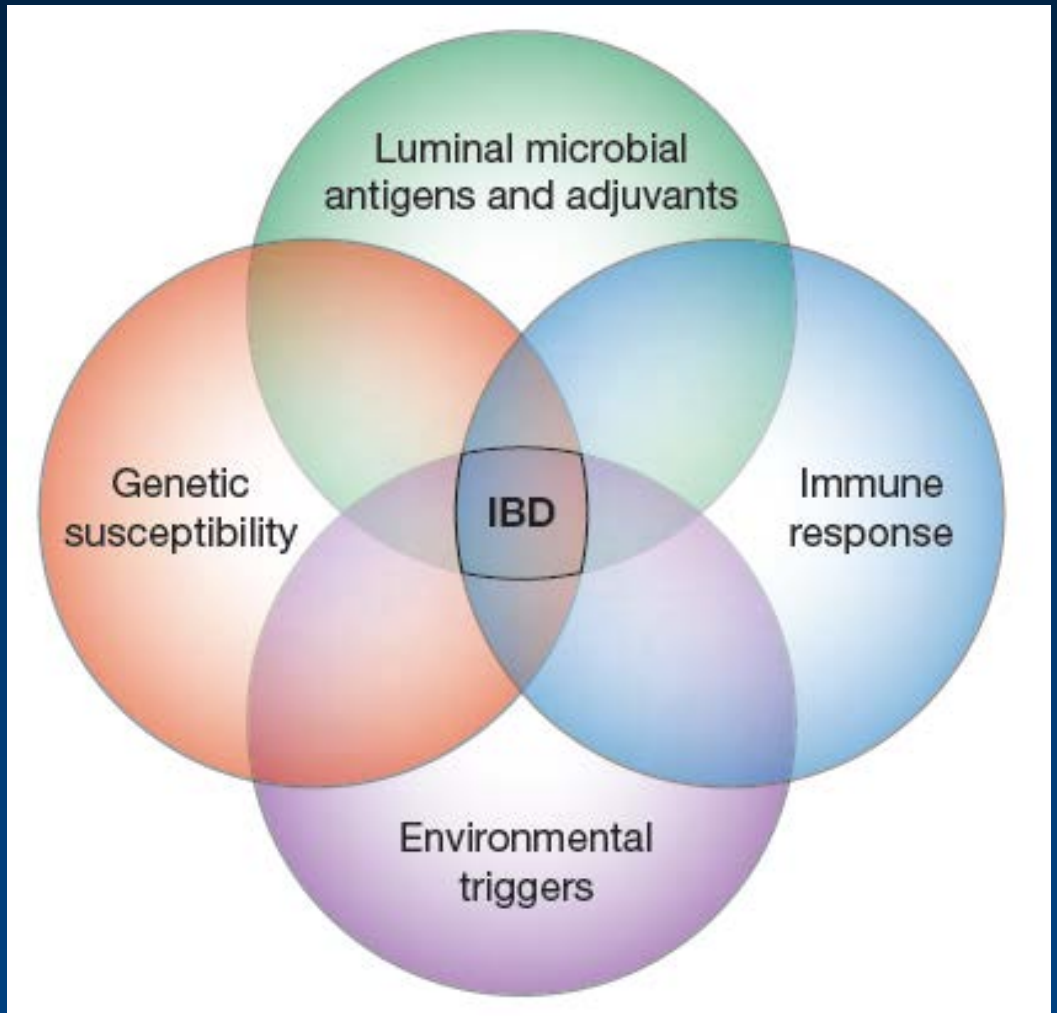
Crohn's Disease: Clinical Features



Internal Fistulae

Etiology of IBD

- Complex Disease.
- Combination of:
  - Genetics
  - Environmental Factors
  - Gut Bacteria
  - Abnormal Immune Response



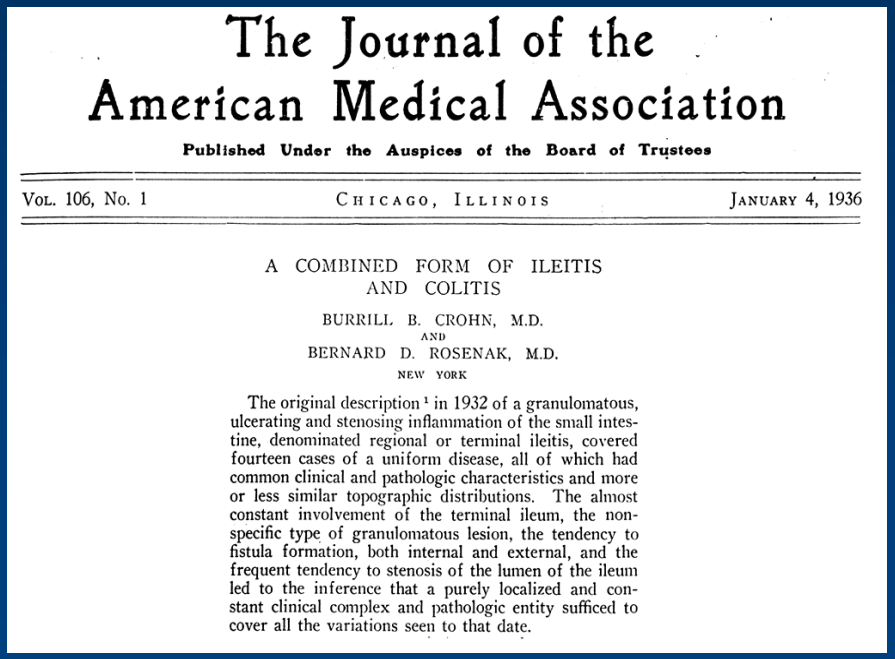
JULY 2006 VOL 3 NO 7 SARTOR NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY

Diseases of Modern Times

Ulcerative colitis

Early description:

Wilks 1875



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A COMBINED FORM OF ILEITIS AND COLITIS

BURRILL B. CROHN, M.D.
AND
BERNARD D. ROSENAK, M.D.
NEW YORK

The original description [1] in 1932 of a granulomatous, ulcerating and stenosing inflammation of the small intestine, denominated regional or terminal ileitis, covered fourteen cases of a uniform disease, all of which had common clinical and pathologic characteristics and more or less similar topographic distributions. The almost constant involvement of the terminal ileum, the nonspecific type of granulomatous lesion, the tendency to fistula formation, both internal and external, and the frequent tendency to stenosis of the lumen of the ileum led to the inference that a purely localized and constant clinical complex and pathologic entity sufficed to cover all the variations seen to that date.

Burrill B Crohn, M.D.

Crohn's disease

First described:

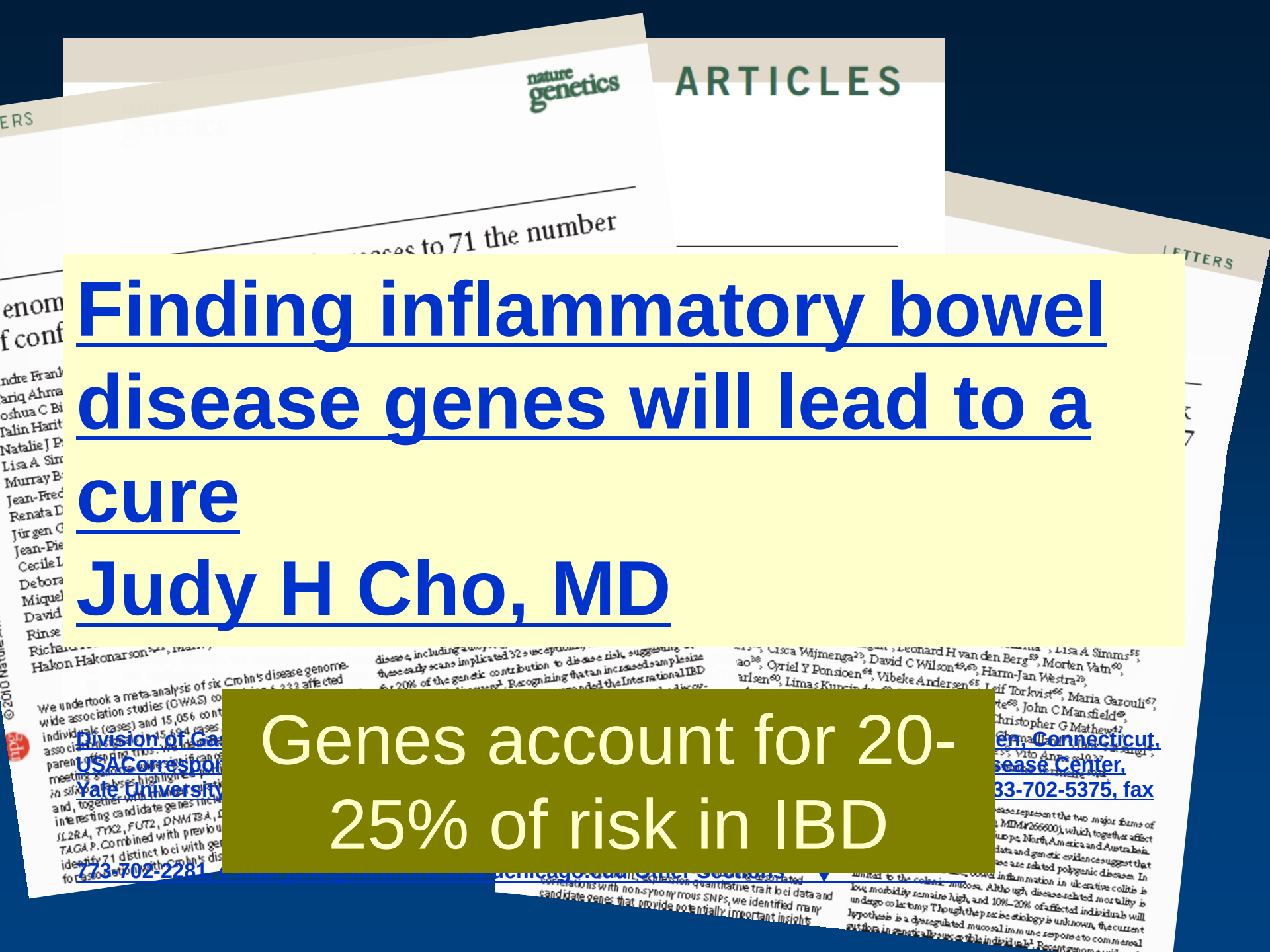
Dr T.K. Dalziel 1913

Genetic Factors

Finding inflammatory bowel disease genes will lead to a cure

Judy H Cho, MD

Genes account for 20-25% of risk in IBD



2015

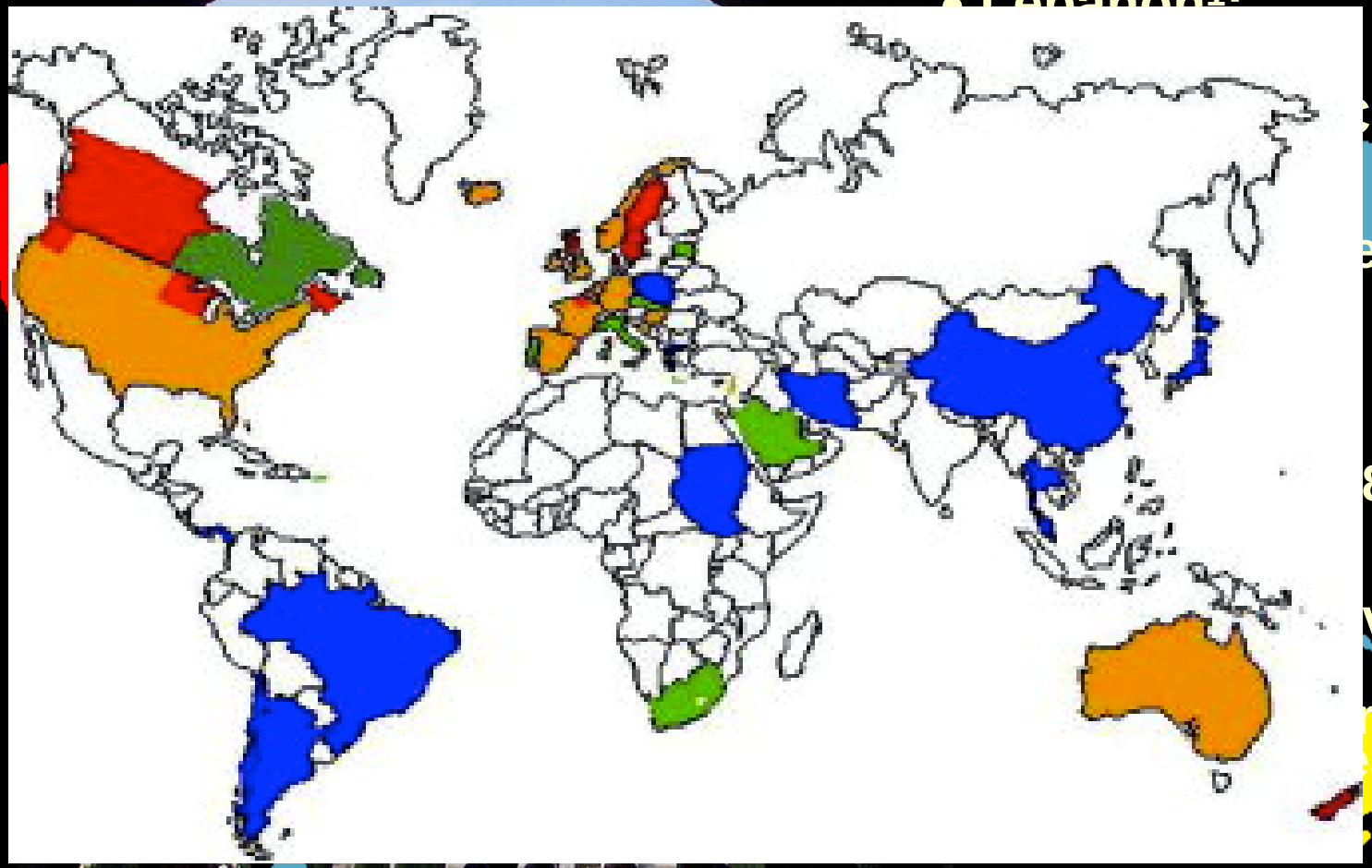
Risk Factors

- Appendectomy
- Smoking and IBD
- Breast feeding[1]:
- Hygiene hypothesis[2,3]:
- Gastrointestinal infections (discordant twins)[4:]
- Antibiotic use 2-5 years prior to diagnosis[5]
- NSAID use
- Diet

1) Klement, Am J Clin Nutr,2005 2) Amre, AJG, 2007 3) Bernstein, AJG,2007
4) Halvarson IBD 2006 5)Card,GUT, 2004

Globalization of IBD

- UC enters a population 40 years before CD?
- Lebanon[1]:



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1) Abdul-baki IBD 2006 2) Park, IBD 2007 3) Indian J Peds 2006 4) Yao, Dis Col Rectum 2000

1930-1960's

Psychosomatic Hypothesis (UC)

- "Well-marked time relationship between ..emotional disturbance and symptoms."

  -- Murray, Am J Med Sci,1930

- UC patients "couldn't cope, giving up." "Diarrhea is substituted for real accomplishment." "..childish, dependent personality"

- "Degree of difference so gross as to make a control group unnecessary."

  -- Wittkower, BMJ, 1938

1930-1960's

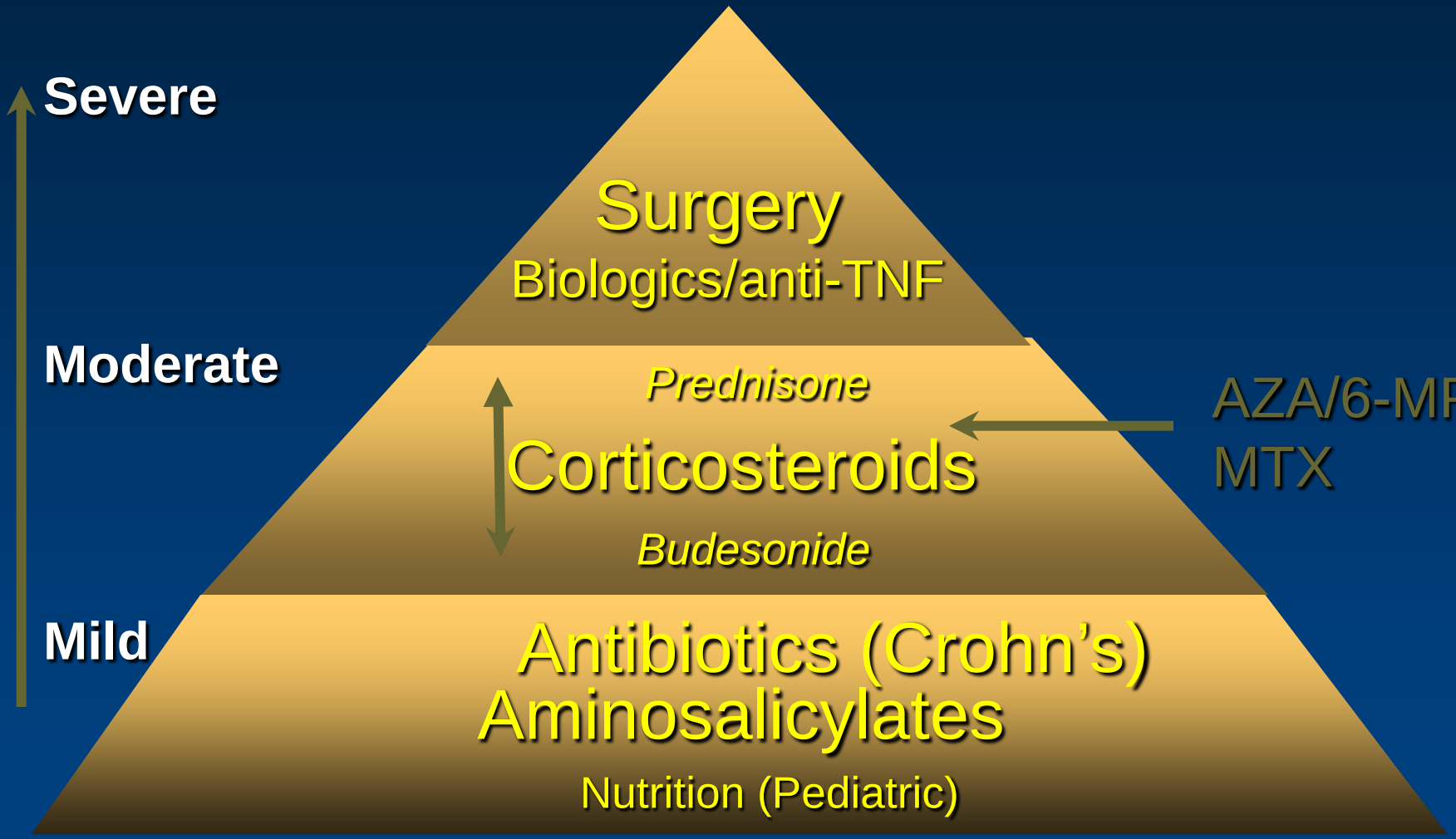
"Stress Reduction Therapy"

- Institutionalization
- Psychotherapy
- Prefrontal lobotomy "to counteract the neurotic focus"

Case #4

- **43 yo man with a 4 year hx of Crohn's ileitis has been on steroids for 3 months and tried taper once before without success. Now down to 15 mg of prednisone and having pain and diarrhea.**
- **The best next step is:**
  - **A) Colonoscopy**
  - **B) Increase prednisone to 60 mg**
  - **C) Start Pentasa**
  - **D) Start an anti-TNF agent**

Current Approach to Therapy for Inflammatory Bowel Disease



5-ASA Release Sites

sulfasalazine
Azulfidine
Dipentum
Colazal
Lialda

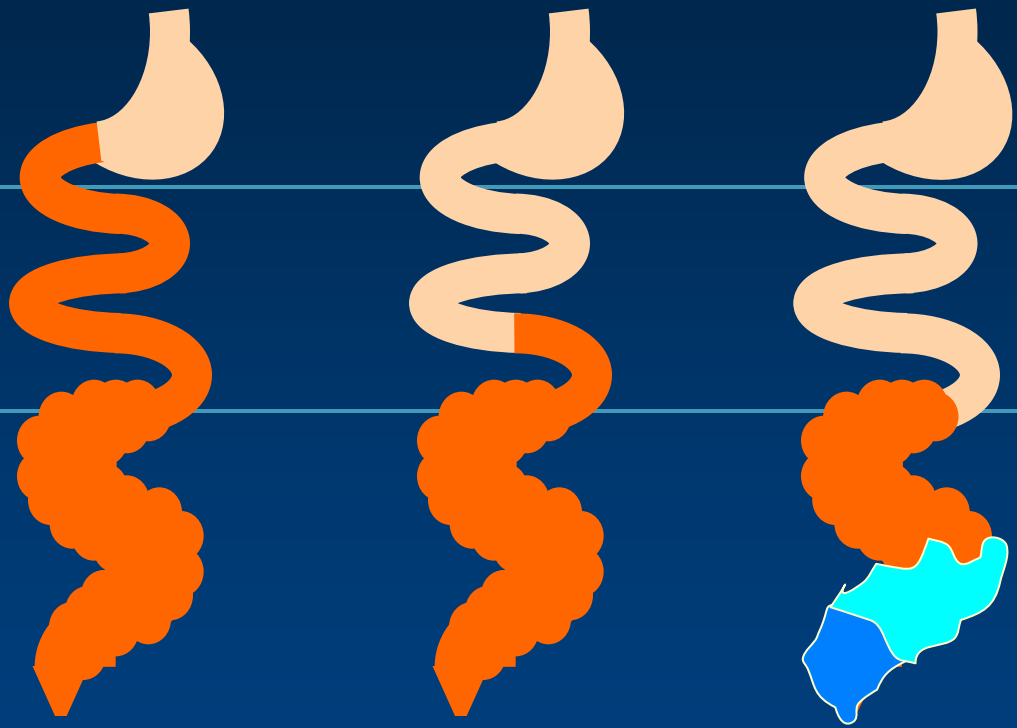
Pentasa

Asacol

Stomach

Small Intestine

Large Intestine



Rowasa

Canasa

Mesalamine microgranule

Mesalamine w/ eudragit-S

Azo bond

Efficacy of Pentasa (mesalamine) in Active Crohn's: Meta-Analysis of RCT

Trial	Mesalamine (n)	Placebo (n)	Mesalamine D in CDAI	Placebo D in CDAI	Mesalamine - placebo D in CDAI	*P* value
1	75	80	-72	-21	-52	0.005
2	75	75	- 41	-35	-6	0.7
3	154	156	-72	-64	-8	0.5
Pooled	304	311	- 63	-45	-18	0.04

CDAI, Crohn's Disease Activity Index.
Hanauer SB et al. Gastroenterology. 2001;120(suppl 1):A-453.

Corticosteroids

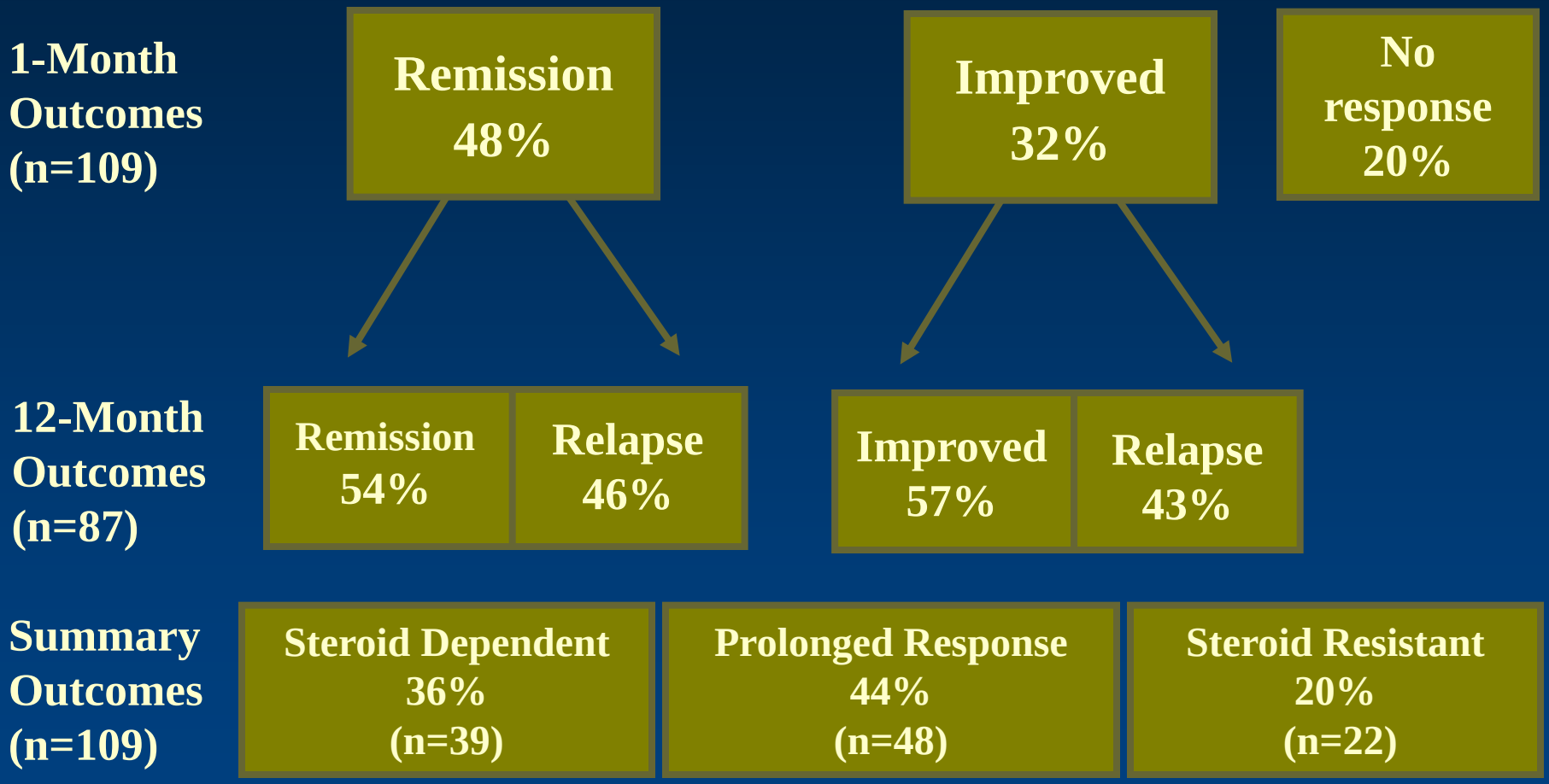
Benefits

- Induces remissions
- Quick fix
- Inexpensive
- Oral or rectal

Risks

- No long-term benefits
- Numerous side effects
  - Cushingoid changes
  - Adrenal suppression
  - Weight gain
  - Hypertension
  - Diabetes
  - Osteoporosis
  - Acne
  - Cataracts
  - Depression
  - Growth retardation
  - Sleep disturbance
  - Mood swings
  - Avascular necrosis of bone

Outcome of Steroid Therapy* for Patients With CD



*Prednisone 1 mg/kg for 1 month.

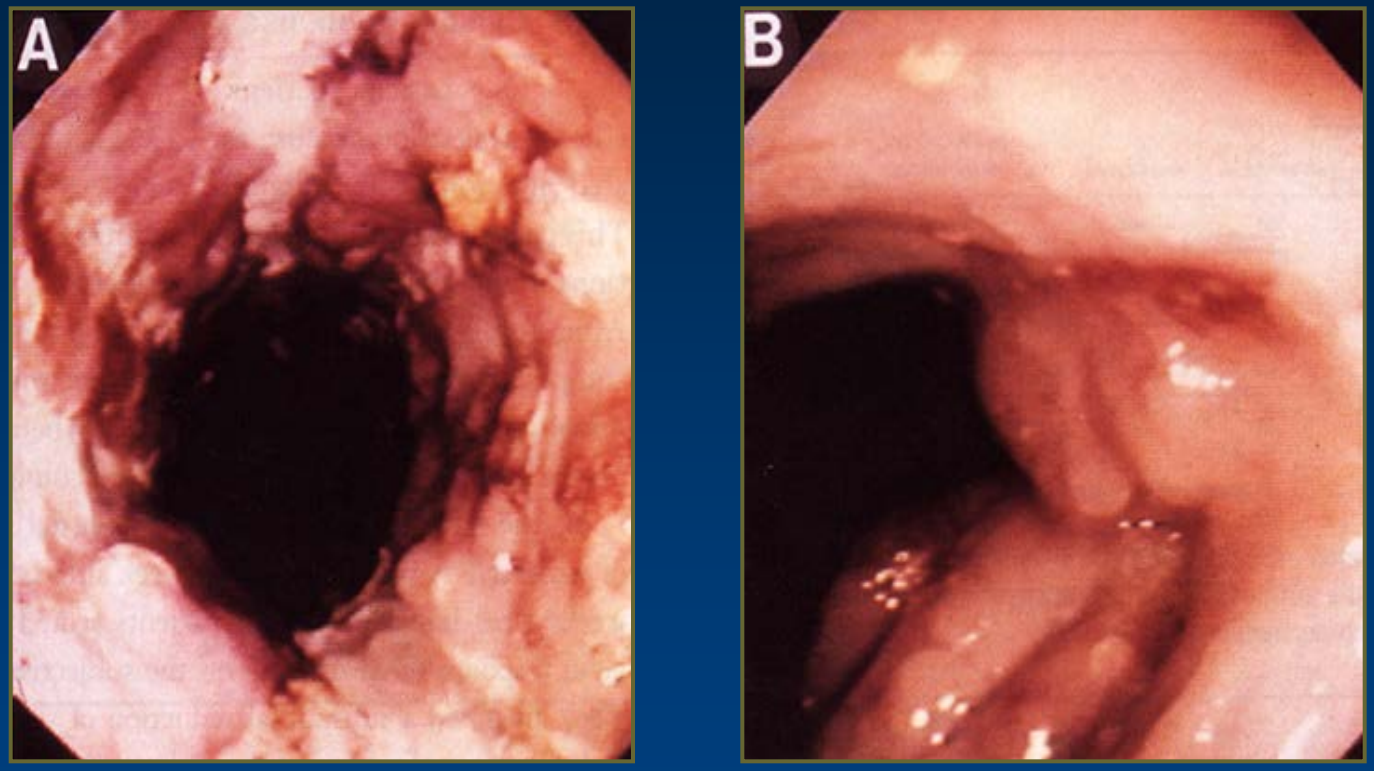
Munkholm P et al. *Gut*. 1994;35:360.

Immunomodulators in CD

- **Purine antimetabolites**
  - 6-mercaptopurine (6-MP) 1.5 mg.kg
  - Azathioprine (AZA, prodrug) 2.5 mg/kg
  - In active CD, must be used with other agents due to slow onset of action (2-6 months for onset)
  - Potential AEs: allergic reactions, leukopenia, hepatitis, pancreatitis, rare lymphoma

Sands BE. *Gastroenterology.* 2000;118(suppl):S68-S82; Sandborn WJ. In: Sartor RB, Sandborn WJ, eds. *Kirsner's Inflammatory Bowel Diseases.* 6th ed. Philadelphia, Pa: Saunders; 2004:531-554; Navarro F, Hanauer SB. *Am J Gastroenterol.* 2003;98(suppl):S18-S23.

Healing of Colonic Ulceration With Infliximab

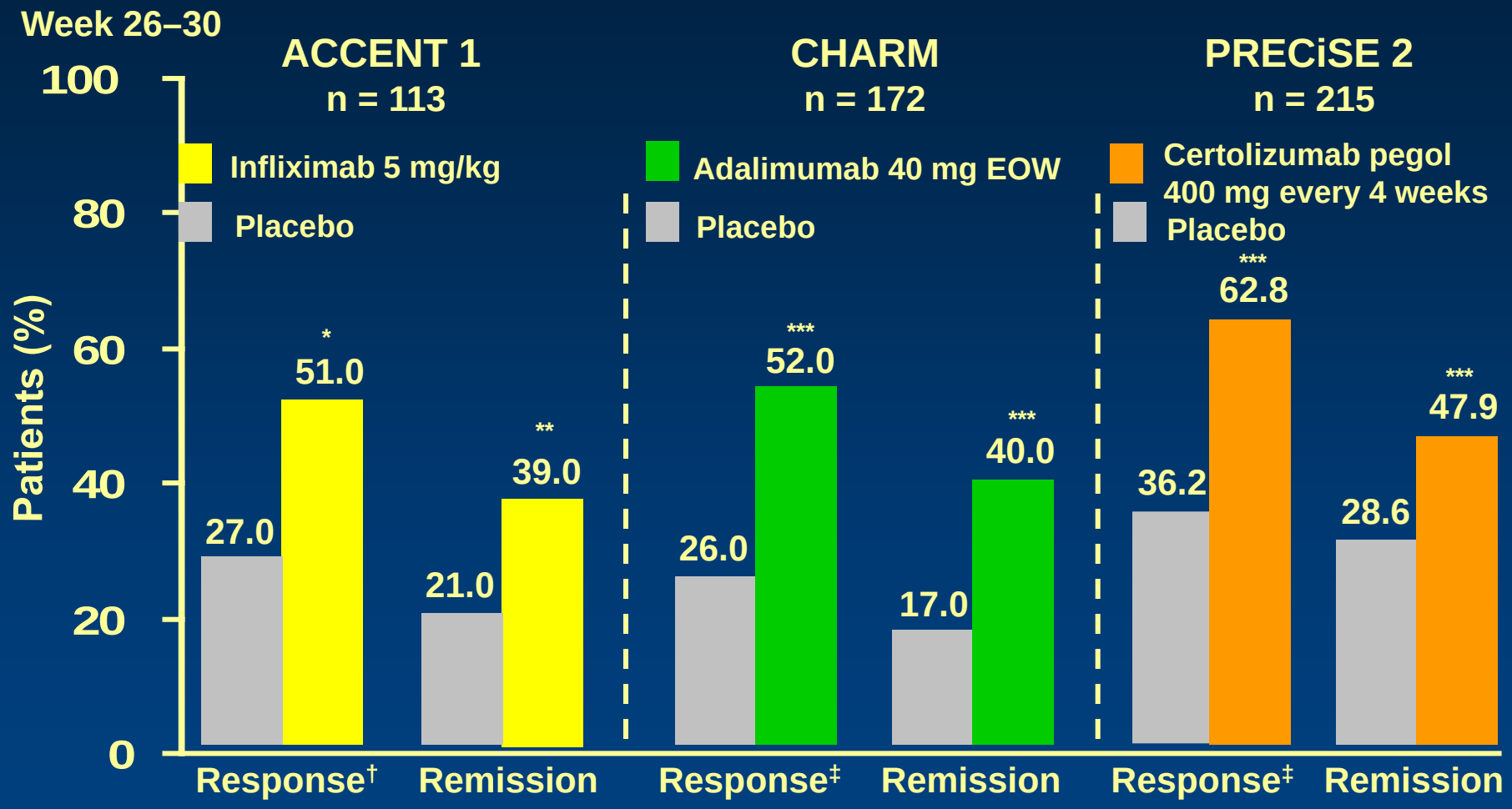


Pretreatment

4 Weeks posttreatment

Reprinted with permission of van Dullemen HM et al. *Gastroenterology.* 1995;109:129.

Overview of Results of Long-Term Anti-TNF Trials



Hanauer SB et al. *Lancet*. 2002;359:1541–1549.
Colombel J et al. *Gastroenterology*. 2006;131:950.
Schreiber S et al. *Gut*. 2005;54(Suppl VII):A82.

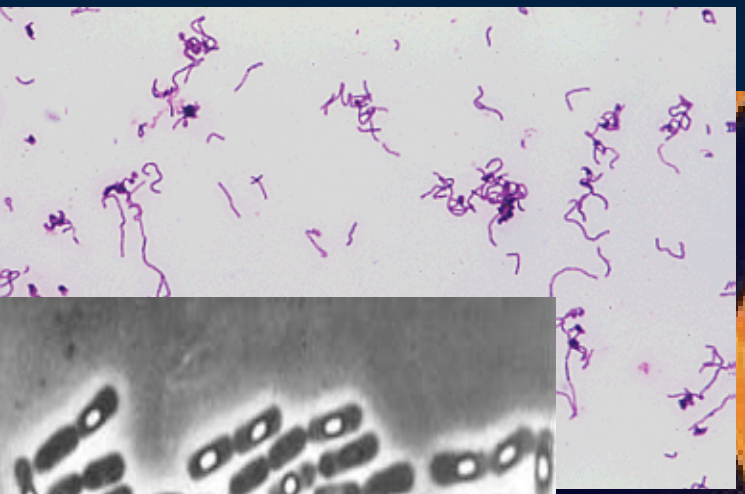
Remission = CDAI score < 150
† Decrease in CDAI score of ≥ 70 points and ≥ 25%
‡ Decrease in CDAI score of ≥ 100 points
**P* = .0002; ***P* = .003; ****P* < .001

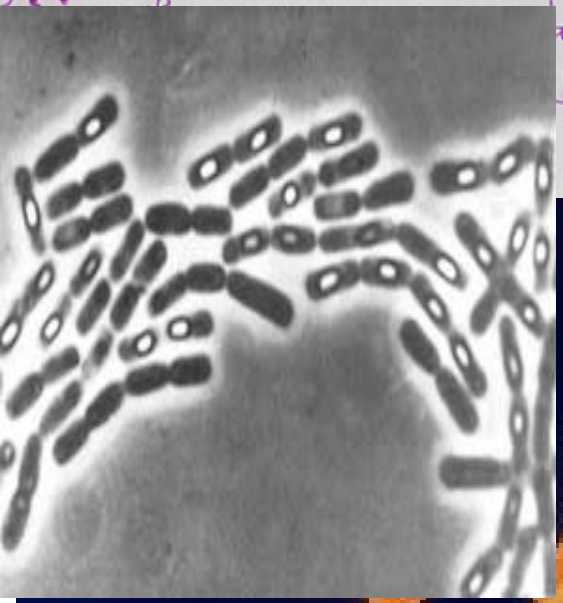
Anti-TNF agents: Adverse effects

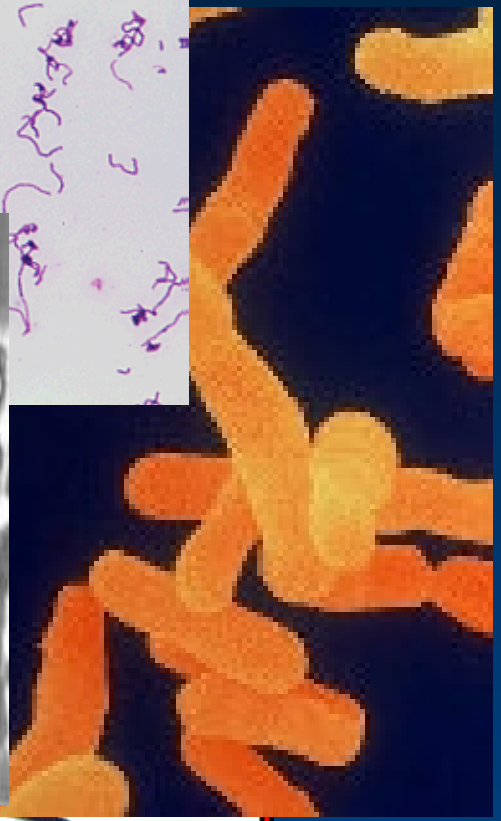
- Infusion reactions (infliximab)
  - Acute 3.8%
  - Delayed 2.8%
- Immunogenicity
- Infection (8.2% overall, 4% serious)
  - Risk of TB: black-box warning
- Autoimmune phenomena
  - ANA (57%)
  - anti-ds/ssDNA, anti-histone Ab
  - Lupus-like syndrome (0.6%)
- Demyelinating disease (0.2%)
- Worsening of / increased mortality in CHF
- Hepatic failure
- Cancer/ Lymphoma
- Death (1-2%?)

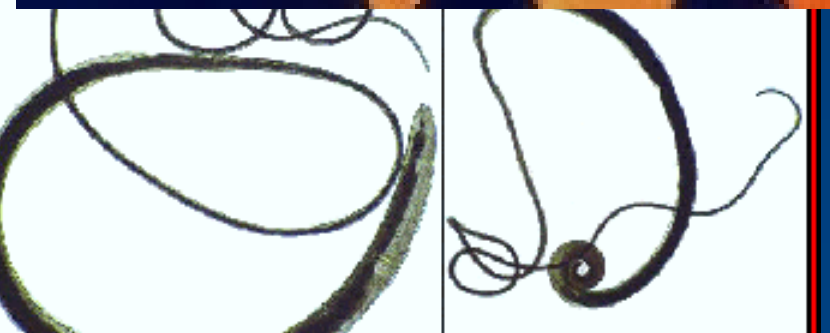
Colombel JF, et al. Gastroenterology 2004;126:19.
Vermeire S, et al. *Gastroenterology.* 2003;125:32.

Biotech vs Low Tech









Antibiotics

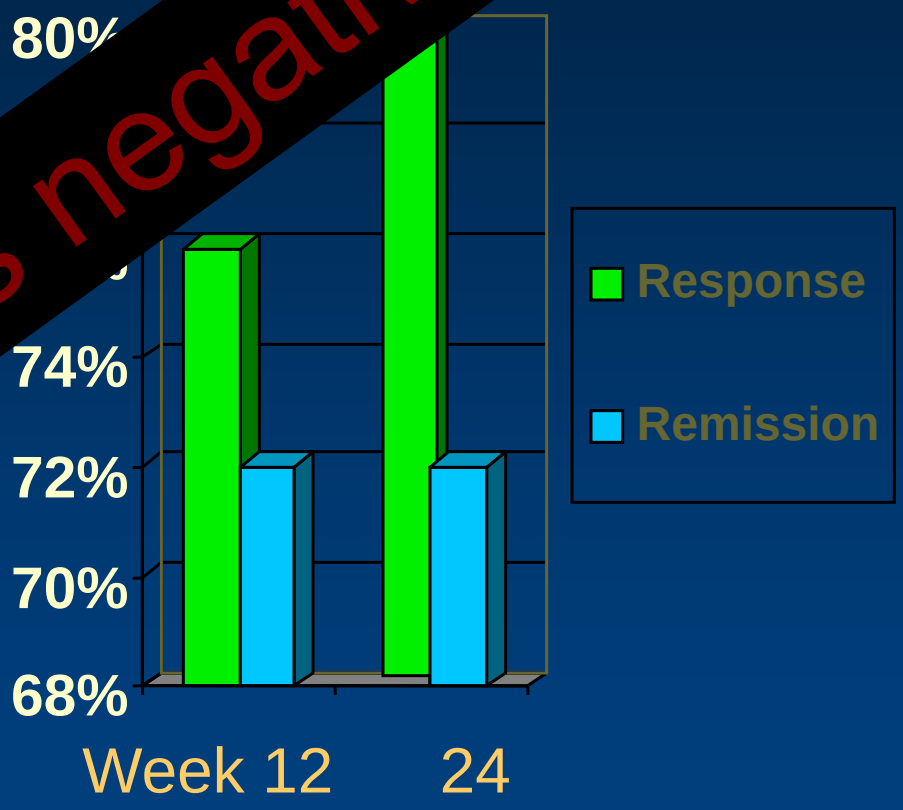
Probiotics

Prebiotics

Parasites

Helminth Ova in Active Crohn's Dis

- 24 week open study
- 29 pts CDAI 220-450
- 2500 *T. suis* ova q
  wks
- Response
  - >100
- Rem



Two recent RCTs negative

Weinstock et al, Gut, 2005

Fecal Microbiome Transplant (Intestinal Microbial Restoration)

UC and "Human Probiotics"

- Rationale:

  Fecal enemas used in recurrent *C. difficile*

- Six patients with longstanding UC
- Received daily infusions for 1 week
- 6/6 "cured"

Borody et al, J Clin Gastroenterol. 2003 37:42-7**.**

Results

- *C difficile*
  - 90% effective in resolution of recurrent disease[1,2]
  - Severe CDI- resolution 84%
- IBD
  - Meta-analysis-of IBD[3]
  - Remission in UC 62.5% (15/24)
- IBS
  - Constipation resolved 60% (30/45)
  - Diarrhea- marked improvement

1) Gough, Clin Infect Dis, 2011. 2) Brandt, Am J Gastro, 2013. 3) Anderson, Aliment Pharm Ther, 2012

Applications

- GI
- Chronic Fatigue
- Obesity
- Non-alcoholic fatty liver disease
- Multiple sclerosis
- Atherosclerosis
- Diabetes
- Allergy

Take home messages

- Mesalamine is minimally effective for Crohn's
- Mesalamine should be used UC maintenance
- Steroids are not effective for maintenance and should not be used for maintenance
- Azathioprine/6-MP can be effective over time but require careful monitoring
- Anti-TNF agents can be effective in Crohn's and UC (?) but patients must be carefully chosen