Orientation 2009
IBD Overview

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Objectives

- Review the etiology of chronic inflammatory bowel disease
- Discuss diagnosis, differential diagnosis
- Review measures of disease activity
- Discuss IBD therapy

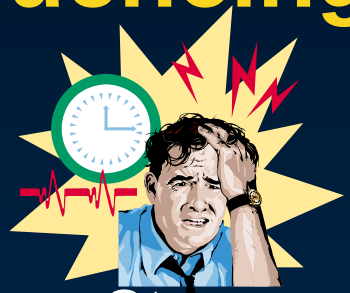
IBD-Background Information

- Inflammation
  - gut's only response to myriad of potential insults
- Minority of new occurrences of IBD associated with straightforward effort of establishing positive diagnosis
  - No gold standard test exists
  - Casual diagnosis of IBD has many ramifications
- Bottom line:
  - Diagnosing IBD continues to be a challenge!

Environmental Factors Influencing IBD

Medications

- NSAIDs
- Antibiotics



Stress

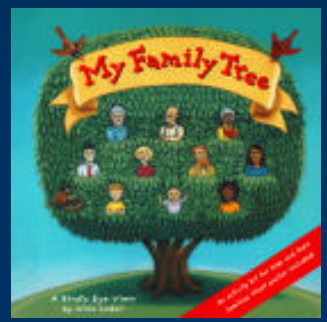
Smoking

IBD

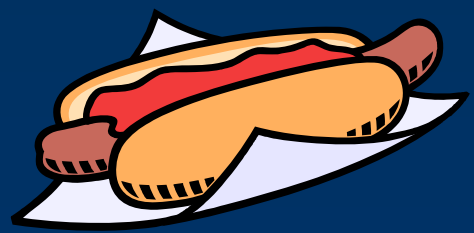
Appendectomy

Enteric pathogens

Family history



Diet



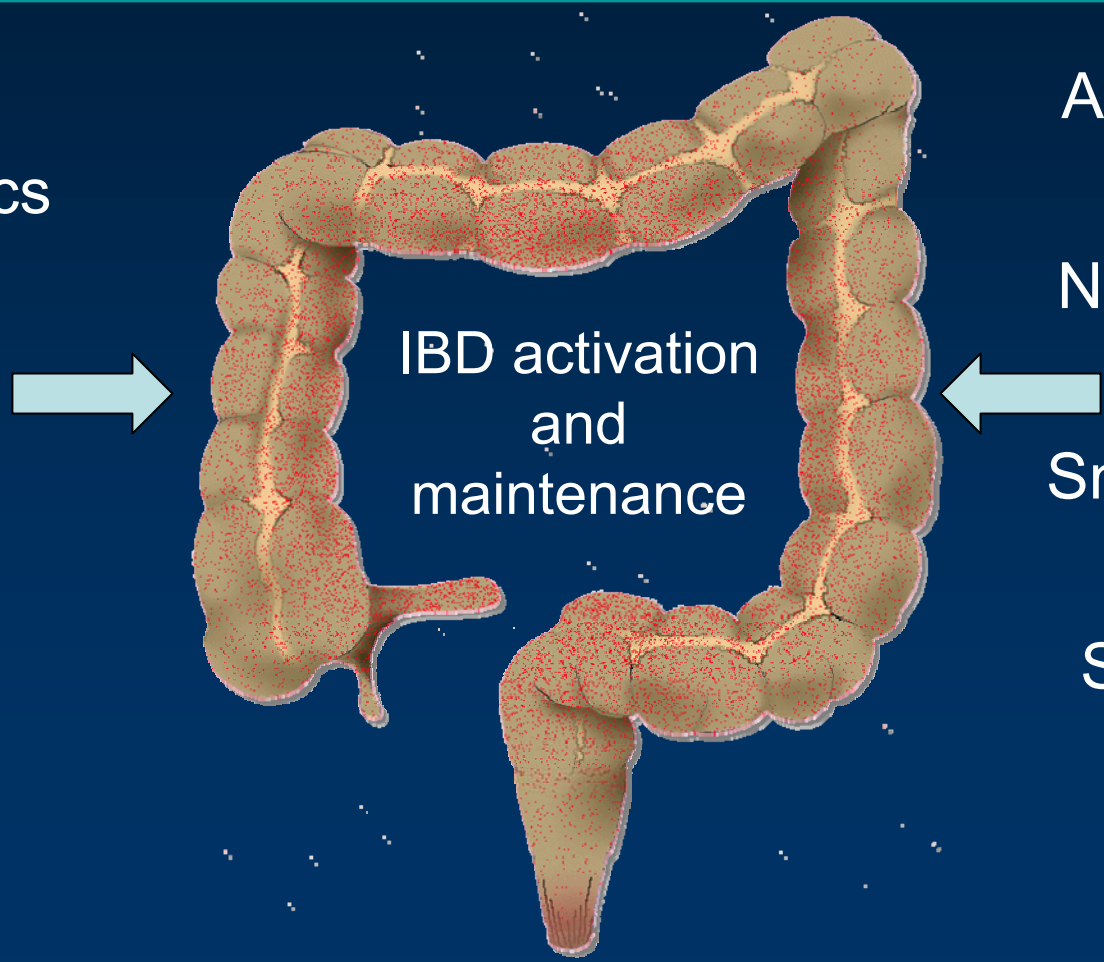
Environmental Triggers of IBD

Alter Flora

Alter Barrier Function

Antibiotics

Diet



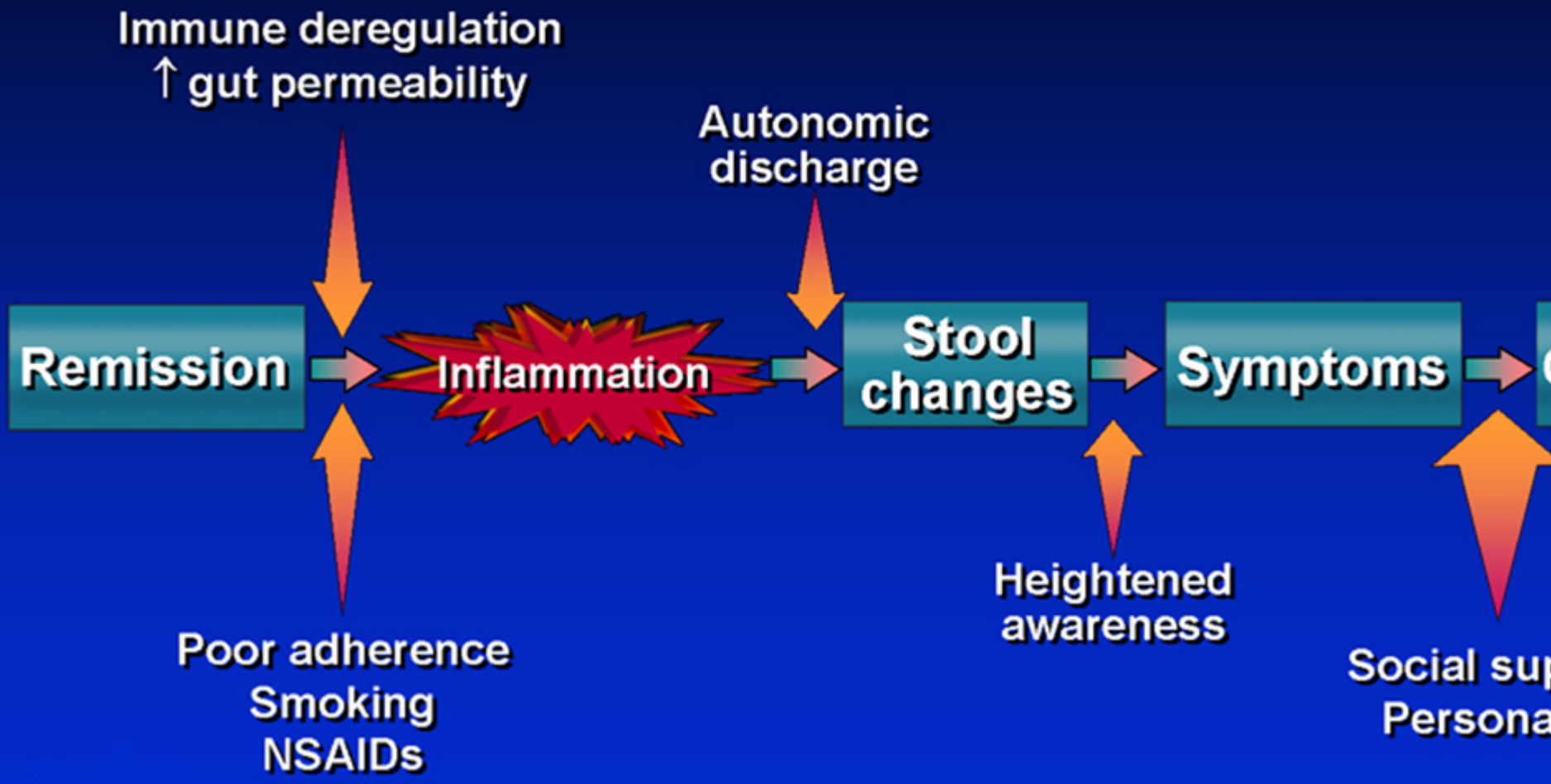
Acute infections

NSAIDs

Smoking

Stress

Psychosocial Factors and IBD: Possible Points of Impact

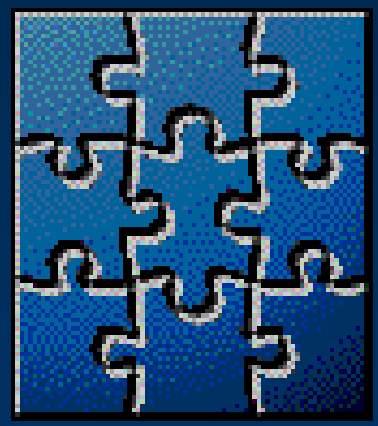


Components of IBD Diagnosis

- Clinical picture
- Endoscopic information/pathologic specimens
- Radiographic evidence
- Chronic course of symptoms

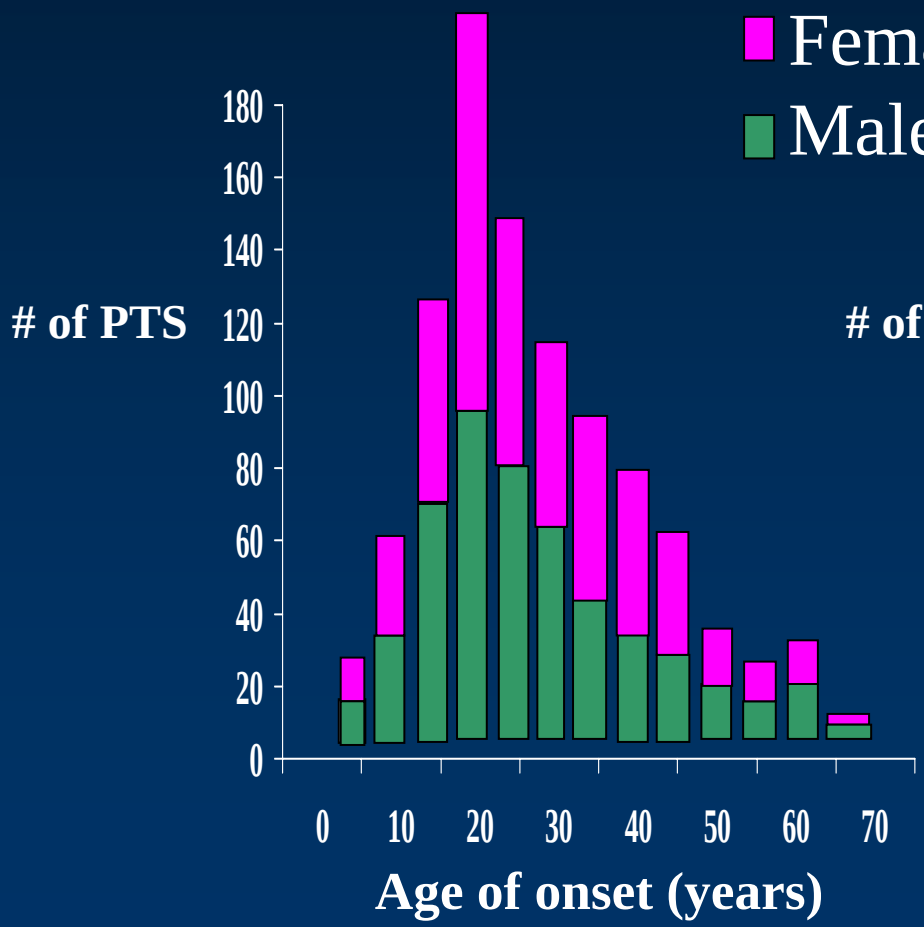
Constructing the Diagnosis of IBD

- Careful process of putting together pieces of a puzzle to accumulate enough evidence to diagnose IBD

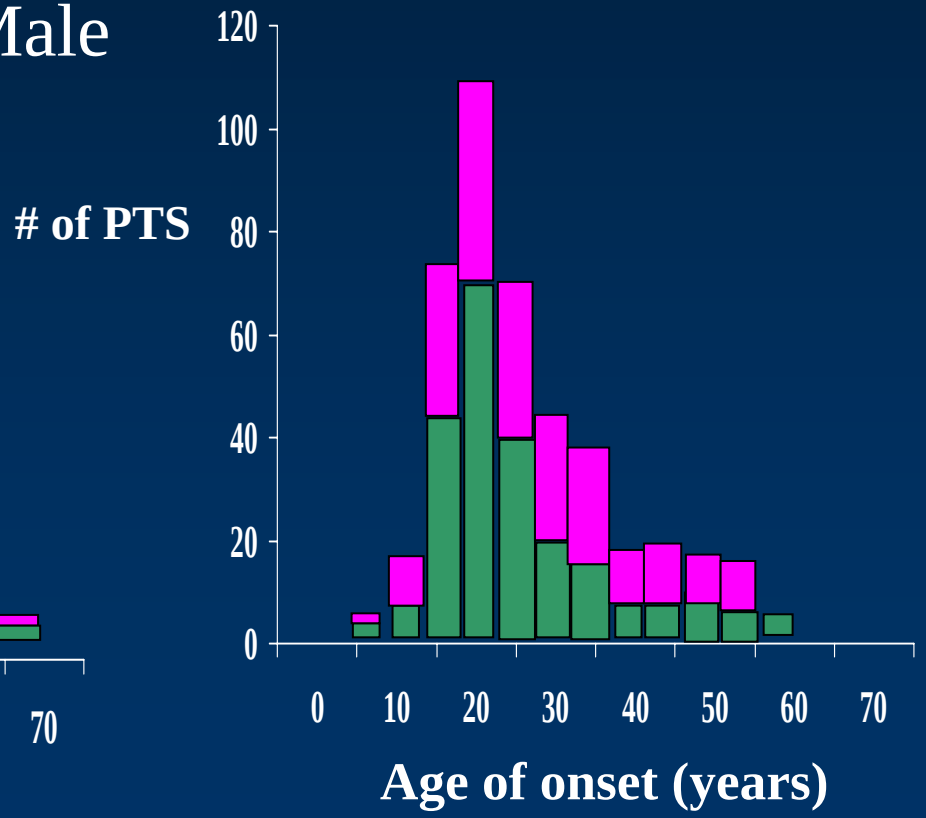


Age & Sex Incidence of IBD

Ulcerative Colitis



Crohn's Disease



Historical Points Suggestive of IBD

- ↑ stool frequency, ↓ consistency most common presenting sx of UC and CD
  - Altered bowel habits need not be present in either
  - Proctitis, in particular, may present with constipation

- Abdominal pain second most common symptom
  - RLQ pain exacerbated by eating: CD
  - LLQ cramping before BM, relieved by BM: UC
  - Tenesmus: proctitis, most likely UC, occ CD

Historical Points Suggestive of IBD

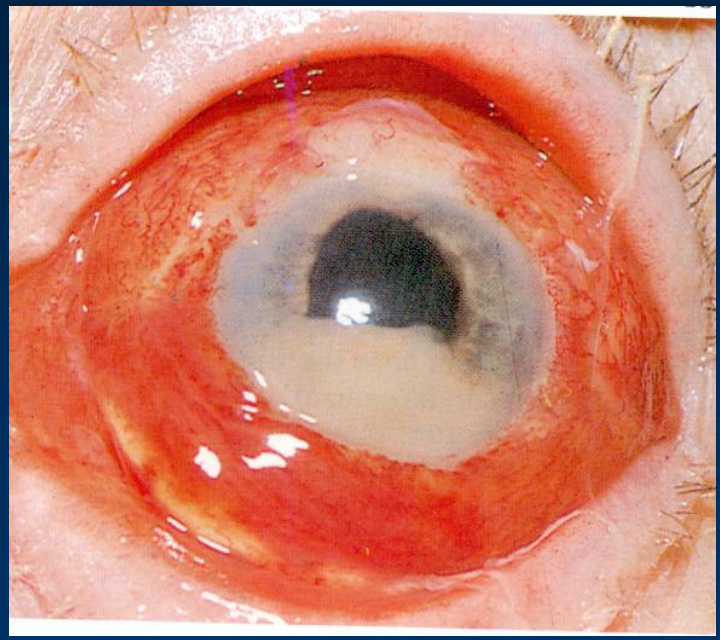
- Alternating diarrhea and constipation more strongly suggest IBS vs IBD
- Nocturnal diarrhea more common in IBD
- Functional symptoms remaining after bout of enteric infection may be confusing
  - Lingering abdominal pain, loose/urgent stools should prompt objective evaluation by endo/path

Physical Findings in IBD

- Crohn's Disease
  - Oral lesions
  - Ocular lesions
  - Skeletal manifestations
  - Skin lesions
    - Erythema nodosum
  - Abdominal exam
    - Mass
  - Perianal disease
    - Skin tags
    - Anal fissure
    - Perianal fistula
    - Anal stenosis
- Ulcerative colitis
  - Oral lesions
  - Ocular lesions
  - Skeletal manifestations
  - Skin lesions
    - Pyoderma
  - Abdominal exam
    - Tenderness
  - Perianal disease
    - Rectovaginal fistula

Oral Lesions

Ocular Lesions



Cutaneous Lesions

Perineal Complications of Crohn's Disease

Common Peri-Anal Conditions
Not to be confused with Crohn's

- Uncomplicated fistula-in-ano
  - Does not traverse the internal anal sphincter
- Anal fissure (posterior mid-line)

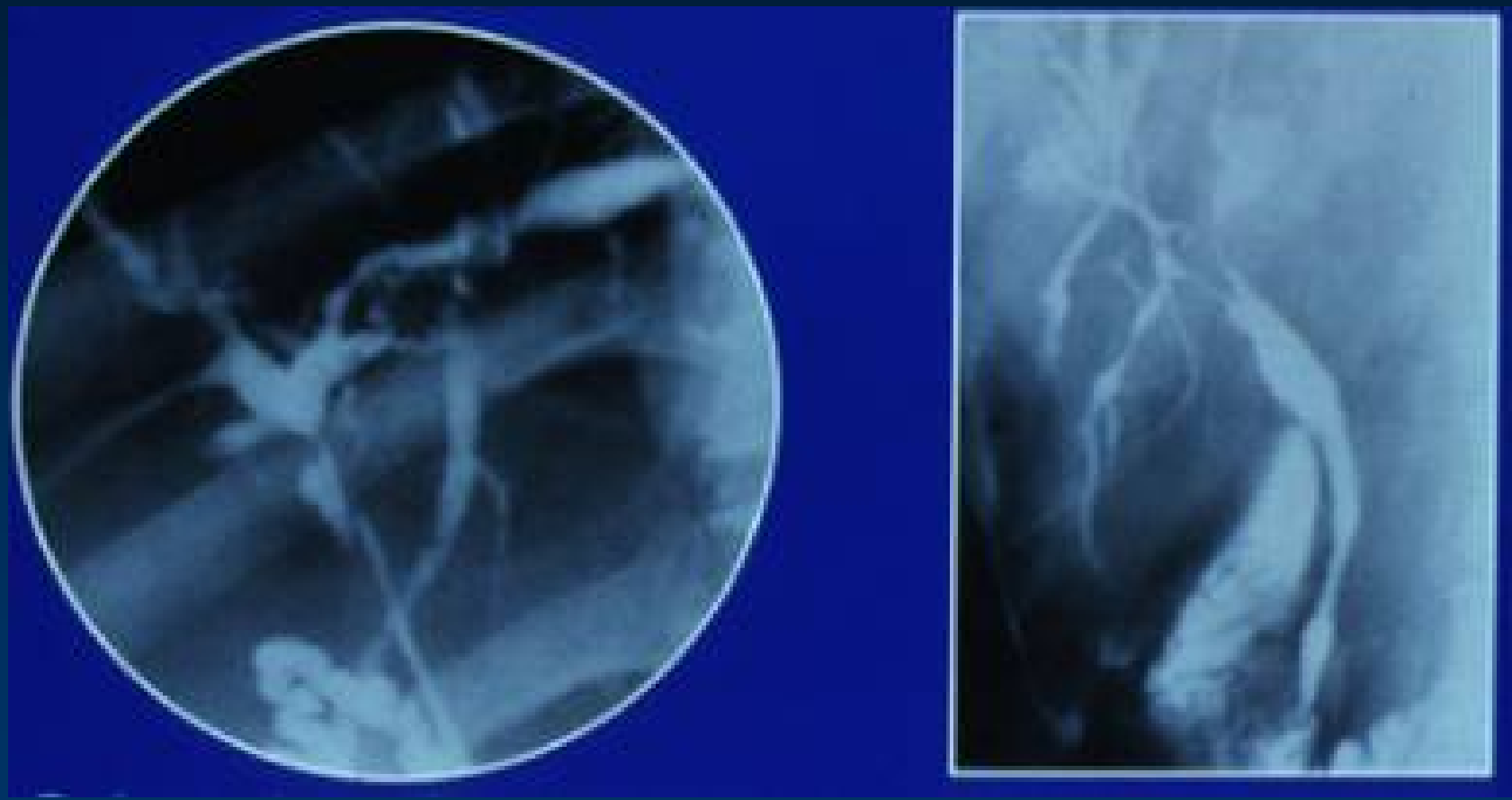
Systemic Complications of Ulcerative Colitis
Peripheral Arthritis

- Monoarticular
- Asymmetrical
- Large > small joint
- No synovial destruction
- No subcutaneous nodules
- Seronegative

Systemic Complications of Ulcerative Colitis
Central (Axial) Arthritis

Ankylosing Spondylitis and Sacro-iliitis

Systemic Complications of Ulcerative Colitis
Bile Duct Lesions



Sclerosing cholangitis

Cholangiocarcinoma

Historical Information-Summary

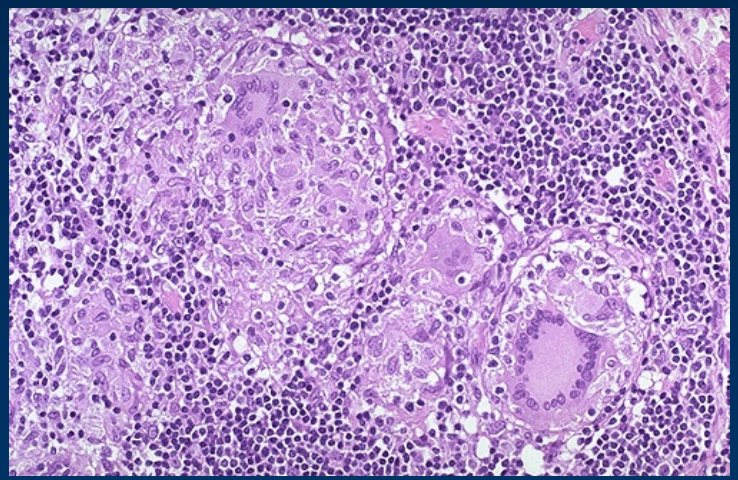
- Presenting signs and symptoms may suggest a particular diagnosis
  - Often not definitive
- Usually requires further investigation!

Useful Laboratory Tests

- Blood work
  - CBC, TSH, ESR, c-RP
- Stool studies
  - Ova and parasites, stool culture, fecal WBC, C. diff toxin A/B
  - Fecal lactoferrin, calprotectin
- Serologic markers
  - ASCA, ANCA, anti-OmpC, anti-CBir1, anti-I2

Diagnostic Tools for IBD

- Endoscopy with pathology



Diagnostic Tools for IBD

- Barium studies (UGI/SBFT, ACBE)

Diagnostic Tools for IBD

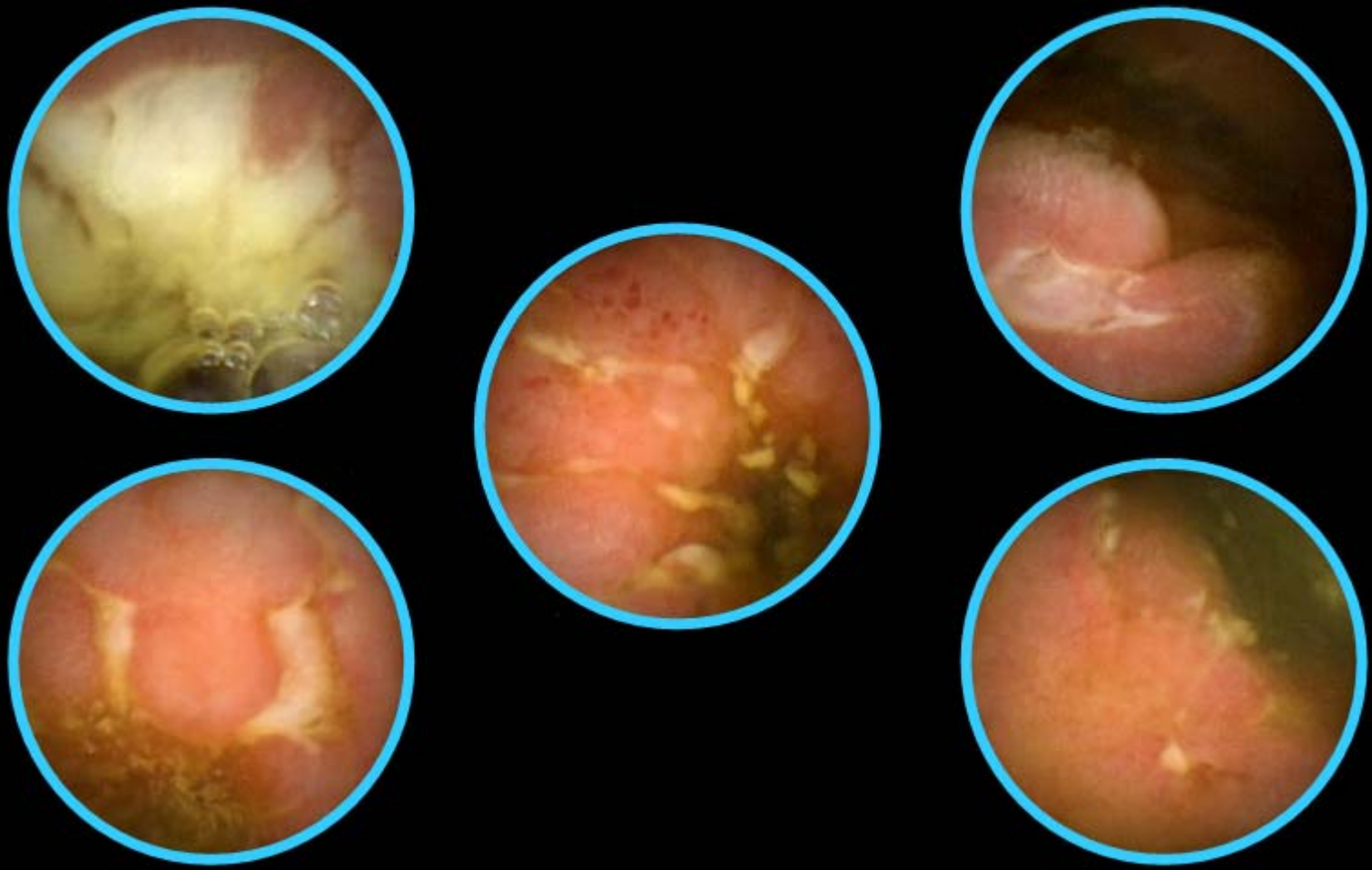
- Capsule/wireless endoscopy

Capsule endoscopy

- Not suitable for routine diagnosis
  - best indication is for strong suspicion of Crohn's despite normal conventional testing (e.g., anemia, weight loss, elevated CRP/ESR, etc)
- Complications
  - capsule retention
    - in established Crohn's disease – 5%
    - in suspected Crohn's disease before obstructive symptoms – less than 1%

Barkin et al, Am J Gastroenterol 2002; 97: A-83

Small intestinal Crohn's disease as seen by wireless capsule endoscopy

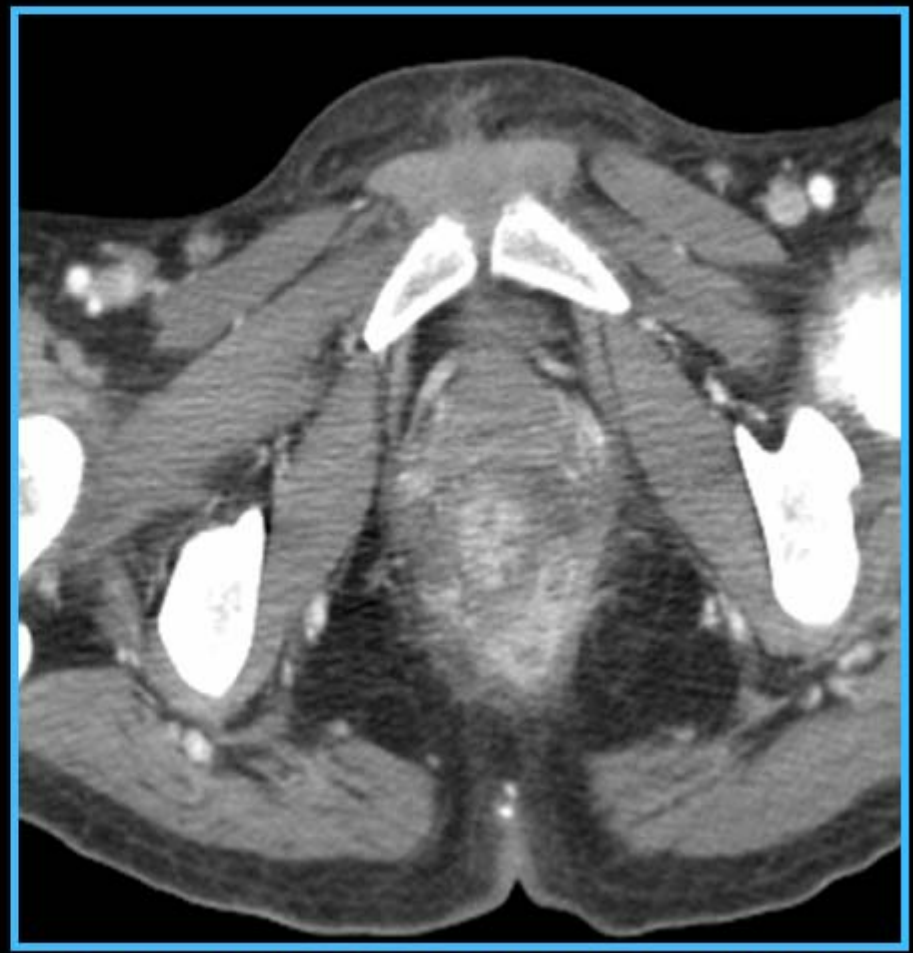


Capsule endoscopy in Crohn's disease

- Detects erosions in suspected Crohn's disease with negative SBFT / colonoscopy
- Need blinded comparison studies *vs* other imaging to calculate true sensitivity and specificity
- Need to determine specificity (prevalence of SB erosions in general population)
- Need to clarify safety in stricturing Crohn's disease – patency capsule may help

CT enterography

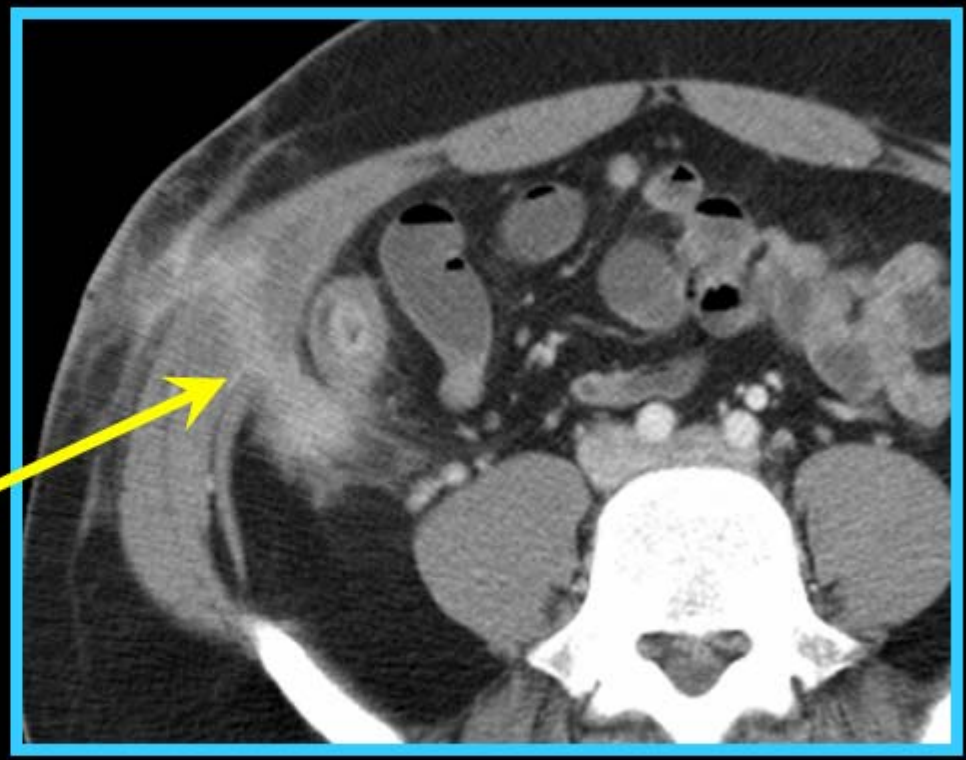
Peri-enteric fat stranding



Adapted from Loftus, Oral presentation, ACG 2006

Fistulas

- Tracts
- Usually enhancing (unless perianal)
- ± fluid / air
- Enterocutaneous



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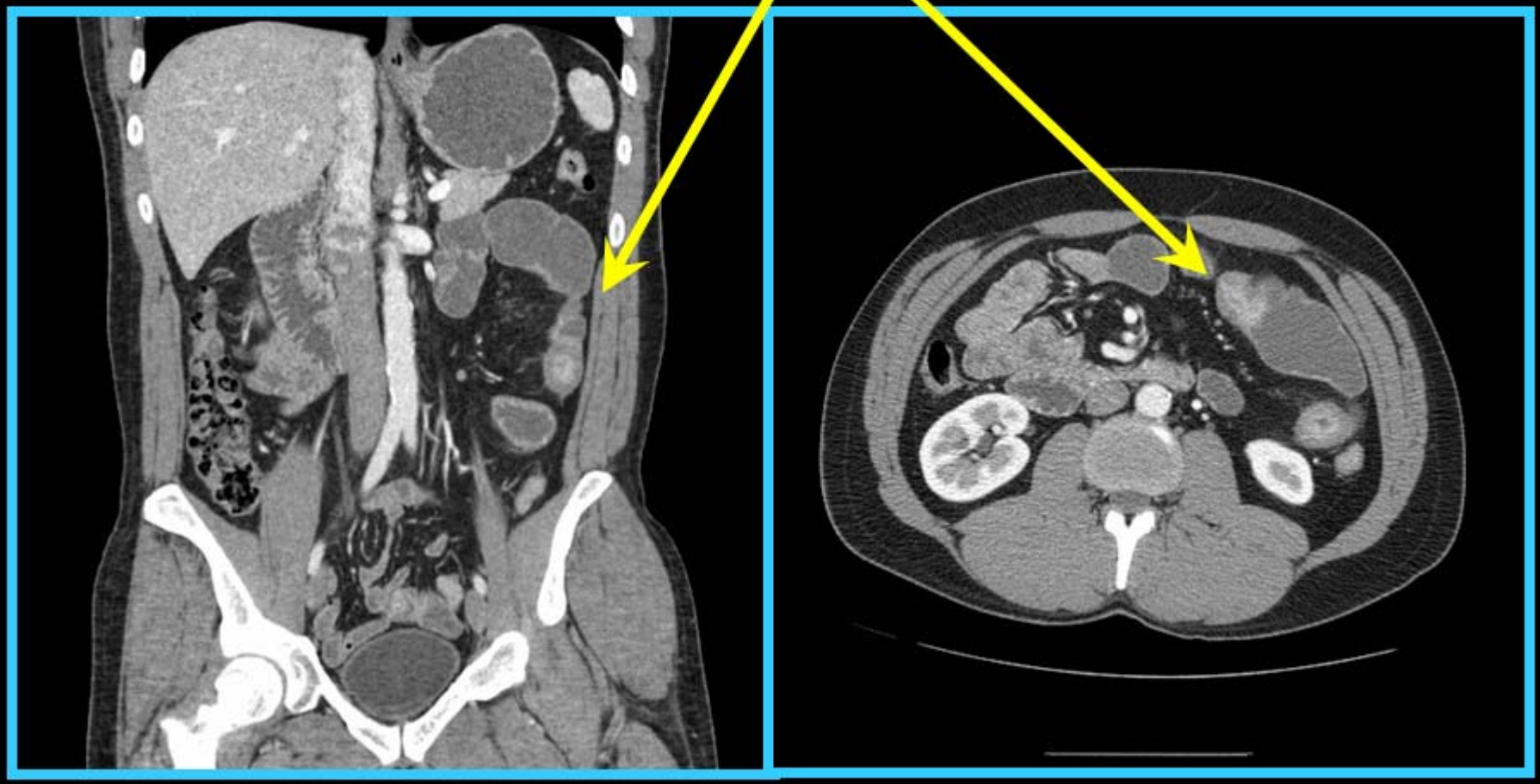
Inflammatory stricture with proximal bowel dilation



MR enterography

MR enterography

- No ionizing radiation
- Comprehensive evaluation of bowel and perianal fistula
- Functional evaluation (is narrowing due to stricture or spasm?)

MR enterography: Crohn's disease findings

- Enhancement
- Wall thickening
- High SI wall / fat
- Deep ulcers
- Comb sign
- Enhancing nodes

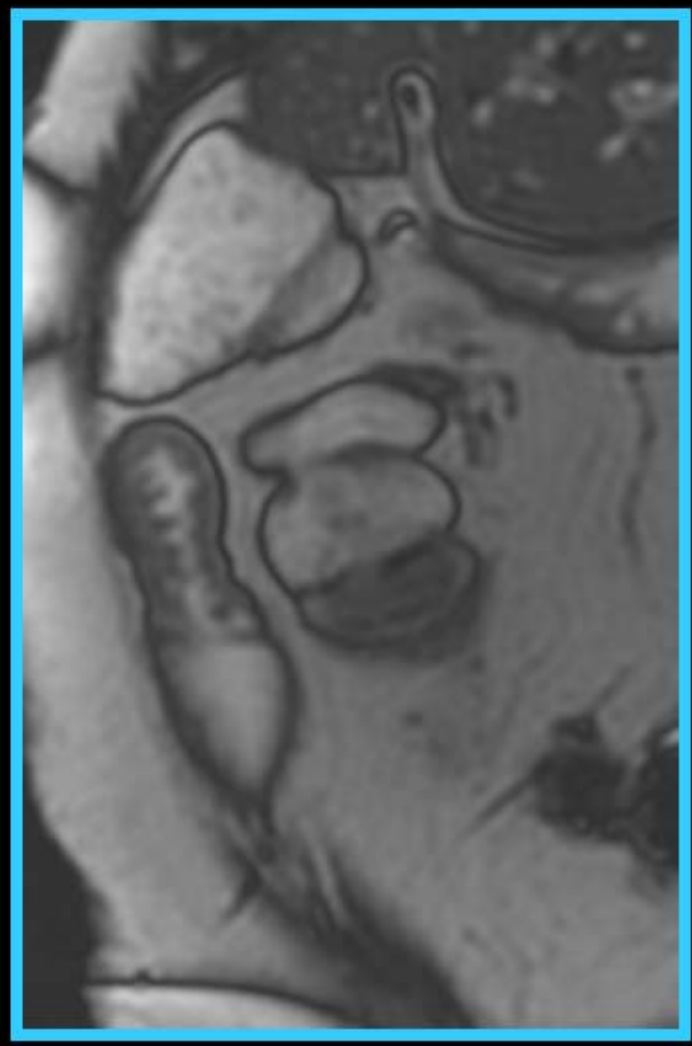


Image courtesy of Jeff Fidler, MD

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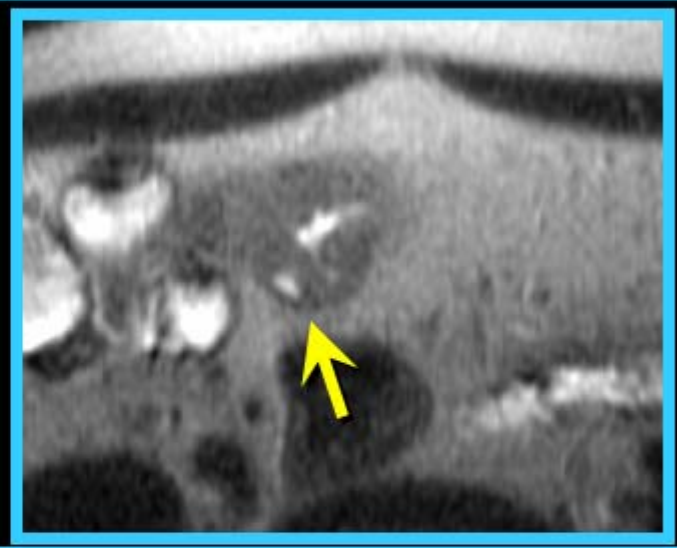

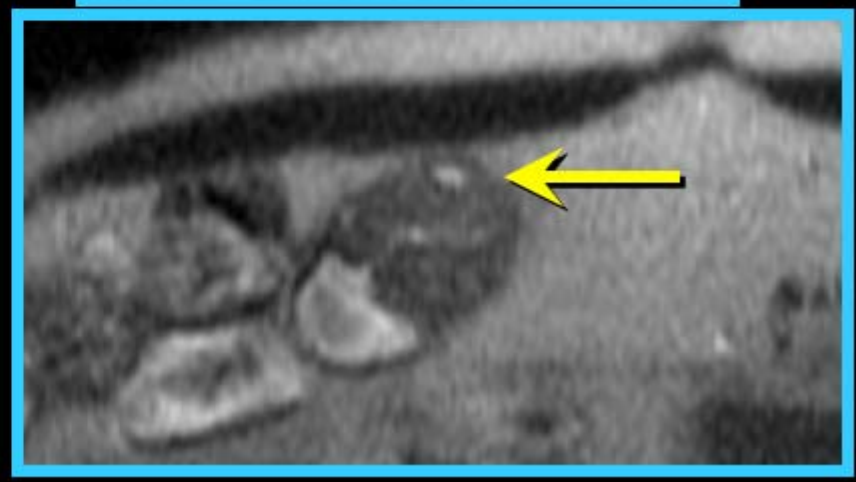

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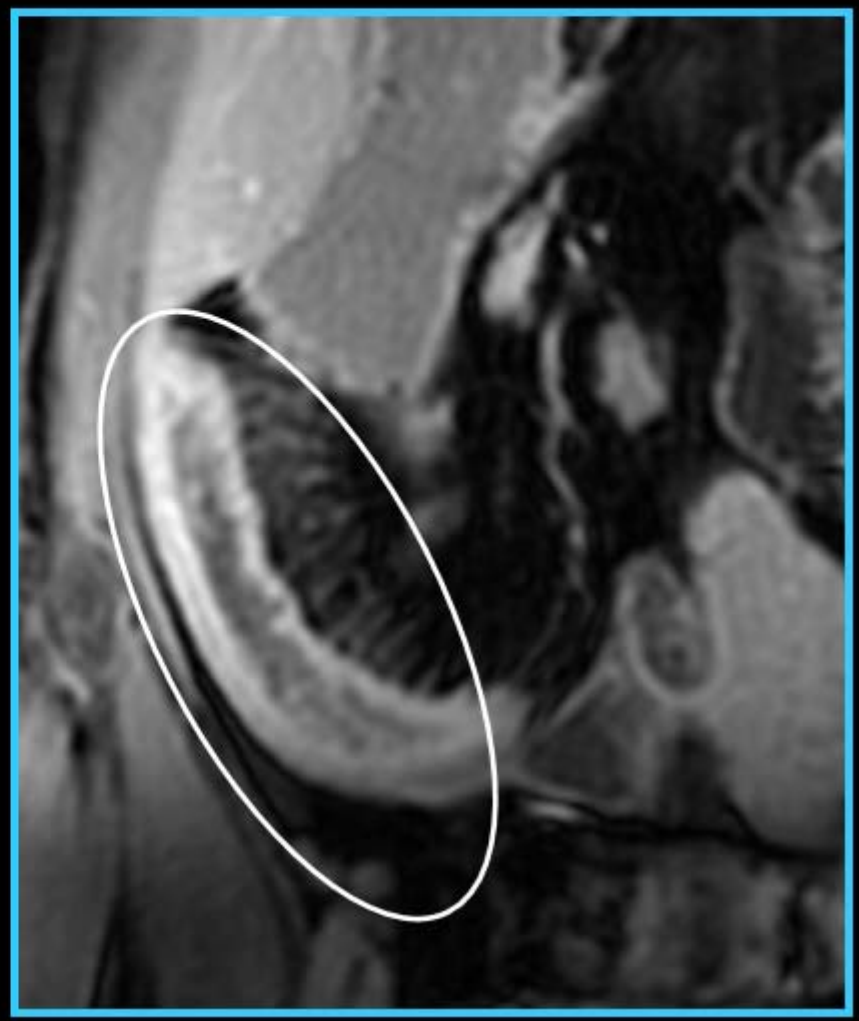
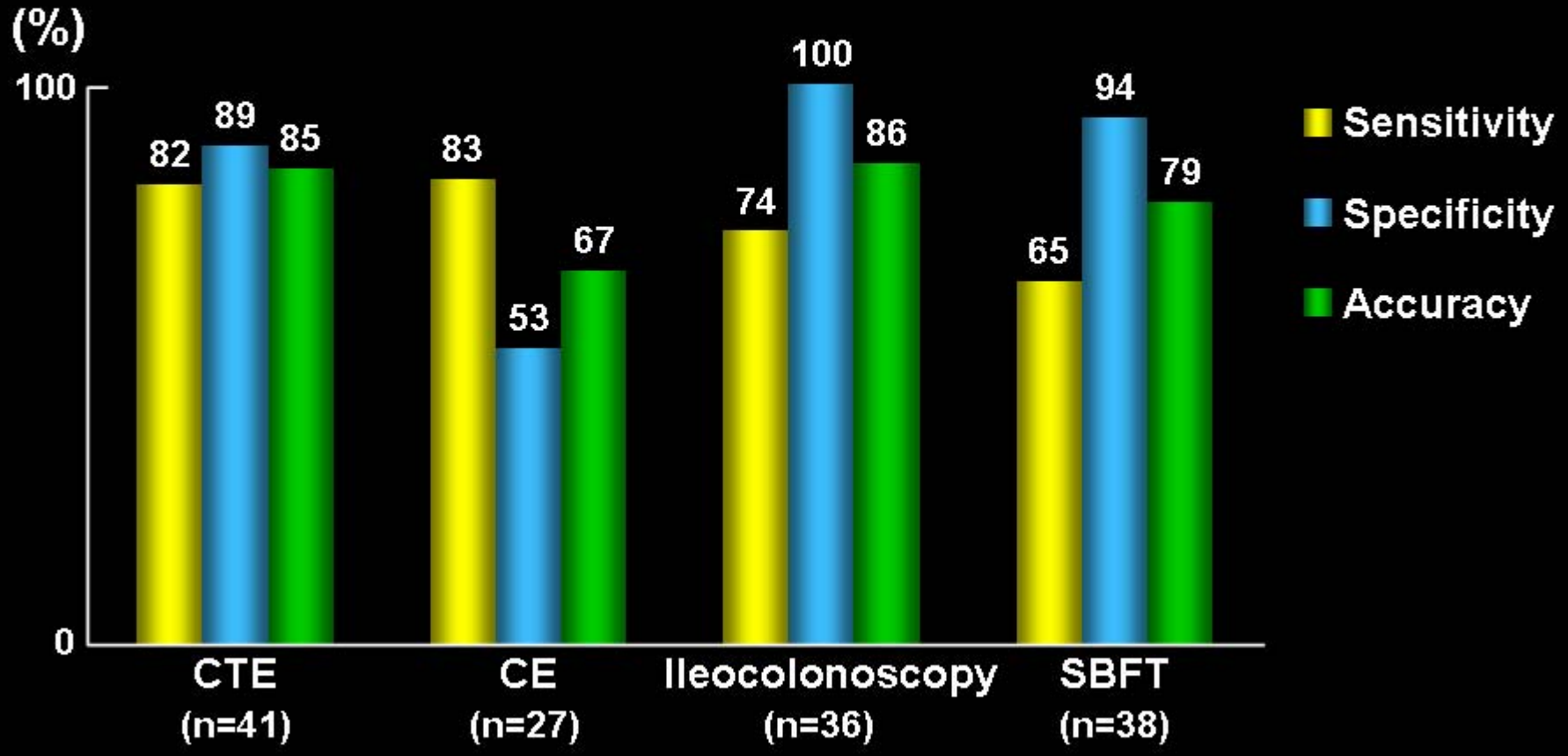


Image courtesy of Jeff Fidler, MD

Small bowel imaging in Crohn's disease: Prospective blinded 4-way study with consensus reference standard



CTE and CE were equally sensitive but CE was less specific than other 3 modalities

Solem et al, Gastroenterology 2005; 128: A74

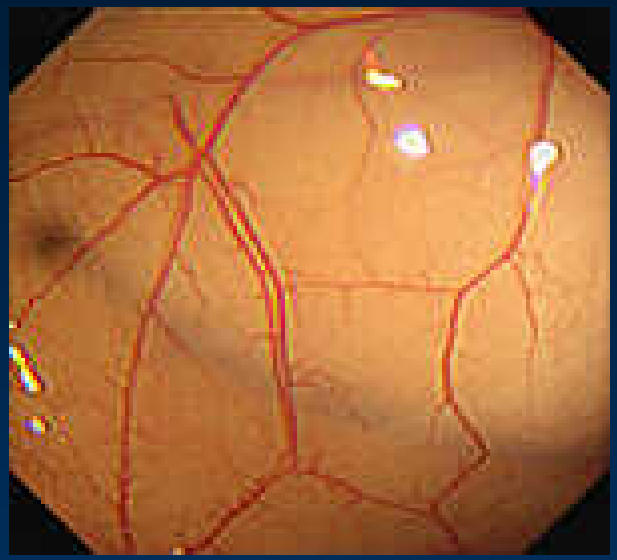
Indications for Endoscopy in IBD

- Obtain an accurate diagnosis
- Assess disease activity or possible extension
- Dilate strictures in fibro-stenotic disease
- Detect cancer precursors in long-standing colonic disease

Hommes Gastro 2004;126:1561-1573

Endoscopic Features of IBD

Ulcerative colitis



- Edema
- Erythema/Loss of vascularity
- Friability
- Erosions
- Mucopurulent exudate
- Spontaneous bleeding
- Ulceration

Endoscopic Features of IBD

Crohn's Disease

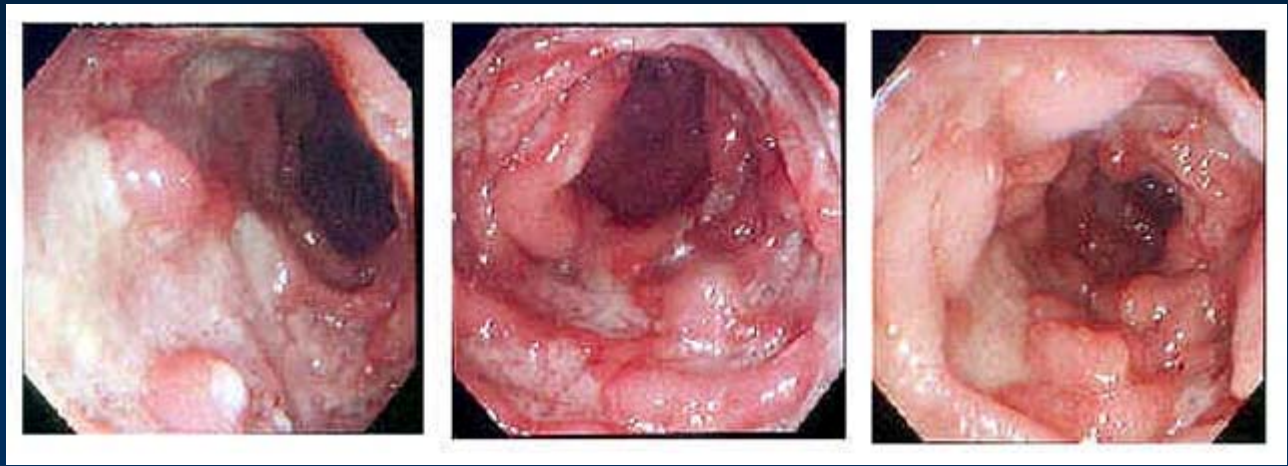
- Patchy edema, erythema
  - Discontinuous
- Apthous ulcerations
- Coalescing ulcerations
- Cobblestoning

Differential Diagnosis of Ileitis

Conditions Mimicking Crohn's Disease

- Lymphoid hyperplasia
  - Adolescents, young adults
  - Could be clue to hypogammaglobulinemia
- Infections
  - *M. tuberculosis*
  - *Y. entercolitica* (cold-chain hypothesis)
  - *E. histolytica*
  - *Actinomyces* (can cause fistulization)
- Lymphoma
- NSAID induced injury
  - Ulcerations
  - Webs/strictures
- Vasculidities
  - Henoch-Schöenlein purpura (GI bleeding, RLQ pain)
  - Spondyloarthropathies
- Eosinophilic gastroenteritis
  - Predominantly eosinophilic infiltrate, sub-mucosal/serosal involvement
- Medications
  - Oral contraceptives
  - Ergot derivatives
  - Digoxin
    - precipitate small vessel thrombosis, ischemic ileitis
- CVID

Intestinal Tuberculosis



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Differential Diagnosis of Proctitis

Conditions Mimicking Ulcerative Proctitis

- Crohn's proctitis
  - Associated with fistulas, fissures, skin tags, anal stricture
- STDs
  - HSV, gonorrhea, chlamydia, LGV, syphilis, whipworm
- Rectal prolapse
  - Inflammation confined to distal 2-3cm of rectum
- Solitary rectal ulcer syndrome
  - Anterior location
  - Fibrosis, muscular hypertrophy on biopsy

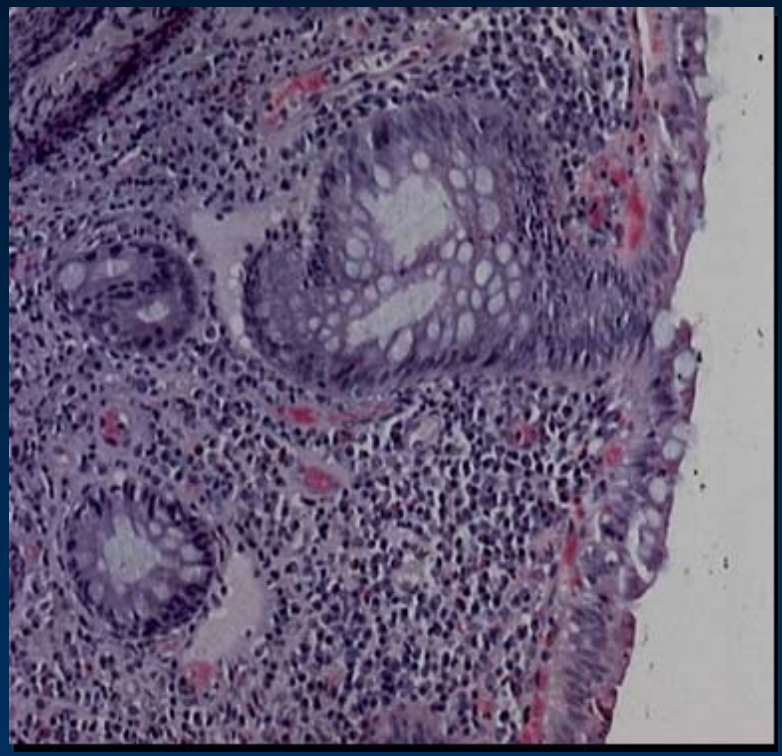
Differential Diagnosis of Colitis

- ASLC
- Ischemic colitis
- Beçets syndrome
- Microscopic or collagenous colitis
- SCAD
- Diversion colitis

Acute Self-Limited Colitis (ASLC) vs IBD

- Strongly suspected to be infectious in nature
  - Whether or not an infectious agent is identified
- When enteric pathogen not identified, signs and symptoms distinguish poorly between ASLC and IBD
- Histopathology takes center stage in guiding accurate diagnosis

ASLC vs IBD



Caveat

- Architectural distortion requires time to develop
- May not be identified in first 6-8 weeks of either form of IBD (potentially longer if inflammation is mild)

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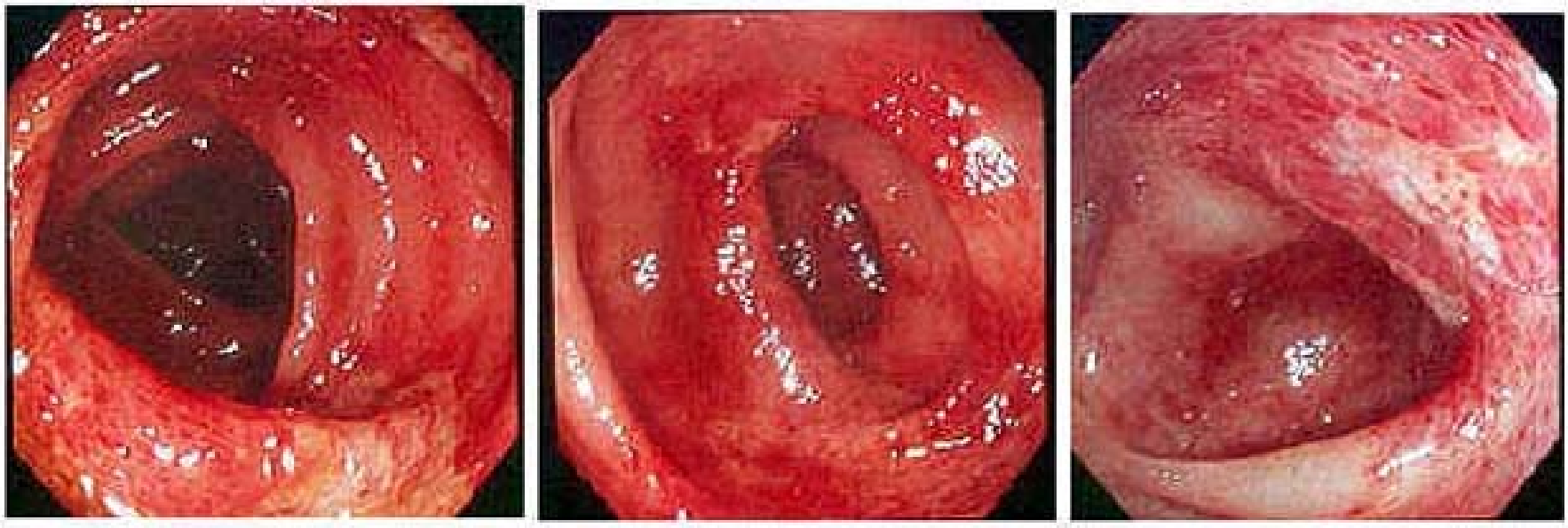
Ischemic Colitis



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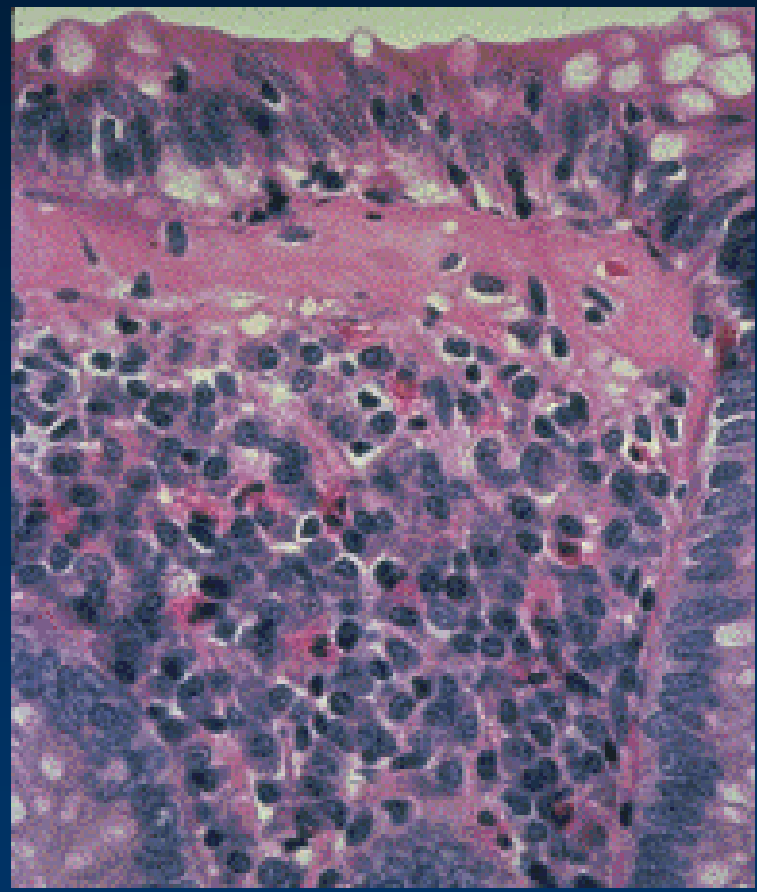

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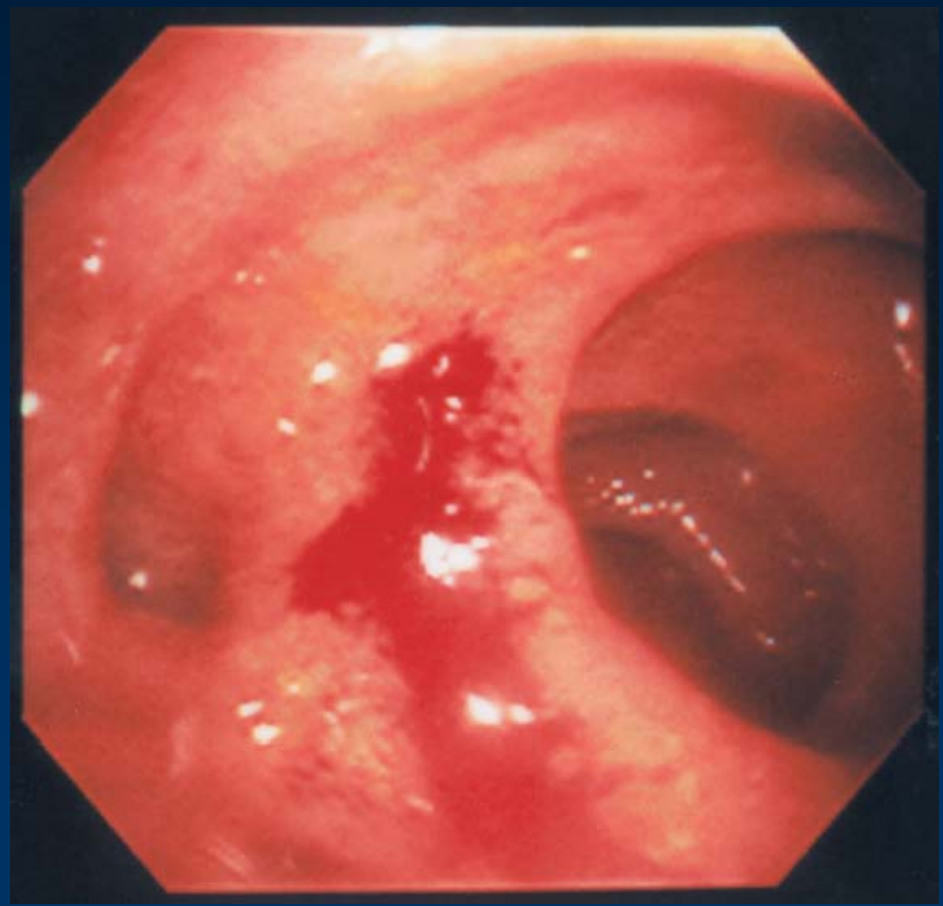


IBD Diagnosis- Summary and Pitfalls

- Inflammation
  - Gut really has limited options for expressing response to myriad of potential insults (one size fits all!)
- Minority of new occurrences of IBD associated with straightforward effort of establishing positive diagnosis
  - No gold standard test exists
  - Casual diagnosis of IBD has many ramifications
- Bottom line:
  - Diagnosing IBD correctly continues to be a challenge!

IBD Treatment Principles

IBD Treatment Principles

Determine underlying cause/location of disease

Tailor therapy to patient's manifestations

Achieve and maintain remission

Monitor for toxicity/complications

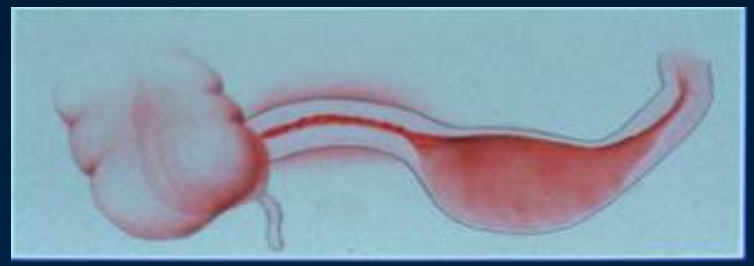
Approach to Crohn's Disease Therapy

Determine Treatment Plan Based on Underlying Clinical Factors

- Disease behavior (inflammatory, fistulizing, stenotic/obstructing)
- Site/extent
- Presence of extra-intestinal manifestations
- Prior response to specific drugs
- Severity

Disease Behavior

- Inflammatory disease



- Mechanical obstruction (fibro-stenotic)

- Penetrating disease

Provide Therapy Commensurate With Severity of Disease

- Clinical gestalt

- Measurement tools
  - Crohn's Disease Activity Index
  - Harvey Bradshaw Index
  - Montreal Classification

Crohn's Disease Activity Index

- Variables
  - Number of liquid or very soft stools
  - Abdominal pain
  - General well-being
  - Number of listed complications
  - -Use of antidiarrheal agents
  - -Abdominal mass
  - -Hematocrit
  - -Change in standard body wt

- Measured over a 7-day period
- CDAI ≤ 150: Remission
- CDAI 151–220: Mild disease
- CDAI 220–450: Moderate to severe
- CDAI > 450: Severe disease

Harvey Bradshaw Index

- General well-being

  0=very well, 1=below par, 2=poor, 3=very poor, 4=terrible

- Abdominal pain

  0=none, 1=mild, 2=moderate, 3=severe

- Number of liquid stools per day

- Abdominal mass

  0=none, 1=dubious, 2=definite, 3=definite and tender

- Complications

  Arthralgia,uveitis, e. nodosum, p. gangrenosum, fistula, apthous ulcer, abscess (score 1 per item)

Grading Activity	
<5	remission
5-7	mild disease
8-16	mod disease
>16	severe disease
Response= ≥ 3pt drop	

Determining Severity
Clinical Gestalt

- Remission
  - Asymptomatic, off systemic steroids
  - No inflammatory sequelae
- Mild to moderate Crohn's disease
  - Ambulatory
  - Nontoxic
  - No abdominal tenderness, mass or obstruction
- Moderate to severe Crohn's disease
  - Unresponsive to mild/moderate therapy
  - Prominent fever, weight loss, anemia
  - Abdominal pain/tenderness, obstruction
- Severe Crohn's disease
  - Persistent symptoms on high dose prednisone
  - High fever
  - Rebound tenderness, abscess

Therapy for Mild Disease

- Oral and topical 5-ASA compounds were first-line agents for patients with mild disease
  - No strong evidence to support therapeutic efficacy in Crohn's disease
- Budesonide: 9mg po daily
  - First choice for mild-moderate ileo-colonic CD
  - More effective than mesalamine
  - Fewer side effects than prednisone

Therapy for Mod to Severe Disease

- Prednisone first-line therapy with Step-up theory of treatment selection
  - Proven efficacy
  - Rapid symptomatic relief
  - Dose as 40-60mg as single AM dose
- Consider early use of biologic therapy
- Immunomodulators
  - Azathioprine/6-mercaptopurine
  - Methotrexate
- Biologics
  - Remicade
  - Humira
  - Cimzia

Therapy for Severe Crohn's Disease

- IV steroids
- Biologics
  - Remicade -Tysabri
  - Humira
  - Cimzia
- Immunomodulators
  - Methotrexate
  - Azathioprine/6-mercaptopurine
- Surgery

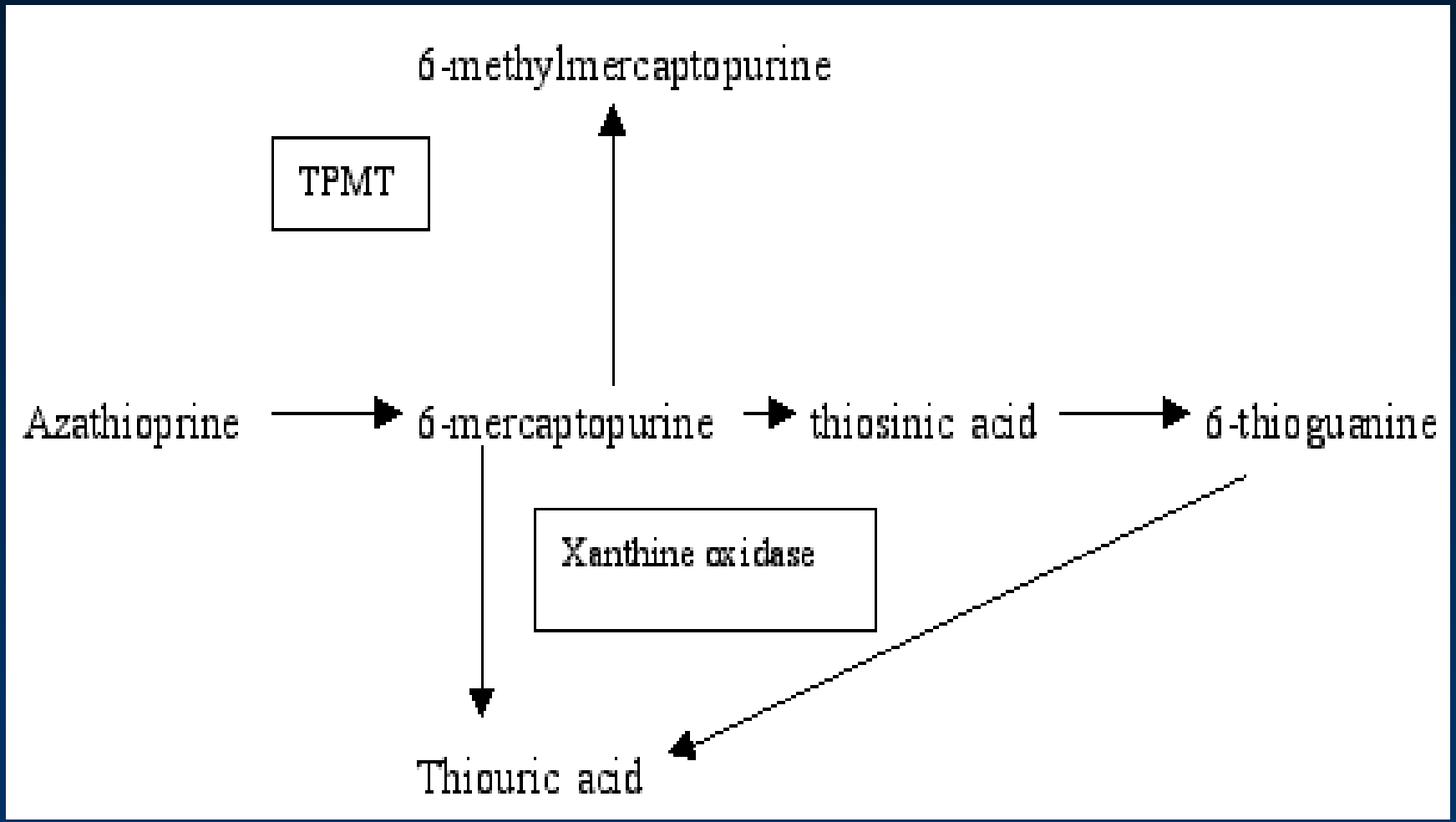
Montreal Classification

- A=age at dx
  - A1 <16
  - A2 17-40
  - A3 >40
- L=location
  - L1 TI
  - L2 colon
  - L3 ileocecal
  - L4 upper
- B=behavior
  - B1 non-stric/pen
  - B2 stricturing
  - B3 penetrating
  - B4 peri-anal dz

Beaugerie Gastro 2006

- Risk factors
  - Age below 40
  - L1, L3
  - Penetrating or stricturing pheno
  - ASCA
  - Anti-OMPc
  - Anti-CBir1
  - Anti-I2
  - Steroid at dx

Azathioprine Metabolism



Approach to Ulcerative Colitis Therapy

Selection of Treatment

- Treatment plan designed is based on
  - Severity
  - Extensive vs. distal
  - Presence of complications/extra-intestinal manifestations
  - Prior response to specific drugs
- Therapeutic decisions rarely based on severity of inflammation seen at endoscopy or histology

UC-Clinical Severity

- Severity of disease can be determined by:
  - Truelove and Witt's criteria
    - mild
    - moderate
    - Severe
- Easy to remember:
  - 2 historical points
  - 2 physical exam points
  - 2 laboratory values

UC Severity
Truelove and Witt's Criteria

Variable	Mild	Severe	Fulm
Stools	<4	>6	Contin
Blood	Intermit	Freq	Contin
Temp	NI	>37.5	>37.5
Pulse	NI	>90	>90
Hgb	NI	<75% nl	Transf
ESR	<30mm	>30	>30

- All mild parameters = mild severity
- Fewer than all six severe = moderate

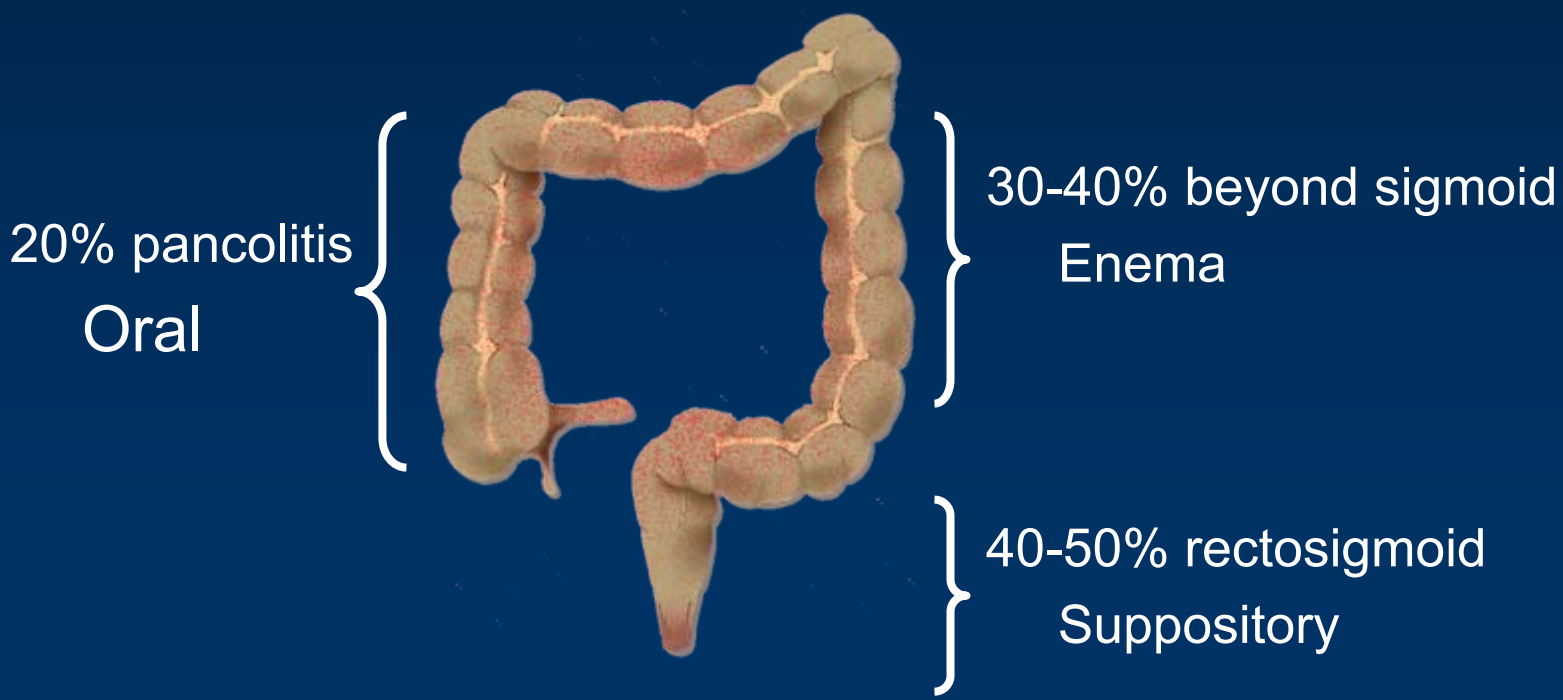
Ulcerative Colitis Activity Index

1. Stool frequency	*0-3*: normal *1-3*: 1-2 stools daily > normal *2-3*: 3-4 stools *3-3*: 4 stools
2. Rectal bleeding	*0-3*: None *1-3*: Streaks of blood *2-3*: Obvious blood *3-3*: Mostly blood
3.Mucosal appearance	*0-3*: Normal *1-3*: Mild friability *2-3*: Moderate friability *3-3*: Exudation, spontaneous bleeding
4. Physician's rating of disease activity	*1-3*: Normal *2-3*: Mild *3-3*: Moderate *4-3*: Severe
Maximum score 3	*13*

- Clinical response
  - Reduction from baseline ≥3 pts
    +
  - Reduction of bleeding ≥ 1 pt
    or
  - Absolute score ≤ 1
- Clinical remission
  - Score ≤ 2pts
    +
  - No individual score >1

Site of Delivery
Based on 5-ASA Formulation

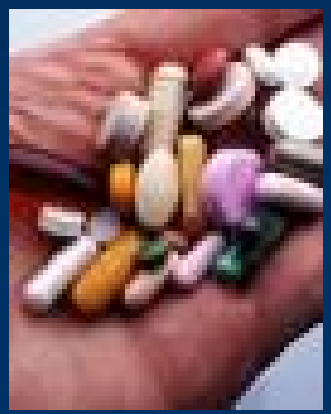
- Topical therapy's ability to reduce inflammation directly linked to ability to reach site of inflammation



5-ASA Therapy

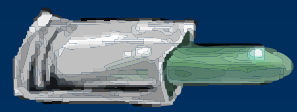
- Best choice for mild to moderate disease

- Sulfasalazine
- Asacol (mesalamine)
- Lialda, (once daily mesalamine)
- Pentasa (mesalamine)
- Dipentum (olsalazine)
- Colazal (balsalazide)



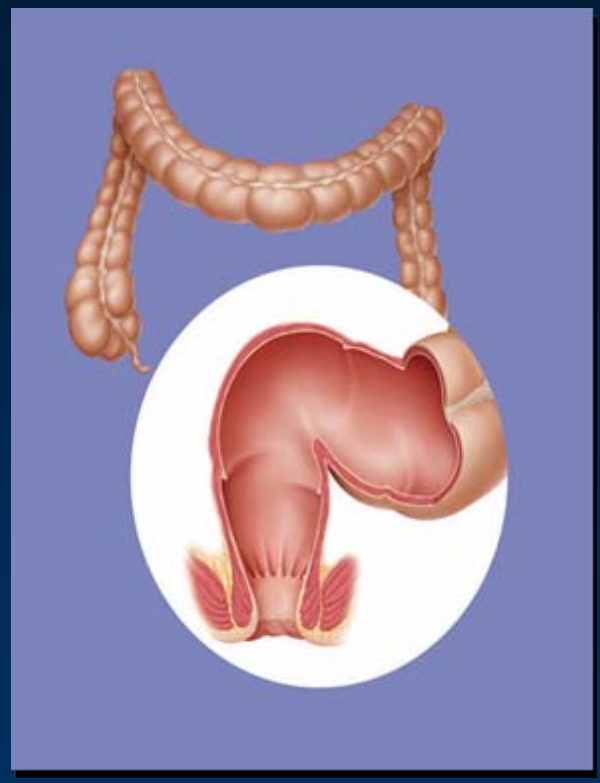
- Rowasa (mesalamine)

- Canasa (mesalamine)



Principles of Topical Therapy

- Treats the rectal/colonic mucosa directly
- Best initial choice for active ulcerative proctitis/sigmoiditis



Topical Therapy Considerations

- Topical mesalamine agents are superior to topical steroids or oral 5-ASA alone for left sided disease
- The combination of oral and topical aminosalicylates are more effective than either alone
- In patients refractory to oral aminosalicylates or topical steroids, mesalamine enemas or suppositories may still be effective (not dose dependent)
- Advantages of topical:
  - Quicker response time
  - Less frequent dosing
  - Fewer side effects than oral

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312

Moderate to Severe UC

- Moderate will often respond to oral prednisone (40-60mg/d)
  - More severe may need admission
  - Outpatient management requires careful monitoring
- May begin steroid taper after patient clinically “well” (2-4 weeks)
  - Decrease prednisone by 5mg/wk until reaching 20mg
  - Below 20mg, taper by 2.5mg to 5mg per week
- Flare during taper should prompt increase to lowest level prior to flare
- Inability to complete taper should prompt consideration of immuno-modulators

Moderate to Severe UC
Immunomodulators

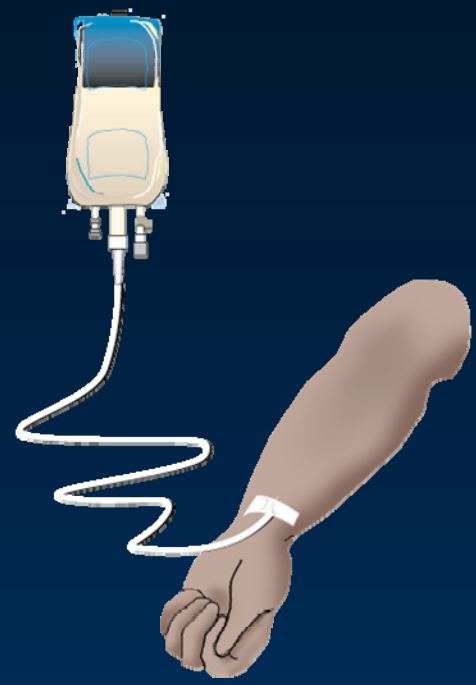
- May require use of concomitant immuno-suppression
- 6-mp/AZA have been shown to be helpful
- No role for methotrexate

Moderate to Severe UC
Anti-TNF Therapy

- If concomitant immuno-suppression ineffective, maximize therapy
- Consider Remicade for persistently active disease
  - 5mg/kg IV infusion 0, 2, 6 weeks, then q8 weeks
  - Same principles apply

Severe Ulcerative Colitis

General Treatment Guidelines



- Admit to hospital
  - 15% require at some point
- IV fluids/steroids
- GI consultation
- Surgical consultation
- Daily KUB/baseline ESR
- Consider clinical trial

Severe Ulcerative Colitis

Steroid Therapy

- Steroids may be administered in continuous or split dose
  - ACTH 120 units/24 hours as continuous infusion
    - If no steroids within previous 30 days
  - Hydrocortisone 100mg q 8 hours
  - Methylprednisolone 16-20mg q 8 hours*
  - Prednisolone 30mg q 12 hours*

- Continue for 7-10 days, as long as improvement continues
  - If no improvement in 5-7 days, consider other therapy

*Less Na retention, K wasting

Severe Ulcerative Colitis
5-ASA Considerations

- No role for NPO (low residue diet)
- If already on 5-ASA products-STOP!!
- However, if not intolerant, concomitant administration of 5-ASA may improve short and long term response rates
  - 90% response rate when started early
  - 71% response without 5-ASA

Loftus AJG 2001 S299

Severe Ulcerative Colitis

Predicting Need for Second-Line Therapy

- Much of the morbidity/mortality associated with severe UC comes from delayed surgery
- Need to select patients who will benefit from additional therapy early in course of disease
- Two models predicted medical failure, early surgery:
  - Stool frequency >8/day, or 3-8/day with CRP>45mg/dL after 3 days steroid therapy: 85% require colectomy[1]
  - #BM + 0.14 x CRP (mg/L)>8.0 as optimal cut-off to predict medical failure[2]

1. Travis et al. Gut 1996;38:905-10
2. Lindgren et al. Eur J Gastroenterol Hepatol 1998;10:831-5

Fulminant Colitis

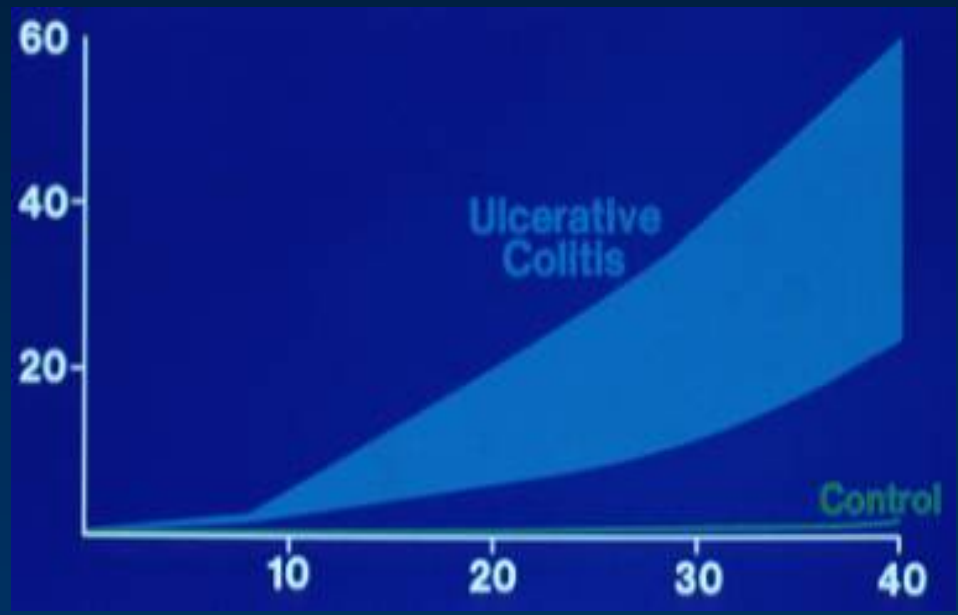
- Medical emergency manifested by
  - high fever
  - abdominal tenderness, abdominal distension
  - hemorrhage
- May or may not have colonic distension
- Morbidity increased by delaying surgical therapy

UC-Indications for Surgery

- Immediate
  - Toxicity and/or perforation
  - Exsanguinating hemorrhage
- Urgent
  - Unresponsive severe colitis
  - Severe/acute complications of disease or therapy
    - Opportunistic infections
    - Steroid psychosis
    - Hemolytic anemia
- Elective
  - Suspected cancer
  - Dysplasia
  - Growth retardation
  - Osteonecrosis or compression fracture
  - Intractability

Cancer Risk from UC/Crohn's Colitis

- Retrospective study of cancer risk from UC
  - 10 years 2%
  - 20 years 8%
  - 30 years 18%

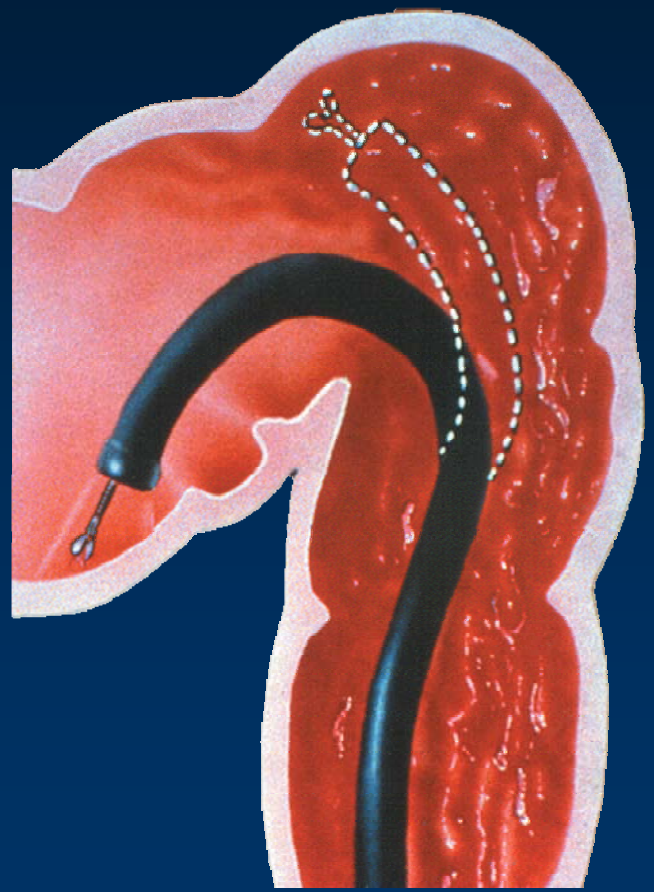


- Extent AND duration of disease predictive factors

Eaden et al. Gut 2001;48:526-535

Colorectal Cancer in Ulcerative Colitis
Dysplasia

- Surveillance begins after 8 years
  - 33 biopsies required for 90% confidence of finding dysplasia[1]
- Low grade dysplasia associated with synchronous cancer 19%
  - Debate over need for colectomy
- High grade dysplasia definite indication for colectomy



1. Rubin et al. Gastro 1992;103:1611-1620

Night Call Scenarios

- Referring physician wants to transfer a 58 year old male with long-standing UC, admitted with a severe flare
  - Hospitalized for five days on IV steroids
    - Minimal relief

- What to do first?

Night Call Scenarios

- ER calls with a 27 year old female with several year history of Crohn's disease
  - Presents with worsening fevers/chills, abdominal pain in RLQ, and diarrhea
    - Started on left-over Enterocort at home
    - No relief
- What to do?