Adult Crohn's Disease ACG Guidelines

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- I have no financial conflicts with any of the drug companies in this lecture.

Topics

- Clinical Features
- Natural History
- Intestinal Malignancy
- Diagnosis
- Management of Disease
- Medical Therapy
- Surgical Therapy
- Postoperative Crohn's disease: maintenance, Prevention, Treatment

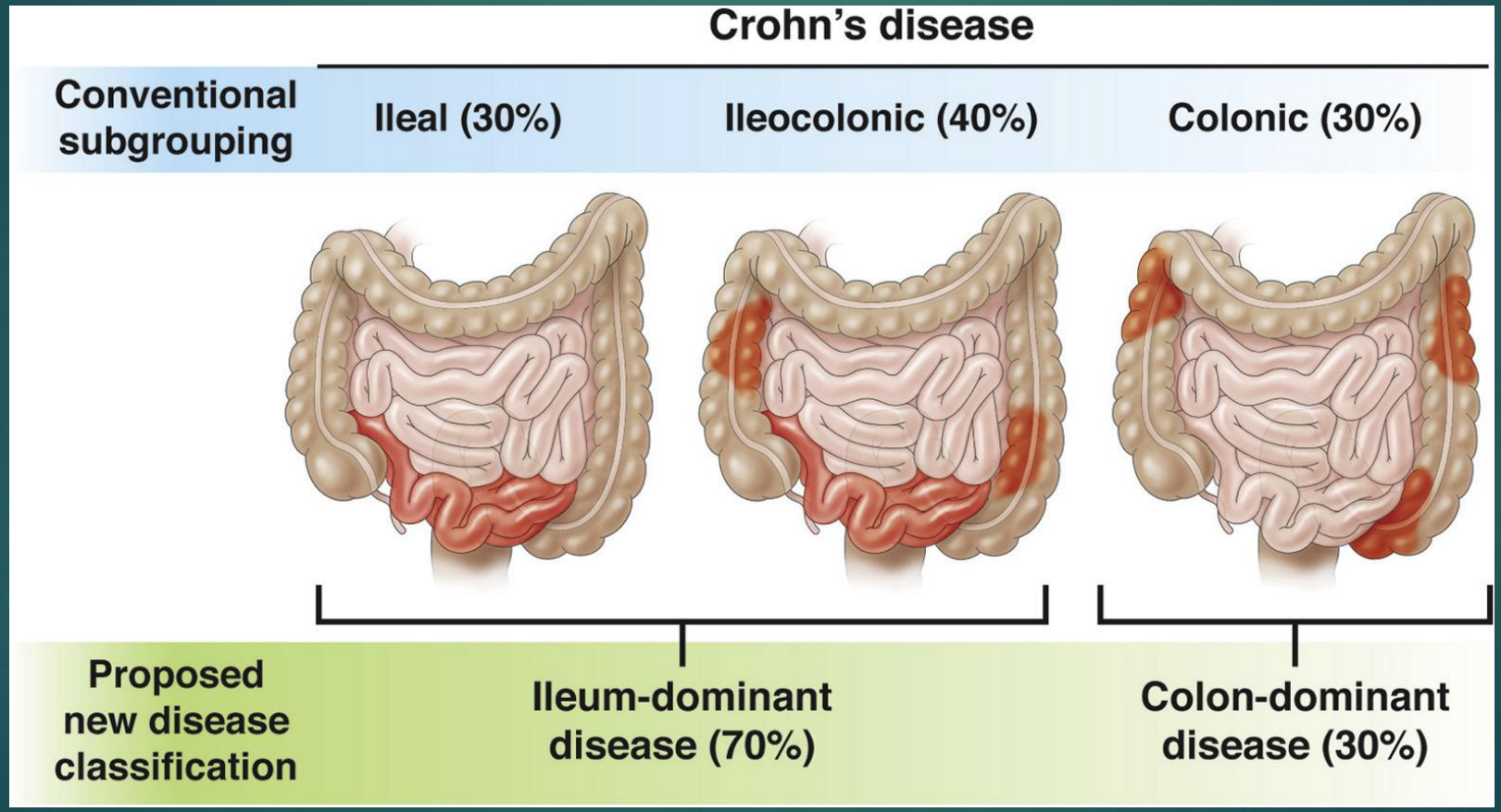
Lecture Goals

- Common presentations of Crohn's disease
- Diagnosis of Crohn's disease
- Historical and newer algorithms of treatment
- Side effects of treatment

Clinical Features

- Abdominal pain (RLQ and post-prandial), diarrhea (most common), fatigue, weight loss, fever, growth failure, anemia, fistulae, extraintestinal manifestations
- CD is diagnosed clinically
- Extraintestinal manifestations: arthropathy (axial and peripheral), dermatologic (pyoderma gangrenosum, erythema nodosum), ocular (uveitis, scleritis, episcleritis), hepatobiliary disease (PSC)
- Increase risk of thromboembolism (venous and arterial)
- Cholelithiasis, osteoporosis, osteonecrosis, nephrolithiasis
- Associations: asthma, bronchitis, pericarditis, psoriasis, celiac disease, RA , MS

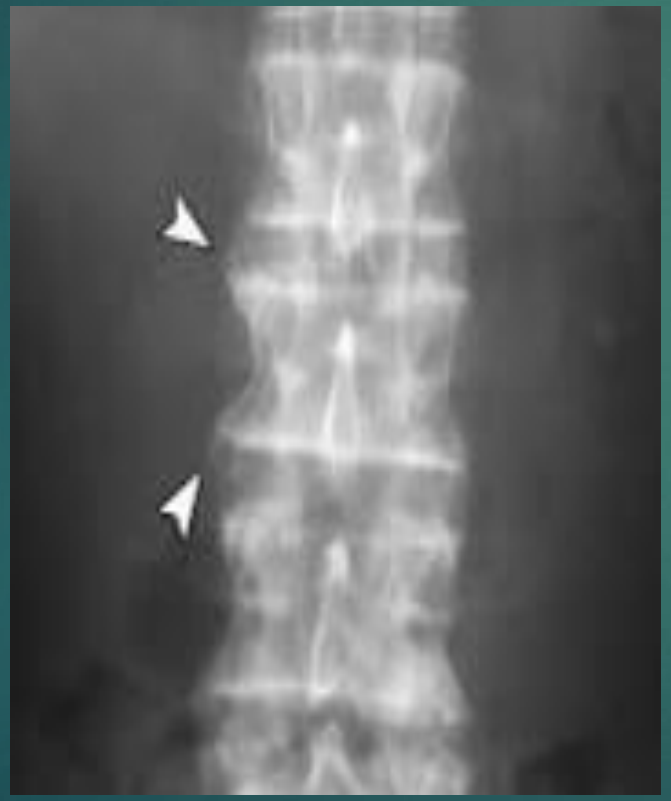
Distribution

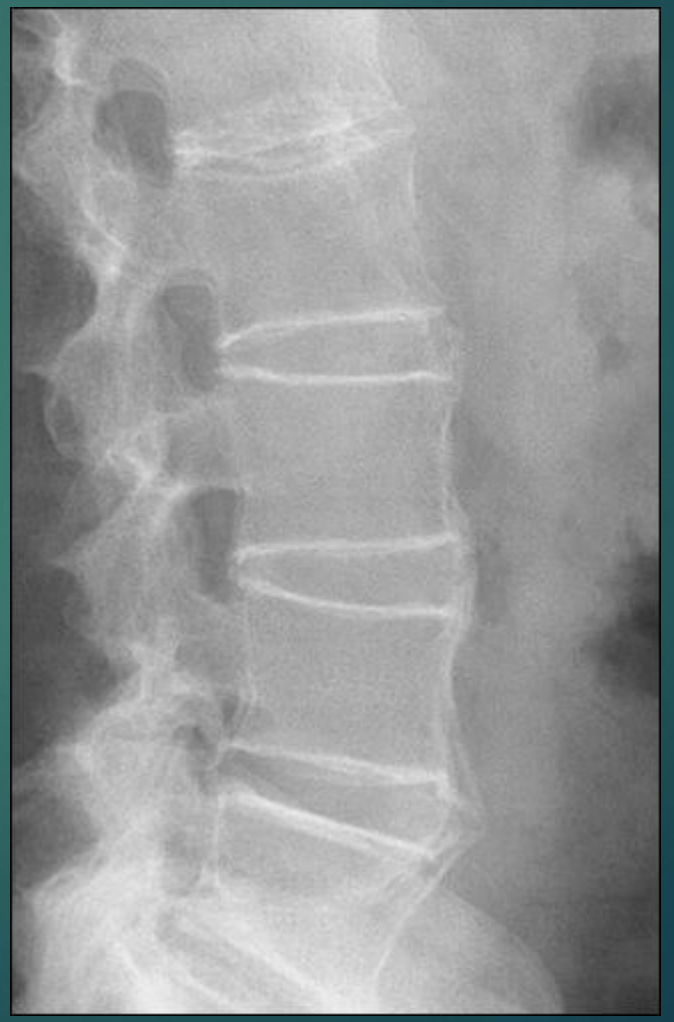


Clinical Features (Cont'd)

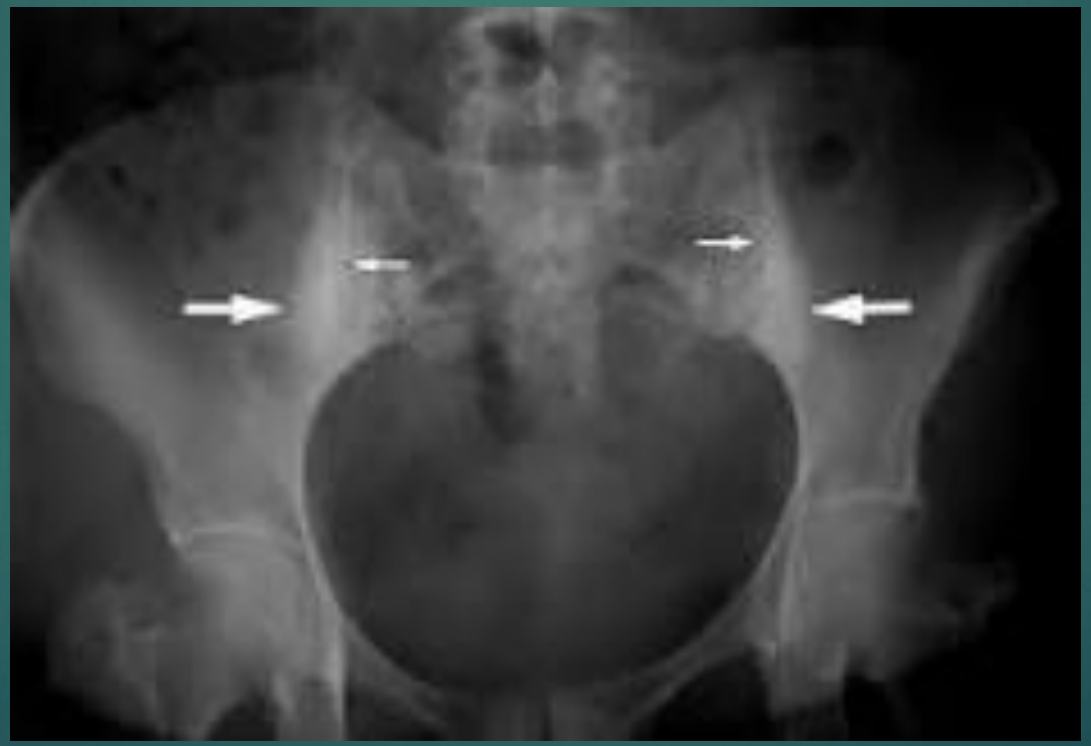
- 1/3 ileum, 1/3 colon, 1/3 both
- UGI involved in ¼
- B/w 5 and 25% present with stricture or fistulae

Ankylosing Spondylitis

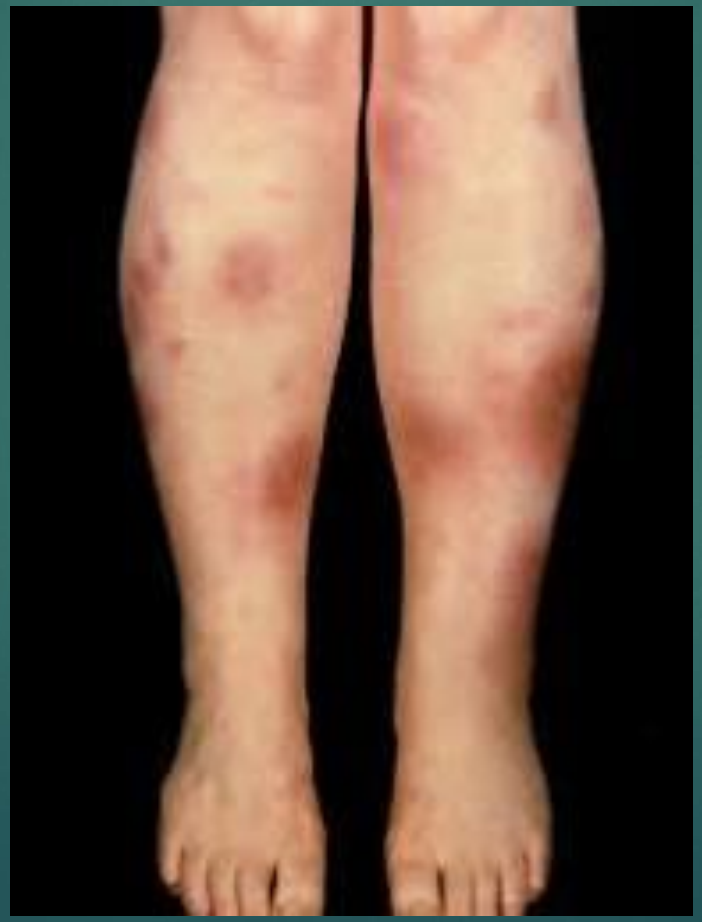




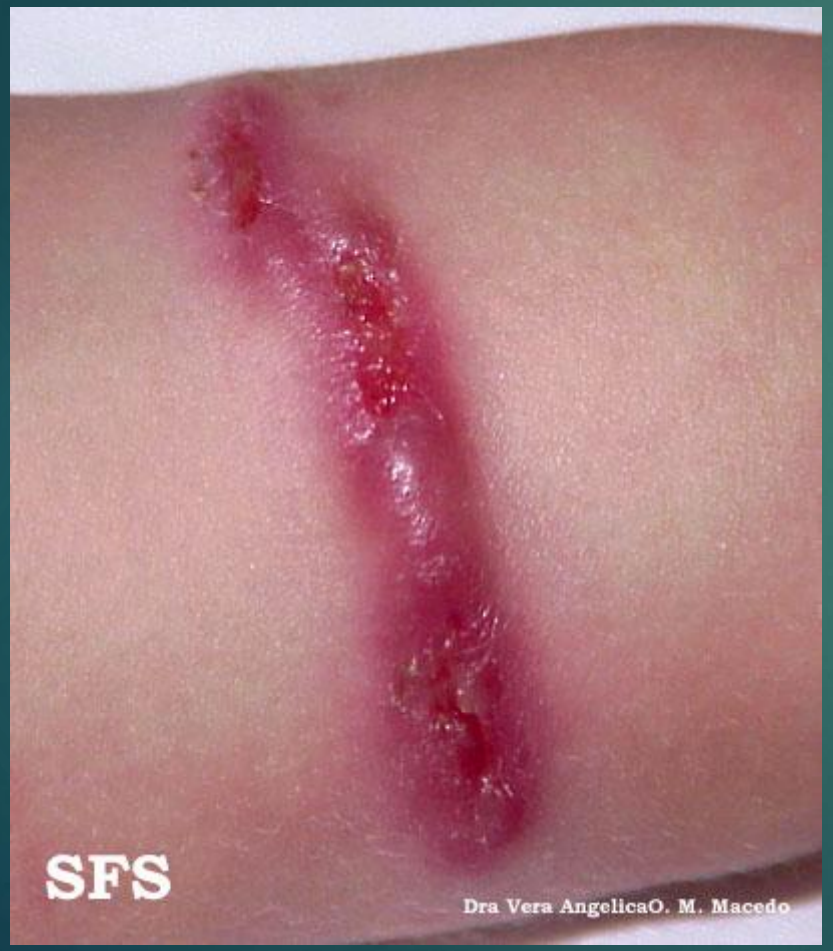
Sacroileitis

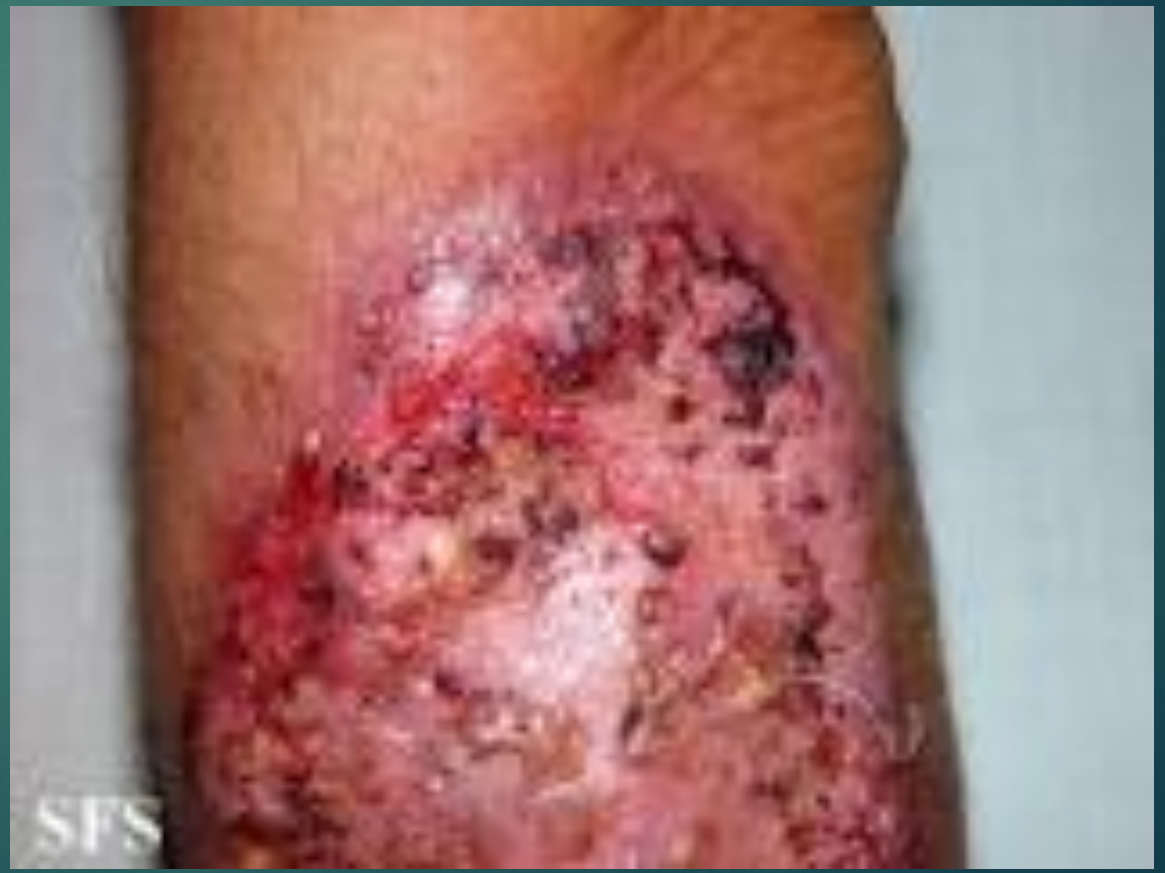


Erythema Nodosum

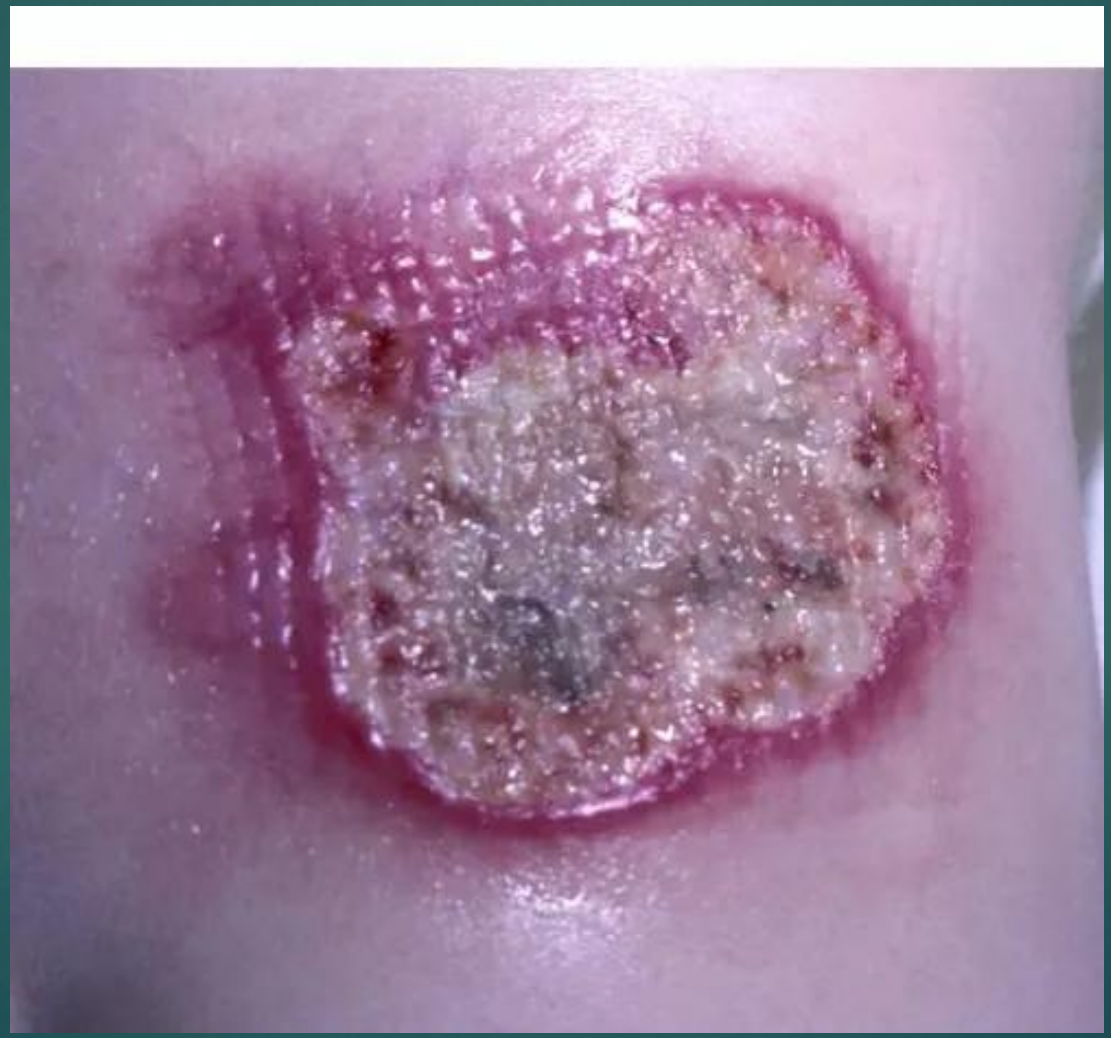


Pyoderma Gangrenosum

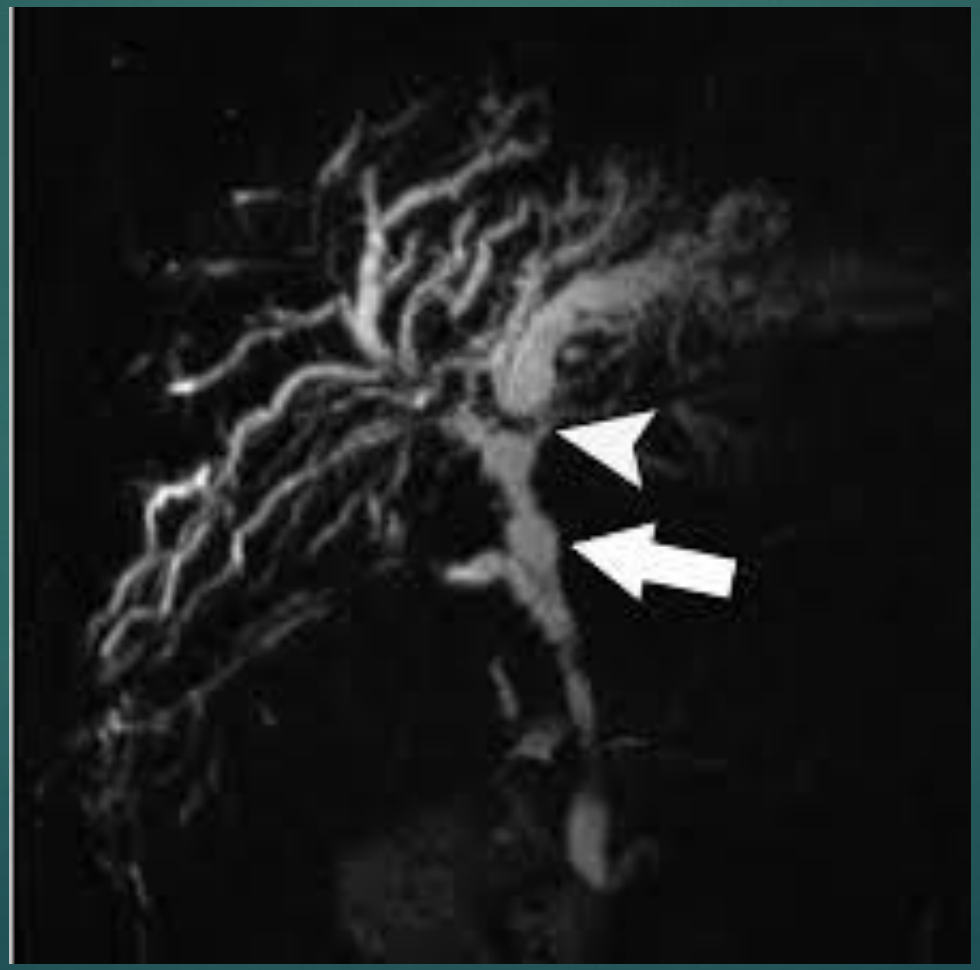




Pyoderma Gangrenosum



Primary Sclerosing Cholangitis



Uveitis

Iritis

Natural History

- Chronic , progressive, destructive
- Location is stable but can extend
- 20-30% will have a nonprogressive or indolent course
- Symptoms do not correlate well with degree of inflammation
- Perianal fistula occur in ¼
- Most have chronic intermittent course
- Steroid dependency or resistance ½ if no 6-mp or biologic agent used
- 80% require hospitalization at some point
- Over 10yrs, abdominal surgery in 50% (may have decreased recently)

Natural History

- 35% risk of abdominal surgery in next 10yrs
- 5yr risk of symptomatic post-op recurrence is 50%
- Overall mortality risk ratio of 1.4. Causes are GI cancer, lung disease, lung cancer
- Symptoms do not correlate with inflammatory markers or endoscopic scoring

Younger age at diagnosis, extensive luminal involvement, perianal disease and severe rectal disease prognosticate more severe course

Natural History

- 83% hospitalized within a year of diagnosis with annual hospitalization of 20%
- Risk factors for recurrent disease post-op are cigarette smoking, shorter duration of disease before operation, more than one resection, and penetrating disease
- Some studies show increased mortality with prolonged steroid usage

Intestinal Malignancy

- Those with colonic involvement have increase risk of CRC more likely with larger extent of disease, PSC, FH of CRC, diagnosed younger than 40 y/o, and severity of ongoing inflammation
- SB involvement at increased risk of SB adenocarcinoma (RR increased 18-fold) but surveillance recommendations not given

Investigation

- Markers for inflammation, anemia, dehydration, malnutrition
- If symptomatic, check stool studies, fecal calprotectin
- FC (>50ug/g) is used to differentiate inflammatory from non-inflammatory, e.g. IBS
- Genetic testing is not indicated to establish diagnosis
- Genetic variants may be used to affect individual treatment or drug toxicity. Routine use of serologic markers not indicated
- Ileocolonoscopy with bx's and photodocumentation
- Disease distribution and severity should be documented.

Investigation

- Anemia and thrombocytopenia most common abnormality on CBC
- CRP produced by liver in setting of inflammation (t1/2 19 hrs) and may be helpful to monitor inflammation
- CRP correlates better than ESR
- (40% with mild disease may have nml markers)
- FC is calcium-binding protein from neutrophils helps regulate inflammation
- Lactoferrin, elastase, lysozyme also derived from neutrophils
- Over 200 genetic loci associated with CD. ASCA, anti BIR 1, omp C, anti-flagella antibody, NOD 2 may be used for individual patients to help with diagnosis and prognostication

Investigation

- HLADQA1*05 and HLADRB1*03 haplotypes associated with immunogenicity against TNF antagonists causing antibody formation and resistance to the medication

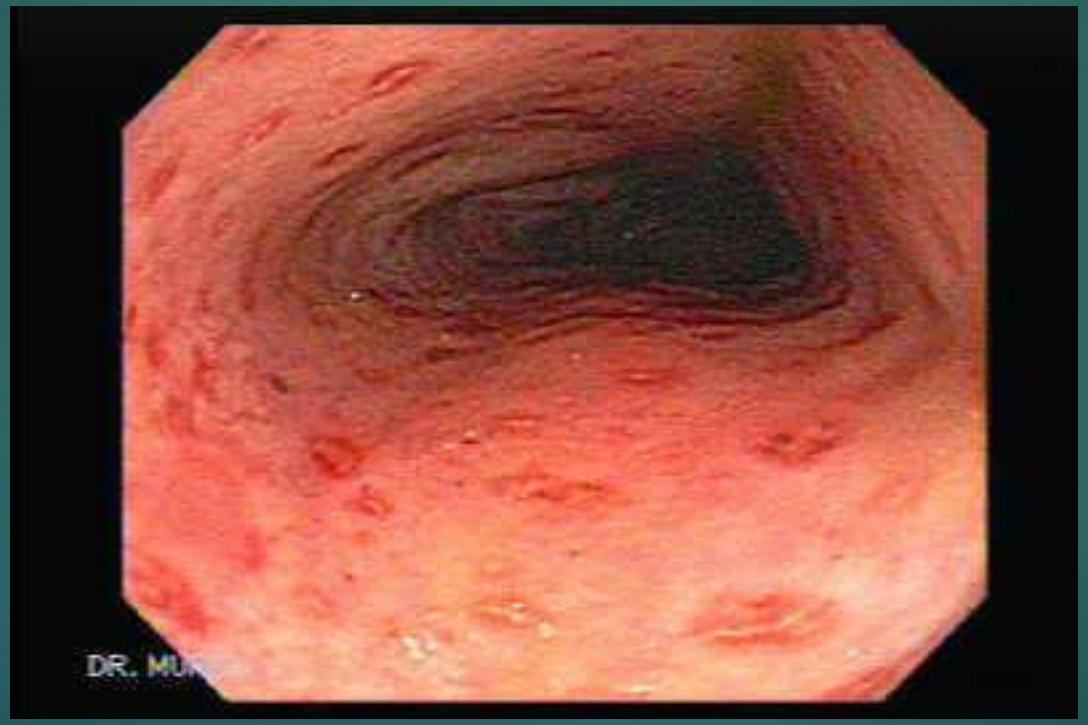
Endoscopy

- Colonoscopy should be performed to diagnose cancer earlier with improved survival; 80% will have disease within range of scope
- Start surveillance after 8 yrs in those with at least 30% of colon involved
- EGD to be performed if UGI complaints
- Video Capsule Endoscopy for those to secure diagnosis in high suspicion patients (96% NPV with retention rate of 0-5.4%)
- SBFT, CTE, or MRE to be performed before VCE in those with obstructive symptoms
- VCE>>CTE>>SBFT

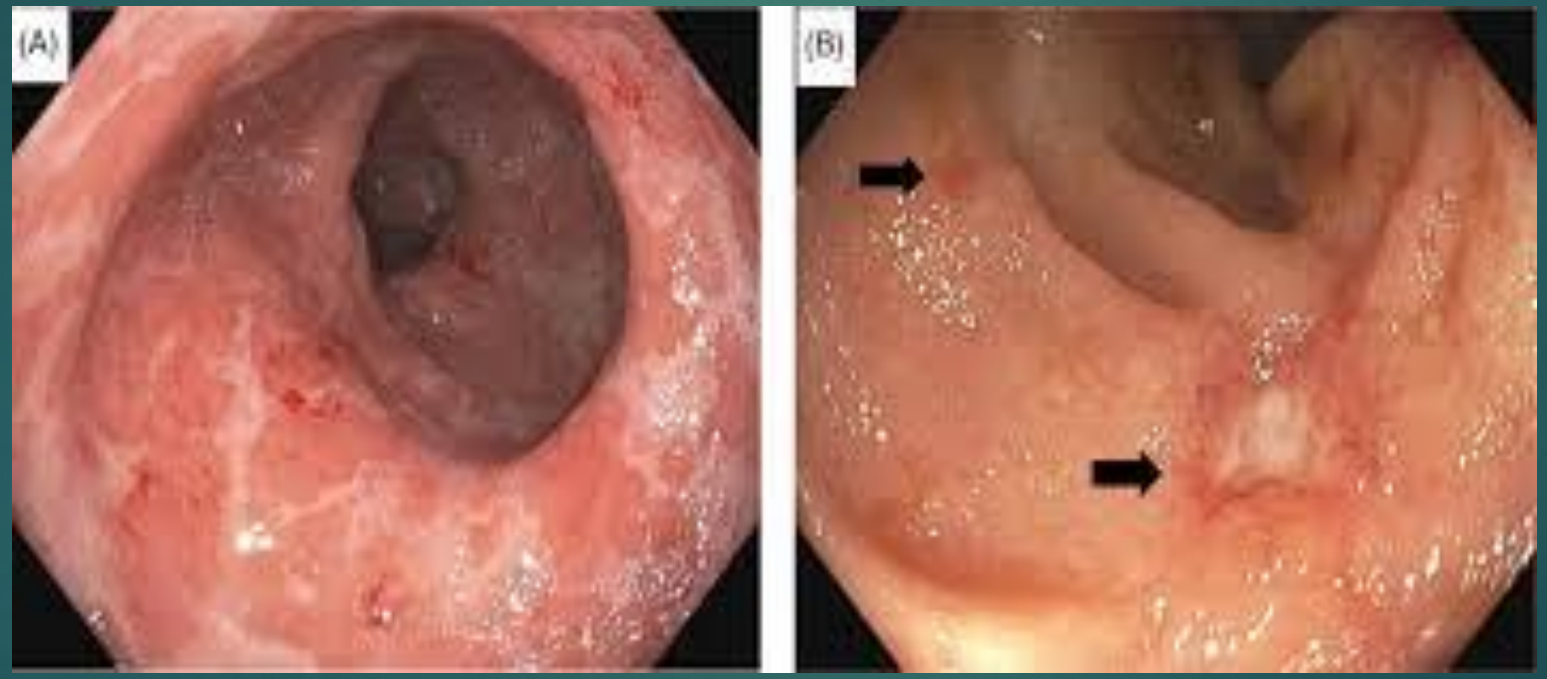
Histology

- Non-caseating granulomas clinch the diagnosis but only present 10% of the time
- Crypt abscesses frequently present but also present in bacterial colitis and UC.

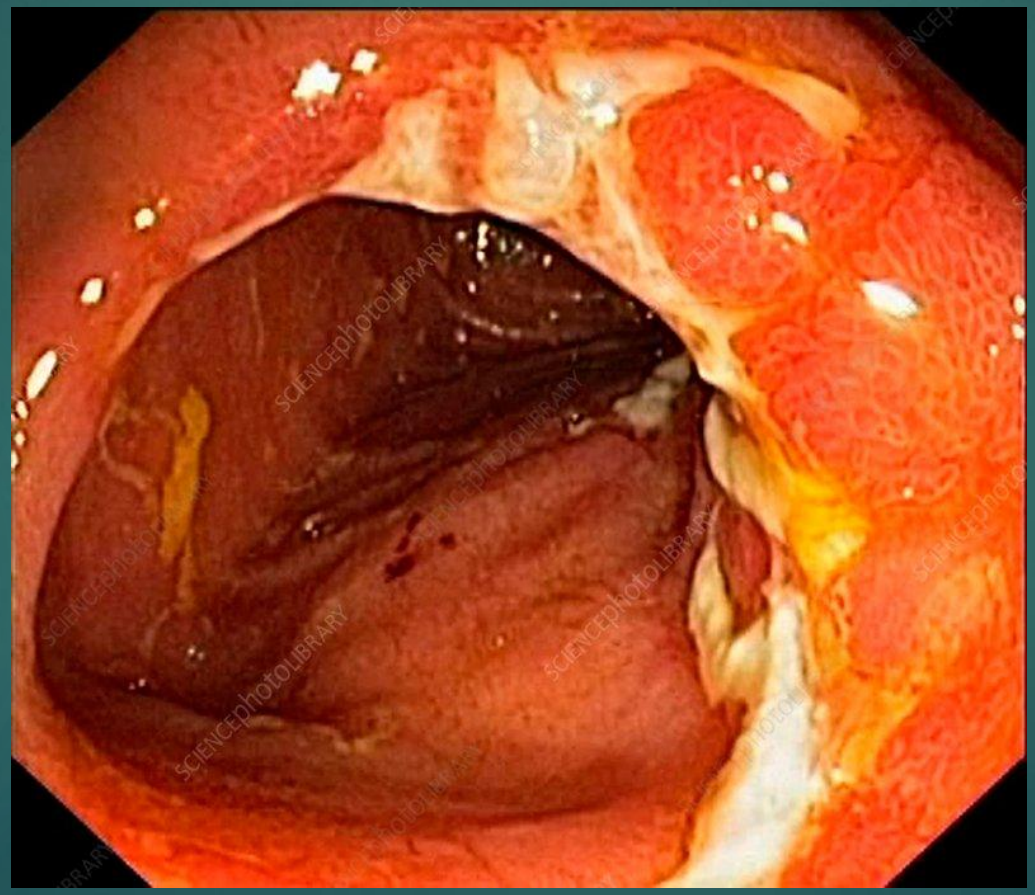
Crohn's Colitis



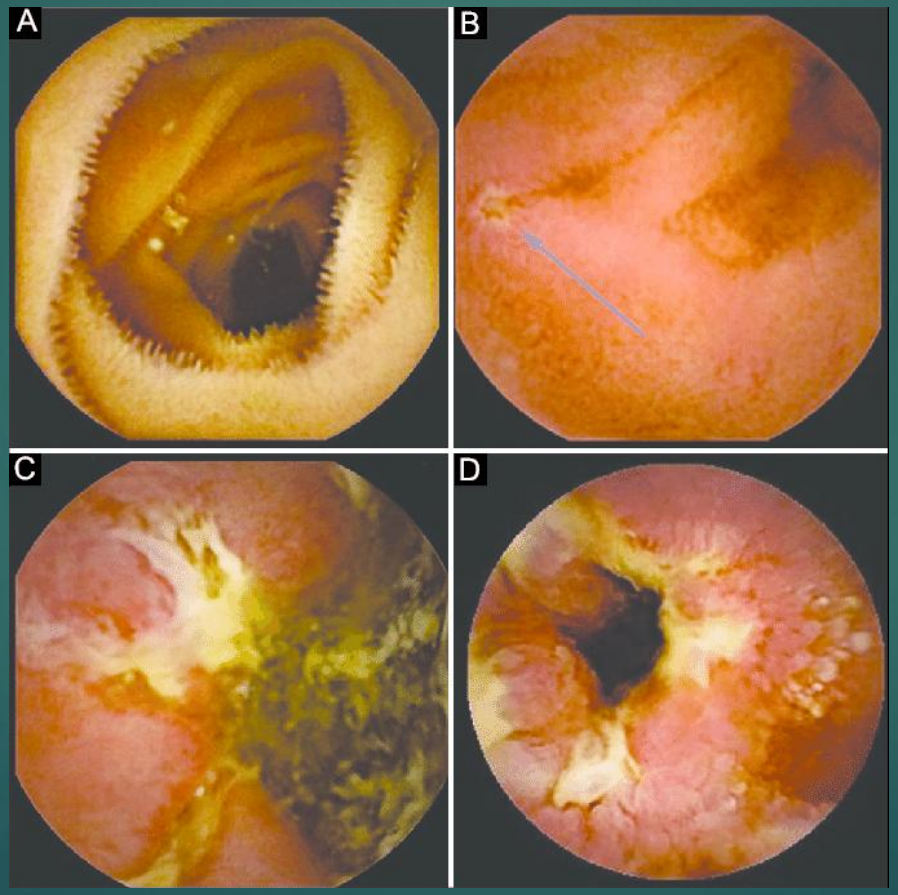
Crohn's Colitis



Terminal Ileum Crohn's

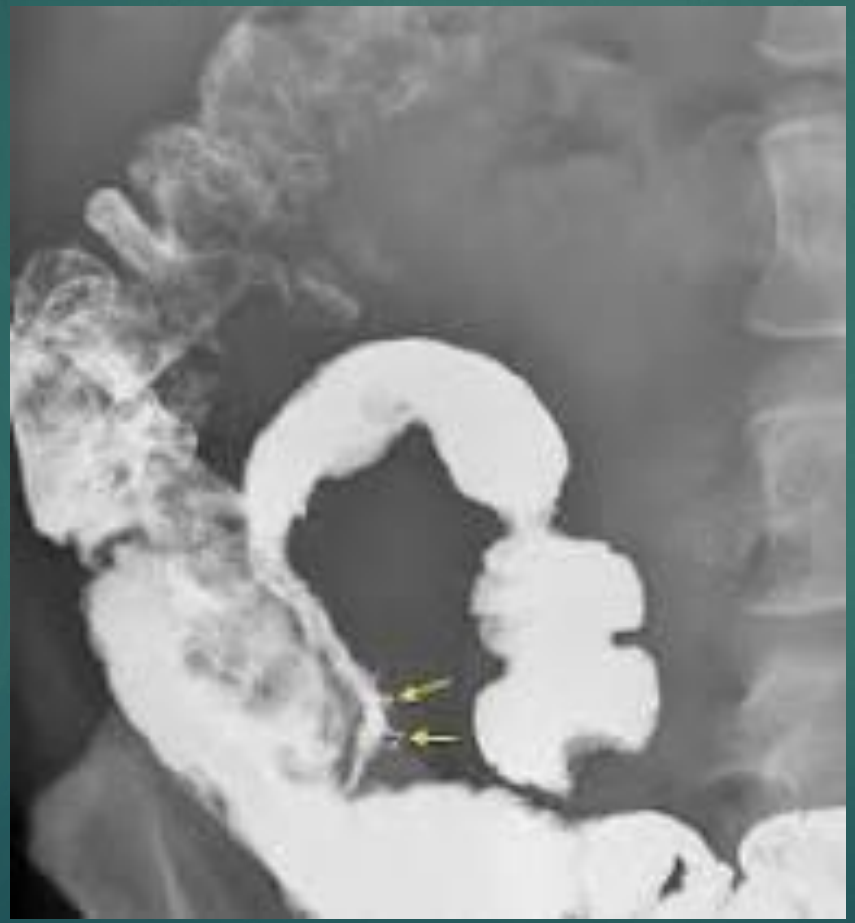


Ileum Crohn's on Capsule Endoscopy

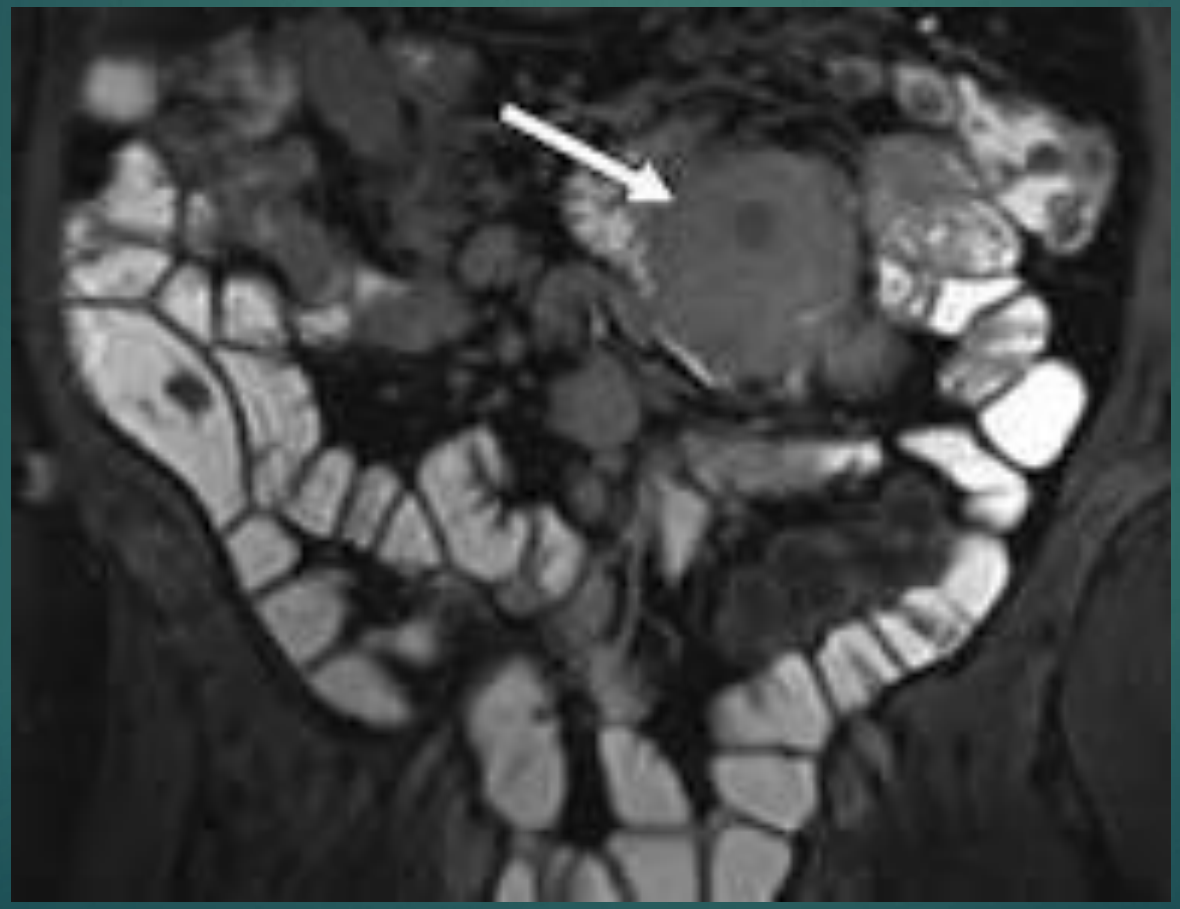


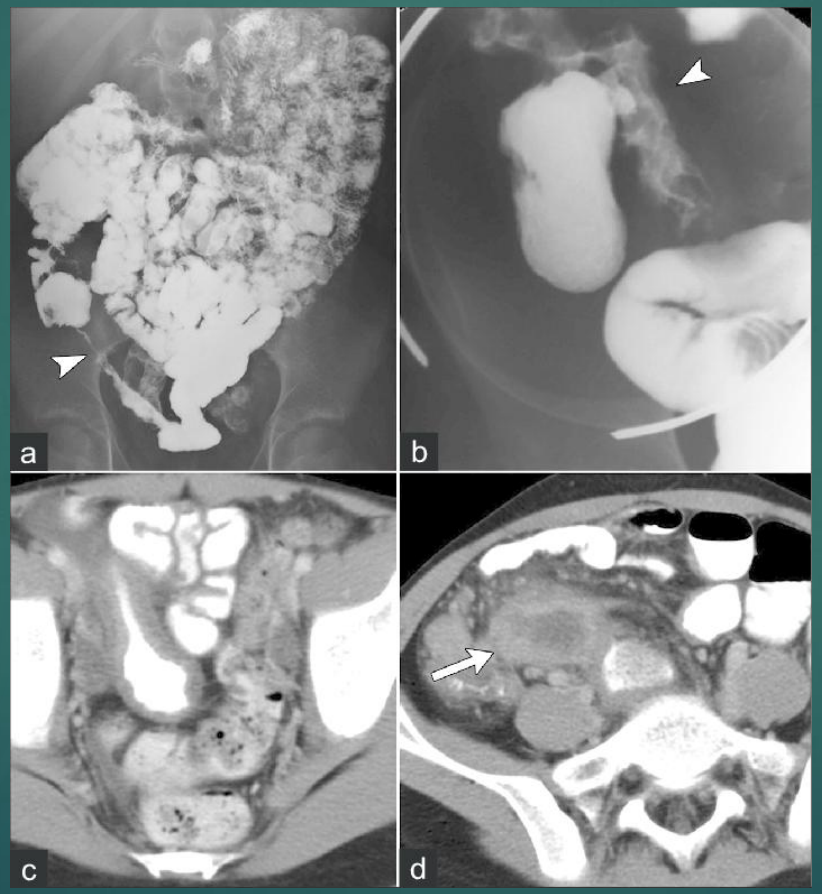
Imaging

- Small bowel imaging should be part of initial w/u
- CTE, MRE
- MRE in young patients (<35y/o) due to radiation exposure in CTE
- Intestinal ultrasound (IUS)
- MRI and EUS best for pelvic disease



MRI- Crohn's

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Disease Modifiers

- NSAIDs exacerbate IBD
- Cigarette smoking exacerbates activity and accelerates disease recurrence
- Assessment of stress, depression, anxiety
- Smokers have increased incidence of IBD hospitalization, peripheral arthritis, and surgery

Disease Management

- Goal: mucosal healing
- Step up vs Step down approach
- Improvement noted within 2 weeks and maximal improvement in 12-16 weeks
- Exclude C.diff and CMV with exacerbations

Mild to Moderate CD

- Mesalamine not indicated
- Controlled ileal budesonide (Entocort EC) 9mg for induction
- Controlled ileal budesonide not indicated for maintenance
- No steroids to be used for maintenance
- No maintenance tx for patients who are asymptomatic, monitor
- Sulfasalazine for mild symptomatic colonic involvement
- Antibiotics are not be be used for luminal disease(just fistulae, abscess)
- Diet therapies for those who are asymptomatic (elemental, semi-elemental, ?Mediterranean)

Classes of Drugs

Immunomodulator

Azathioprine (Imuran, Azasan)

6-Meraptopruine (Purinethol, Purixan)

Methotrexate (Trexall)

Anti-TNF

Infliximab (Remicade)

Adalimumab (Humira)

Certolizumab (Cimzia)

Golimumab (Simponi)

Anti-integrin/Anti Interleukin

Vedolizumab (Entyvio)

Ustekinumab (Stelara)

Risankizumab (Skyrizi)

Natalizumab (Tysabri)

Mirikizumab (Omvoh)

Guselkumab (Tremfya)

Classes of Drugs (cont'd)

- **JAK Inhibitors (Small Molecules)- taken po**
- **Janus- Roman god of gateways and new beginnings (month of January named after him)**

- Tofacitinib (Xeljanz)

- Upadacitinib (Rinvoq)

Moderate to Severe Crohn's disease

- Steroids for short term induction
- Immunomodulators (azathioprine 1.5-2.0 mg/kg or 6-mp 0.75-1.5mg/kg) for induction and maintenance. Better for maintenance than induction as they are slow to act. May cause allergic reactions, pancreatitis, myelosuppression, nausea, infections, hepatotoxicity, non-melanoma skin cancer, lymphoma
- TPMT testing mandatory for those getting immunomodulators
- MTX 25mg weekly IM or SC mainly in males (teratogenic, nausea, vomiting, hepatotoxicity pulmonary toxicity, bone marrow suppression, skin cancer and ?lymphoma)
- Azathioprine, 6-MP, MTX may be used with anti-TNF agents to increase therapeutic trough levels and decrease risk of antibody formation

Anti-TNF Agents

- Recommended for induction and maintenance of remission for moderately to severely active disease (infliximab, adalimumab, certolizumab pegol); check for HBV and TB
- IV infliximab with immunomodulators recommended over infliximab or immunomodulators alone(only TNF available both IV and SC)
- SC infliximab may be used in those responsive to iv infliximab induction

Monitor for antibodies and drug levels for infliximab, adalimumab, certolizumab. Low dose 6-mp, azathioprine, MTX increase levels and decrease risk of antibody formation

Biosimilars (infliximab, adalimumab, ustekinumab) are available and cheaper. Can be switched from brand to biosimilar without issue.

Agents Targeting Leukocyte Trafficking

- Iv vedolizumab indicated for induction and maintenance in moderate to severe disease (alpha 4 B7 integrin antibody). Very gut selective. May be used prior to anti-TNF. Adding immunomodulator not beneficial. Does not cause systemic immunity issues
- SC vedolizumab indicated in those responding to 2 IV induction doses
- Natalizumab (anti-alpha 4 integrin antibody at risk for PML if JC virus positive. Effects gut and brain.

Agents Targeting IL-12 (anti-p40 ab) & IL-23 (anti-p19 ab)

- Ustekinumab (IgG1 anti-p40) for induction and maintenance in mod to severe dx. Inhibits IL-12/23
- Biologic therapy (including anti-IL-12/23, anti –TNF abs, and anti-integrin therapy dose optimization may be considered for those with inadequate or loss of response. Adding immunomodulator not helpful.
- Risankizumab (IgG1 anti- p-19 antibody inhibits IL-23) for induction and maintenance of remission in mod to severe dx
- Risankizumab to be used instead of Ustekinumab in pts with mod to severe dx and prior exposure to anti-TNF therapy.
- Mirakizumab inhibits IL-23p19 and approved for induction and maintenance
- IV guselkumab for induction and remission followed by SC guselkumab or just SC guselkumab for both induction and remission

Agents targeting JAK inhibitor

- Upadacitinib 15mg or 30mg daily approved for induction and maintenance previously exposed to steroids, immunomodulators, or anti-TNF agents
- Improved QOL outcomes in studies
- Tofacitinib caused increased infections, cancers, cardiac events, DVT/PE

Severe/fulminant disease

- For hospitalized pts, iv steroids may be used while evaluating for steroid-sparing agents
- Anti-TNF agents are effective and can be administered as inpatient
- Infliximab is best due to weight-based dosing (5mg/kg or 10mg/kg)

Fistulizing Crohn's Disease

- Infliximab approved for induction of perianal fistulizing disease
- Adalimumab approved for induction of remission of perianal disease
- Recommend use of antibiotics with infliximab or adalimumab
- Vedolizumab is also approved for induction
- Ustekinumab approved for induction
- Upadacitinib also recommended with low evidence
- Antibiotics can be used a primary treatment (imidazoles)
- Drainage of perianal abscess with setons should be done before treating perianal fistulizing disease

Fistulizing Crohn's Disease

1/3 of patients will develop fistulae

Simple fistulae- distal to the dentate line around the anal sphincter with one tract

Complex fistulae_ transsphincteric, suprasphincteric, intersphincteric and multiple tracts.

Proximal diversion may be needed

Treated with infliximab +/- immunomodulator

One study showed cipro + infliximab or cipro + adalimumab better than TNF alone

Stricturing Crohn's Disease

- Symptom, radiologic, and endoscopic assessments are necessary to guide treatment
- Symptomatic strictures and active inflammation may respond to advanced therapy
- May require endoscopic balloon dilation or surgery

When to Recommend Surgery

- May be considered with symptomatic CD localized to a short segment of bowel (stricturoplasty or resection)
- Required to treat enteric complications
- Intra-abdominal abscesses (>2cm) to be treated with antibiotics and drainage. Immunosuppression to be held until drainage is achieved radiographically or surgically
- Pts with abdominal abscess should undergo surgical resection
- Intractable hemorrhage, perforation, recurrent obstruction, abscess, dysplasia or cancer, or medically refractive

Post-op Crohn's Disease

- Those with surgically-induced remission need post-op endoscopic assessment in 6-12 months
- In those with low risk of recurrence of disease, recommend continued observation as opposed to immediate medical tx
- Imidazole antibiotics (metronidazole) at 1-2gm/day after small bowel resection may help prevent recurrence
- In pts with high risk of recurrence, recommend anti-TNF therapy or vedolizumab
- Consider risk factors for recurrence: active tobacco smoking, penetrating disease, h/o 2 or more prior surgeries
- Lower risk: older than 50y/o, 1st surgery for short segment, >10yrs duration of CD, never smoking

Post –op Crohn's Disease

- Follow fecal calprotectin (>100-150ug/g) associated with recurrence

Summary

- Despite present treatments, 20-30% experience primary non-response to TNF ab and 30-40% lose response or become intolerant within first year of treatment. The latter may respond to dose escalation, addition of immunomodulator, or switching to a different class

- Use the step- down approach, not step-up especially if severe
- Get on anti-TNF or biologic ASAP, the earlier the less long term issues
- In the future, the use of genetics and serologic markers may allow us to individualize the best treatment for each patient (who will respond and who maintains remission long term)