Fellows Weekend

April 2025

Case study

- 35yo male, married, 2 children, IT specialist
- Initially seen by general surgeon 4 months ago – colonoscopy apparently showed pancolitis – and histology showed chronicity ie features of ulcerative colitis (UC)
- Initially presented with sudden-onset abdominal pain and then developed bloody diarrhoea
- Well prior to this
- Admitted, given antibiotics and course of prednisone
- Then asacol 400mg twice daily – no follow-up

- Presents to you with:
  - 4 week history of bloody stools, 10-12 daily
  - Fatigue, weight loss of 8kgs
  - O/E Ill-looking, dehydrated, PR 110, apyrexial but clammy
  - Abdo – tender over LIF, not peritonitic

- Initial investigations:
  - Hb 8, CRP 180

- What is your impression / diagnosis?

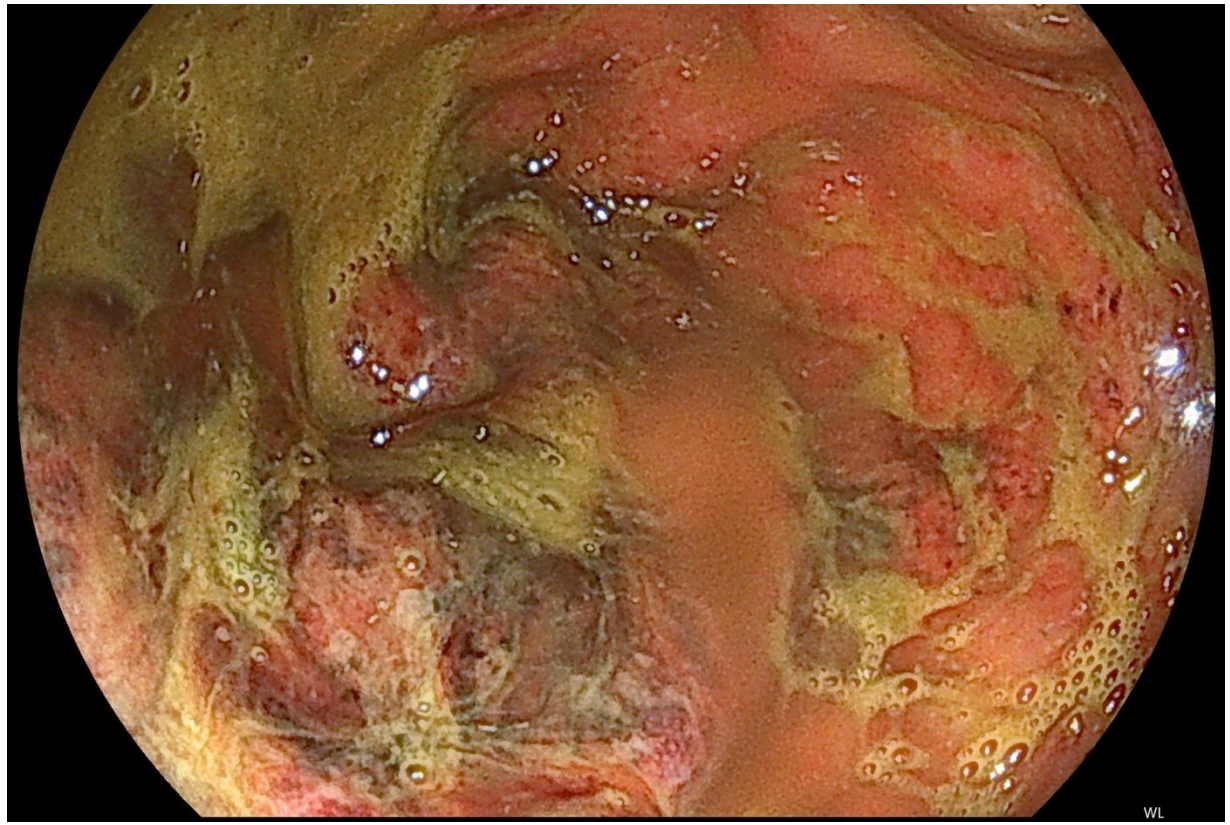
- What do you do?

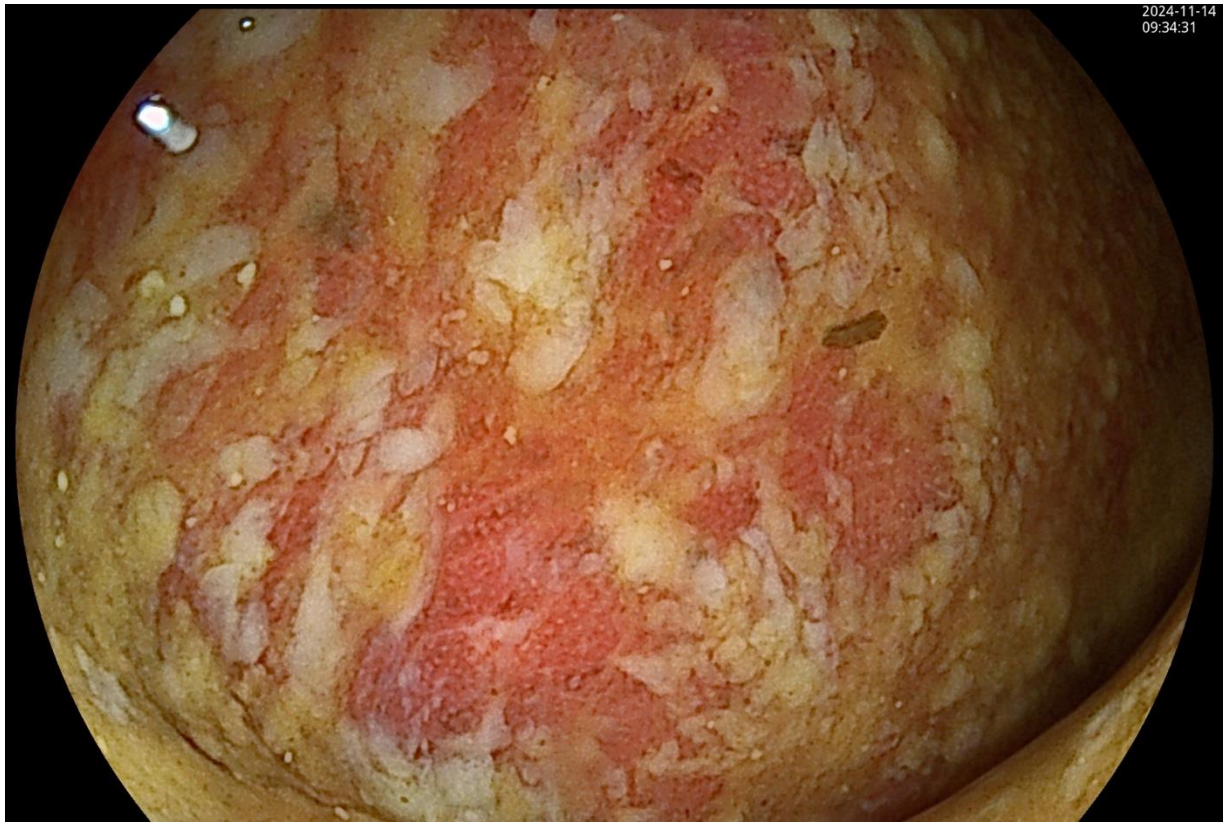
True Love and Witts Criteria for ASUC

	Mild	Moderate	Severe
Bloody stools per day	< 4	4-6	> 6
Pulse	< 90 bpm	⩽ 90 bpm	> 90 bpm
Temperature	< 37.5 ℃	⩽ 37.8 ℃	> 37.8 ℃
Hemoglobin	> 11.5 gm/dL	⩾ 10.5 gm/dL	< 10.5 gm/dL
ESR	< 20 mm/h	⩽ 30 mm/h	> 30 mm/h
CRP	Normal	⩽ 30 mg/dL	> 30 mg/dL

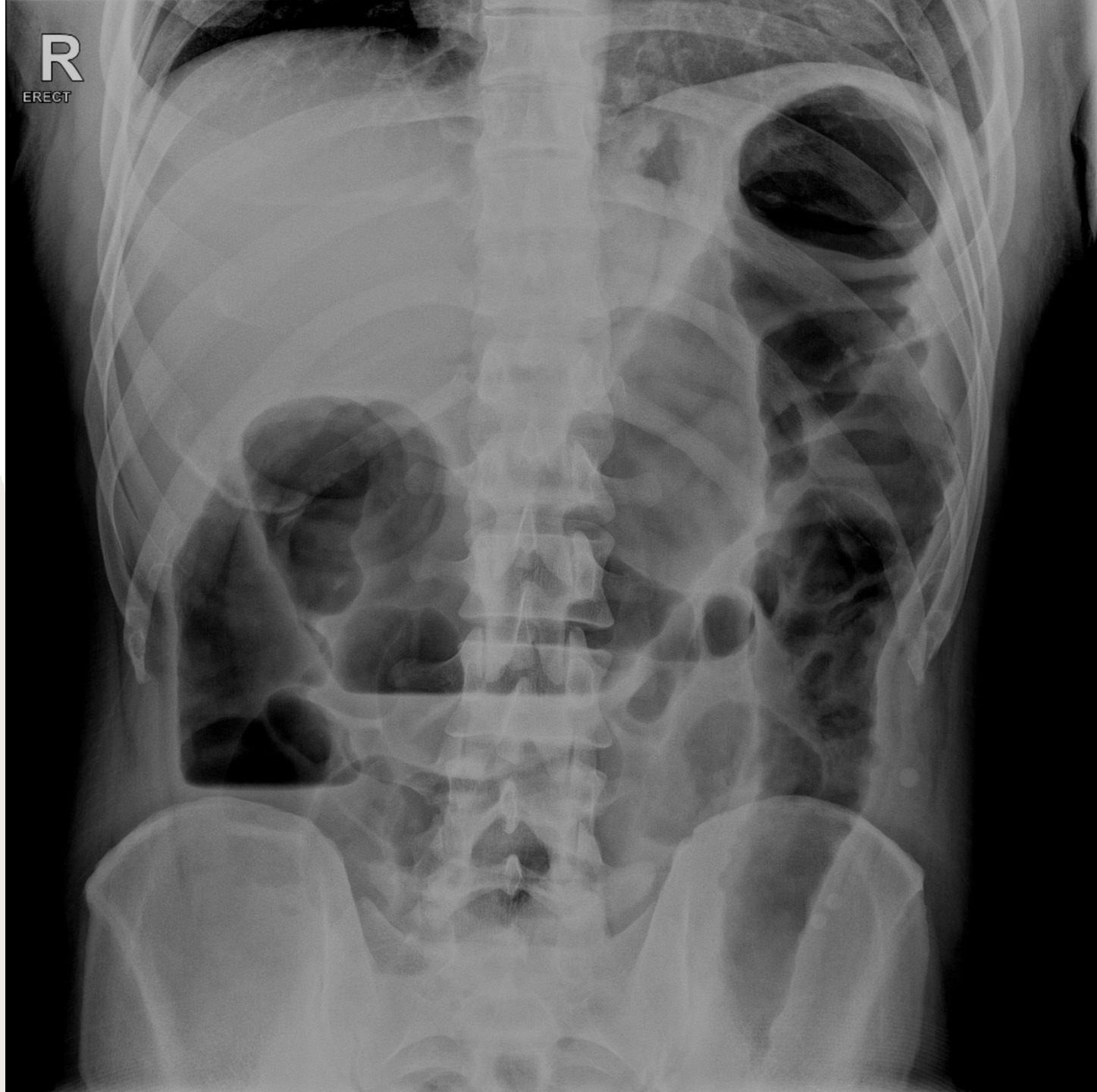
- Admitted to ward
- Stool MCS and C diff and calprotectin
- U&E, LFTs, Hep B/C, HIV, TB quantiferon, CRP (baseline)
- CXR and AXR
- CT scan : collections, abscesses, perforation
- Surgical review
- IV fluids and resuscitation
- IV ciprofloxacin and flagyl (not routinely recommended for uncomplicated ASUC, may be considered if infection is suspected, particularly in cases of toxic megacolon, perforation, or worsening symptoms despite other treatments)
- IV solucortef 100mg 6-hourly for 5-7 days (first-line therapy)
- Thromboprophylaxis with LMWH
- Flexi

Flexi

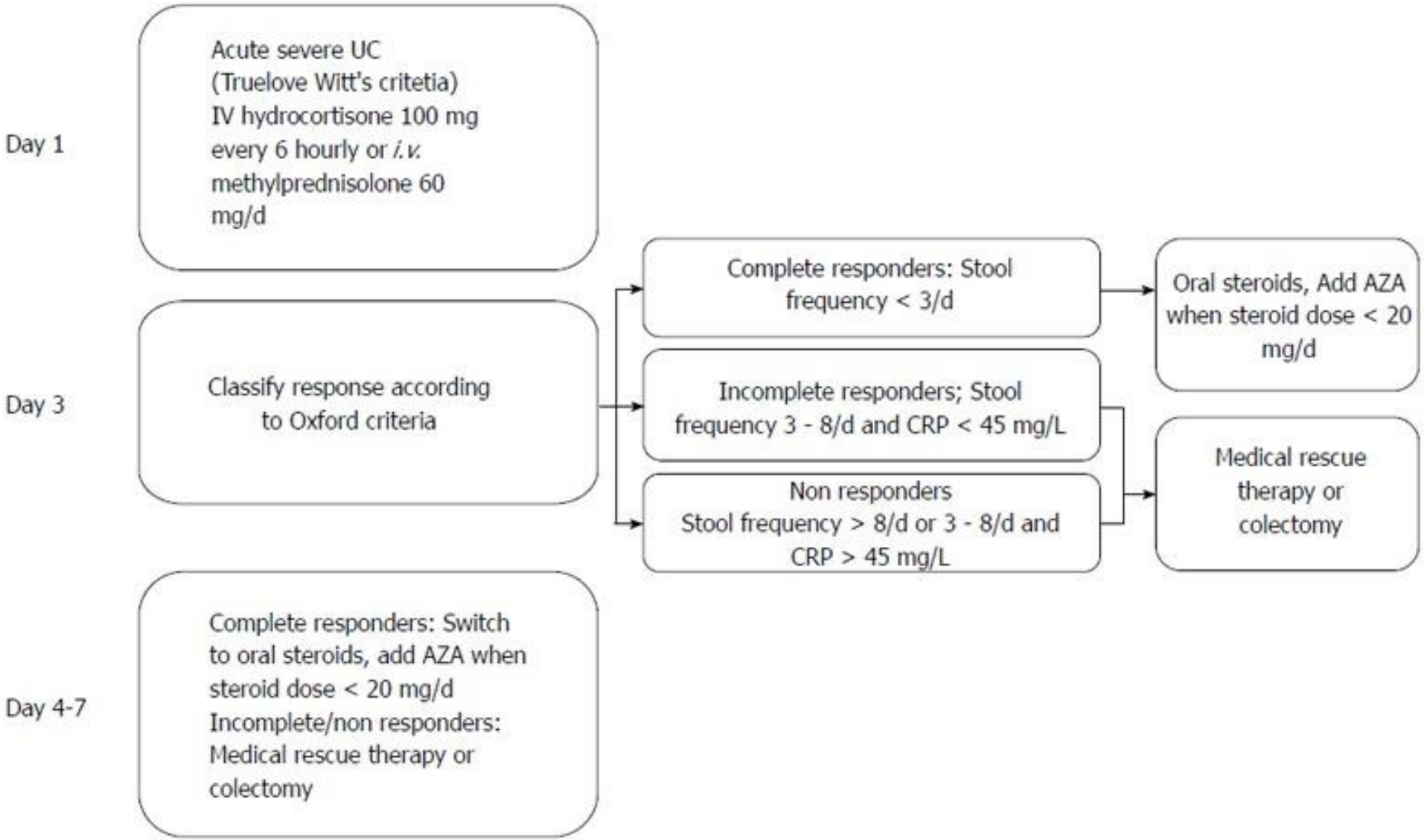




AXR



- What next?


Day 1
Acute severe UC
(Truelove Witt's critetia)
IV hydrocortisone 100 mg every 6 hourly or *i.v.* methylprednisolone 60 mg/d
Day 3
Classify response according to Oxford criteria
Complete responders: Stool frequency < 3/d
Incomplete responders; Stool frequency 3 - 8/d and CRP < 45 mg/L
Non responders
Stool frequency > 8/d or 3 - 8/d and CRP > 45 mg/L
Oral steroids, Add AZA when steroid dose < 20 mg/d
Medical rescue therapy or colectomy
Day 4-7
Complete responders: Switch to oral steroids, add AZA when steroid dose < 20 mg/d
Incomplete/non responders: Medical rescue therapy or colectomy

Rescue therapies

- **Ciclosporin** 2-4mg/kg/day
  - Target [150-250ng/ml] – need to monitor levels
  - Major SEs: nephrotoxicity, seizures, anaphylaxis, hypertension
  - Short-term response rates 70-80%, half of pts require colectomy at 11 years
  - Can be used as bridge therapy
  - CYSIF and COBSTRUCT trials

- **Tacrolimus** 0.1-0.15mg/kg/day oral, 0.015mg/kg/day IV
  - CNI with good oral bioavailability
  - Need to monitor drug levels [10-15ng/ml]
  - SEs: nephrotoxicity, hypertension
  - Short-term efficacy about 70%, long-term colectomy-free rate 50% (observation period 1-2 years)

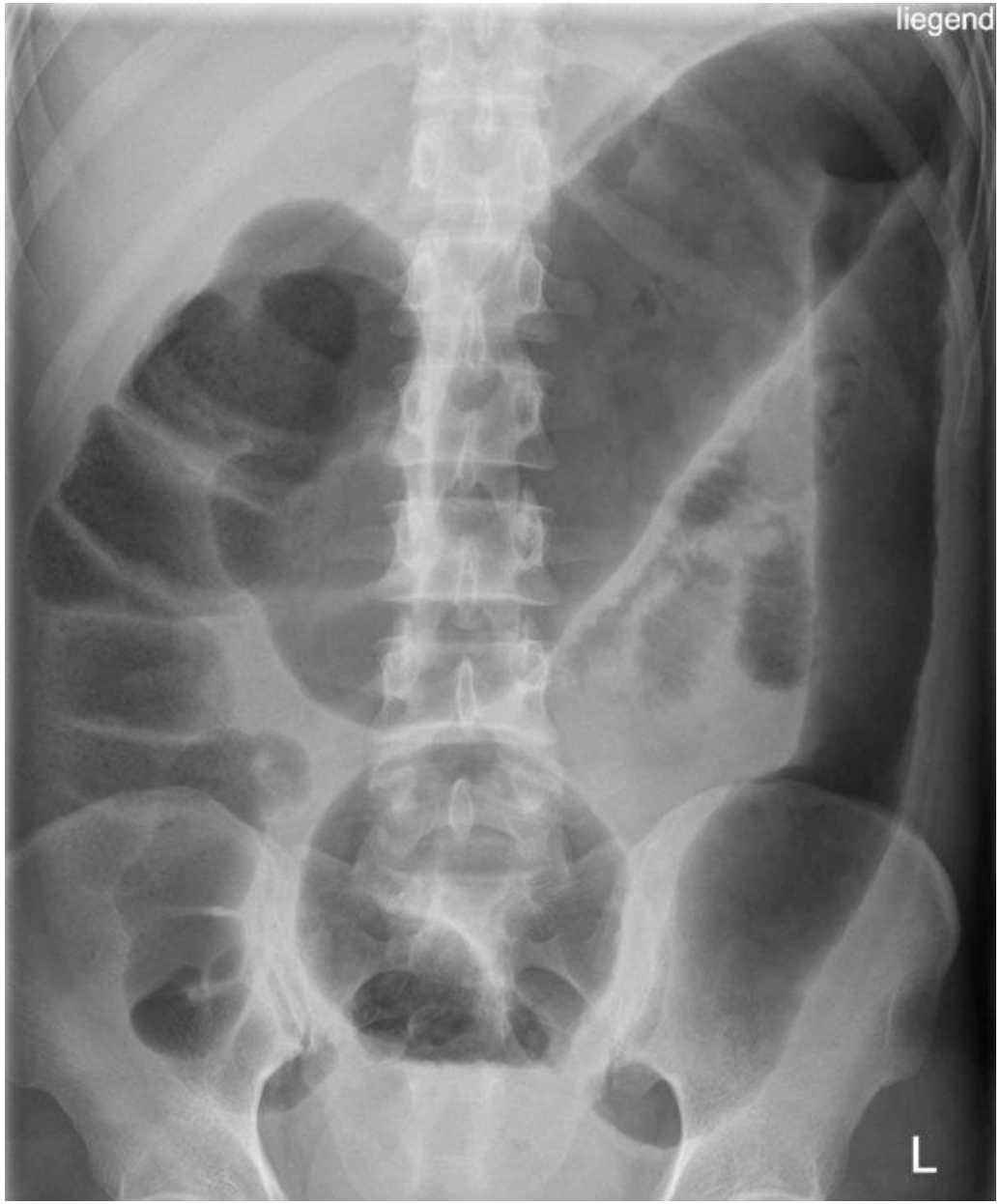
- **Infliximab** 5-10mg/kg
  - Intensified versus standard dose infliximab induction therapy for steroid-refractory acute severe ulcerative colitis (PREDICT-UC): an open-label, multicentre, randomised controlled trial
  - In steroid-refractory ASUC, a first dose of 10 mg/kg infliximab was not superior to 5 mg/kg infliximab in achieving clinical response by day 7
  - Intensified, accelerated, and standard induction regimens did not result in a significant difference in clinical response by day 14 or in remission or colectomy rates by month 3.

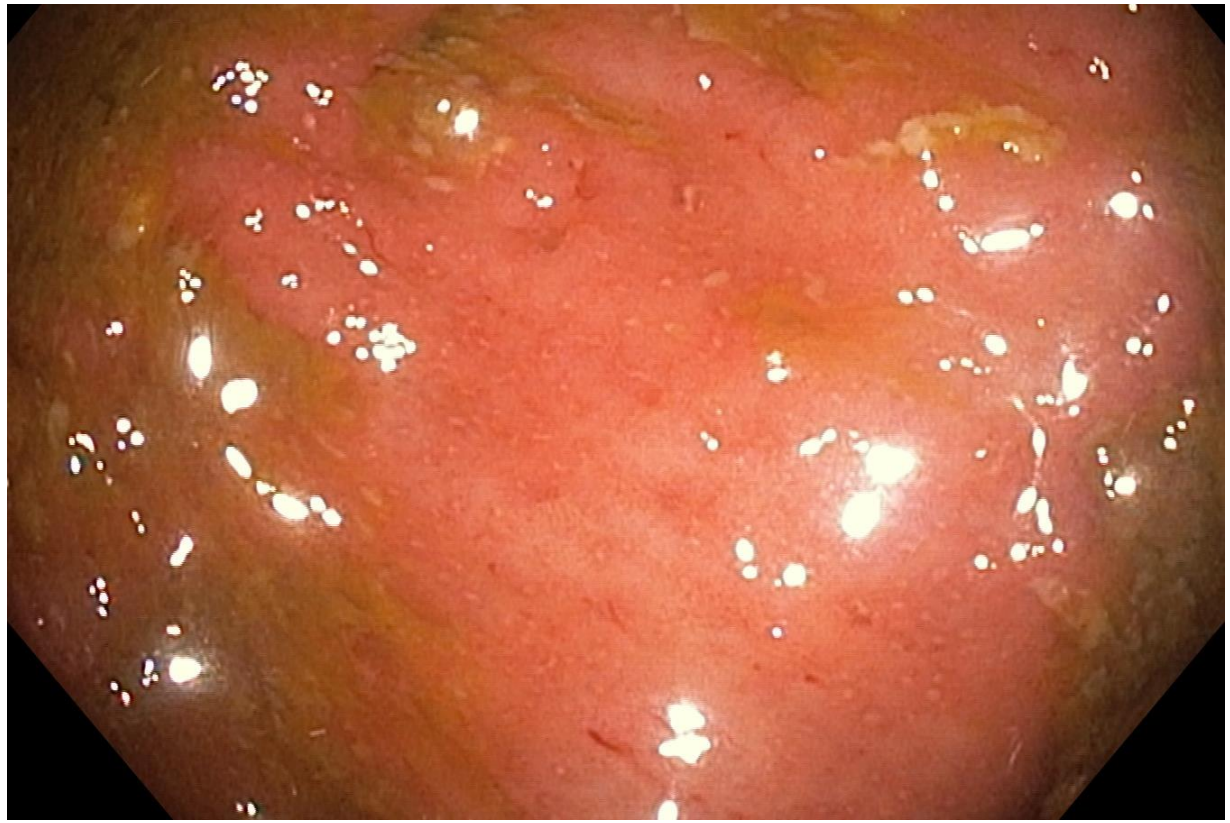
- Tofacitinib:
  - Tofacitinib as salvage therapy for 55 patients hospitalised with refractory severe ulcerative colitis: A GETAID cohort.
  - Rates of clinical response 60%, clinical remission 45.5% and steroid-free CR 37.5% at week 6
  - Colectomy-free survival approx 75% at both 3 and 6 months

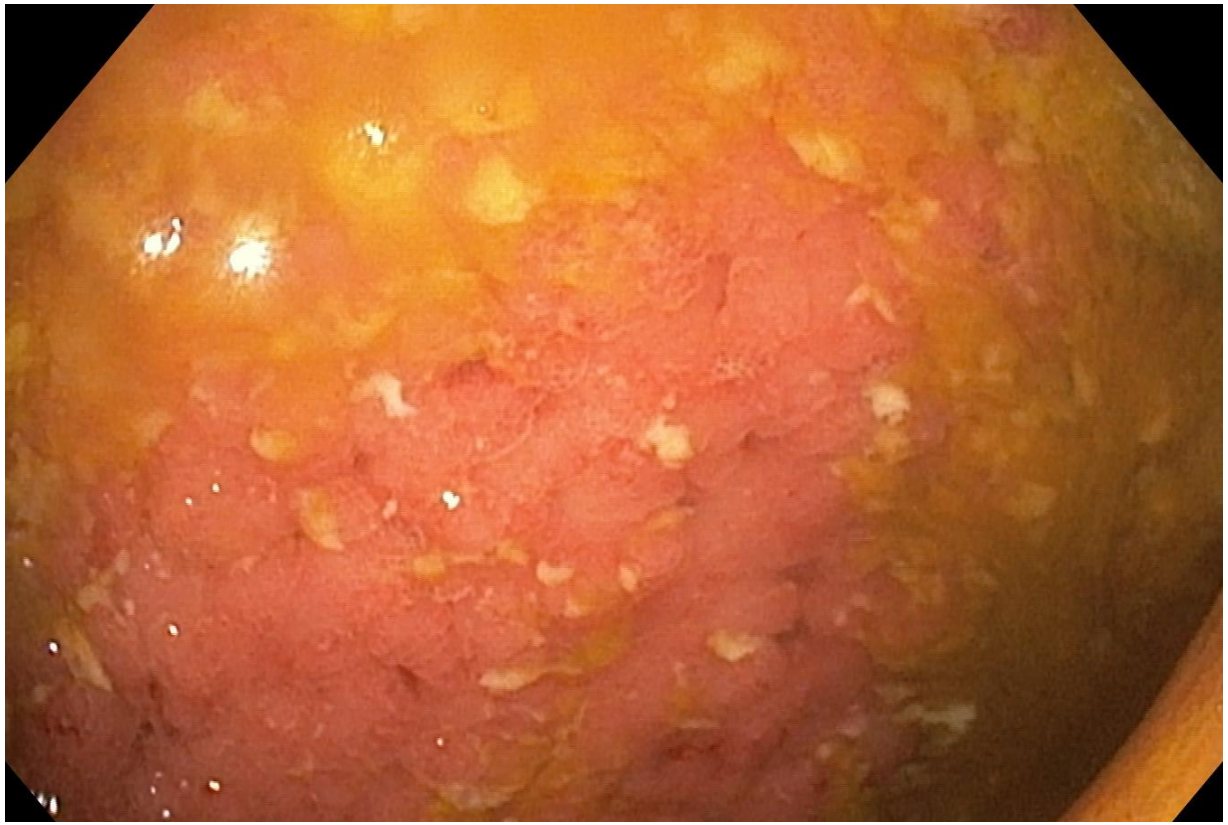
Surgery

Table 4. Indication for Surgery in Patients Who Do Not Respond to Rescue Therapy

· Toxic dilatation with impending perforation
· Intestinal perforation
· Massive hemorrhage
· Longstanding colitis with "intractability"







Test Name	Result	Flag	Reference Range
INFLIXIMAB ANTIBODY	8.20		AU/mL

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Antibodies to Infliximab/biosimilar:
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No antibodies detected
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Antibodies detected > 10.00 AU/mL
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DRUG ANTIBODY
* Drug antibodies may be transient and should be confirmed on a second
specimen.
* If drug antibodies persist on a second specimen, consider:
* Switching to another drug.
* Adding azathioprine or methotrexate if not already prescribed.
* Decreasing drug dose and increasing interval between doses.
* Concomitant immunosuppressive therapy to decrease risk of infusion
reactions.
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INFLIXIMAB MONITORING	< 0.30		ug/ml

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The main indication for infliximab (or biosimilar TNF-alpha inhibitor) drug
monitoring is lack of clinical response to the drug from the onset or
worsening
of symptoms after an initial response. Trough levels (TL) should be done just
before the next infusion is due.

DRUG LEVELS
---------------------------------------- ----------------------------------
TL < 3.0 ug/mL sub-therapeutic, dose adjustment and
drug antibody levels recommended.
---------------------------------------- ----------------------------------
TL < 3.0 ug/mL infliximab consider increase of drug dose and
(or biosimilar)but no drug antibodies decrease drug interval.
---------------------------------------- ----------------------------------
TL is between 3-7 ug/mL no dose adjustment is necessary
---------------------------------------- ----------------------------------
TL > 7.0 ug/mL considered high, dose adjustment is
recommended.
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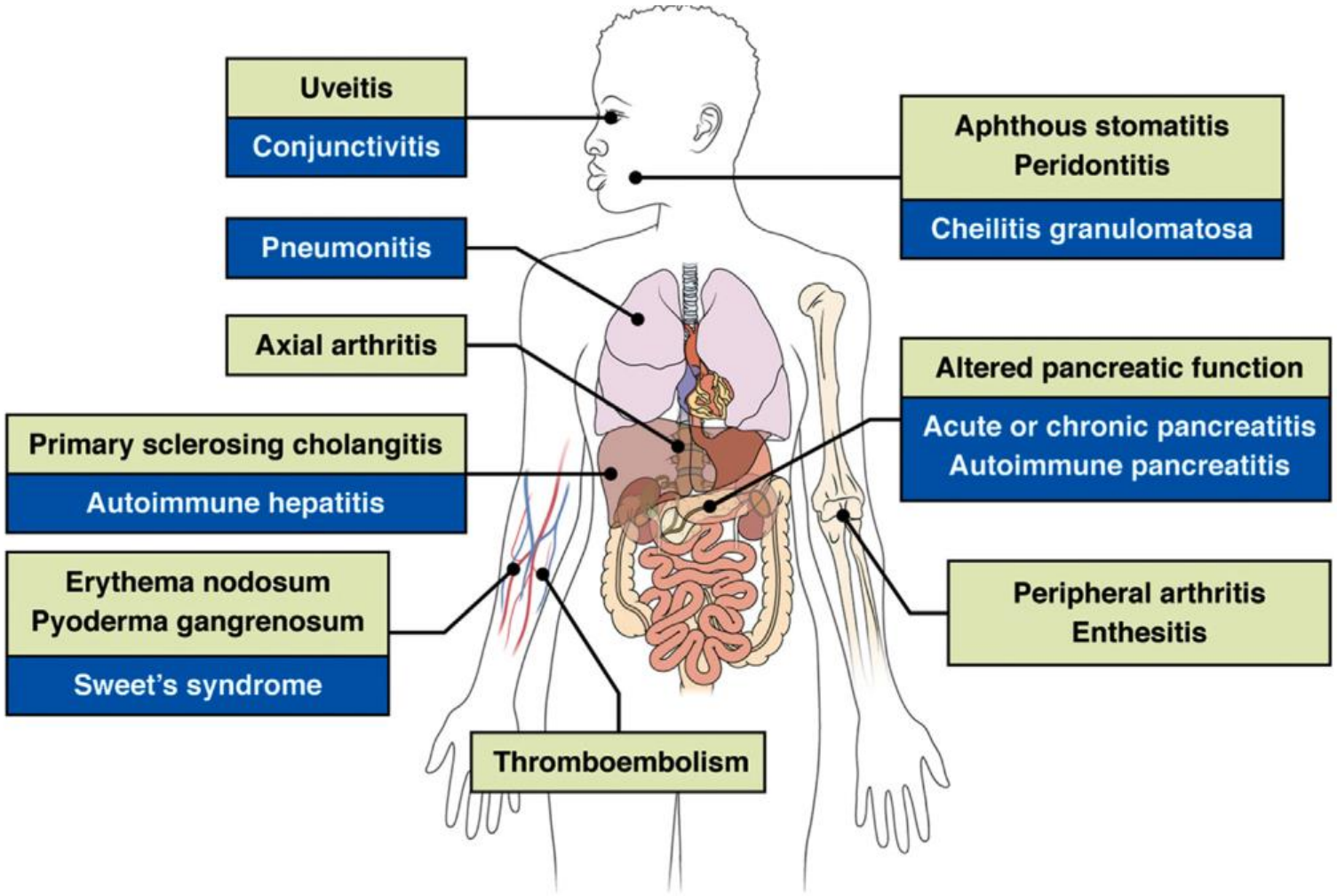
- Let’s say this pt had moderate-to-severe, good response to therapy, now on oral prednisone taper, ready for discharge
- Treatment plan?

EXTRAINTESTINAL MANIFESTATIONS OF IBD



- ‘an inflammatory pathology in a pt with IBD that is located outside the gut and for which the pathogenesis is either dependant on the extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD’
- common in both UC and CD
- can occur before or after IBD dx
- can substantially impact QoL, sometimes more than intestinal disease
- Can occur together with IBD flares and respond to treatment of intestinal inflammation or can be independent of IBD activity
- Most commonly M/S system, skin, HPB and eyes; but can affect almost any organ

Organ system	Manifestations	Prevalence
Gastrointestinal	PSC	UC: up to 5%; CD: rare
	Autoimmune pancreatitis	Rare
	Autoimmune hepatitis	Rare (< 1%)
Mucocutaneous	EN	5%–15% in CD; 2%–10% in UC
	PG	0.4%–2.6% in IBD
	Oral aphthous ulcers	5%–50% in CD
	Sweet syndrome	Rare
	Orofacial granulomatosis	Rare
Musculoskeletal	IBD-related arthritis	CD: 10%–20% ; UC: 4%–14%
	Peripheral arthritis	Up to 50% in CD (asymptomatic)
	Axial arthritis	
	Enthesitis	
Ocular	Episcleritis and scleritis	Scleritis: up to 1%;
	Anterior uveitis	CD: 5%–12%; UC: 3.5%–4.1%
Pulmonary	Pneumonitis	Rare
Vascular	Cardiovascular disease	NA
	Thromboembolism	3- to 4-fold increase
	Portal vein thrombosis	Rare

Musculoskeletal

- Most common, up to 46% of IBD pts
- Both peripheral and axial skeleton
- **Peripheral arthritis**:
  - 5-14% UC, 10-20% CD, mainly clinical diagnosis (US, MRI)
  - Oligoarticular (</= 4 joints) or Polyarticular (>4 joints)
  - Can have normal or raised ESR/CRP
  - RF and anti-CCP generally negative (+ve result does not exclude dx)
  - Type 1 : classic form, oligo-, asymmetric, <5 joints, larger joints , usually acute self-limiting attacks <10 weeks, strongly associated with other EIMs such as EN and uveitis, and often with active IBD
  - Type 2 : polyarticular, >/= 5 joints, symmetric, mainly small joints hands, usually persists for months-years, largely independent of IBD activity, RA-like

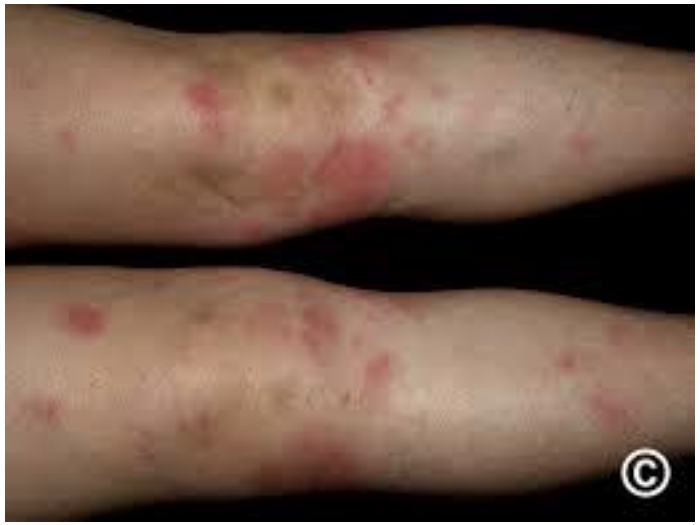
- **<u>Axial arthritis / spondyloarthropathy:</u>**
  - Variety of symptoms due to axial involvement seen in active sacroiliitis or spondylitis
  - AS-IBD less association with HLA-B27 (50-70% cf 90% idiopathic AS)
  - AS independent of intestinal inflammation
  - Persistent inflammatory LBP
  - MRI supports diagnosis
  - Sacroillitis usually bilateral, can symptomatic or asymptomatic (seen on imaging in up to 50% CD pts), symptomatic : LBP and improves with activity

- Enthesitis, tenosynovitis, dactylitis
- Arthralgia

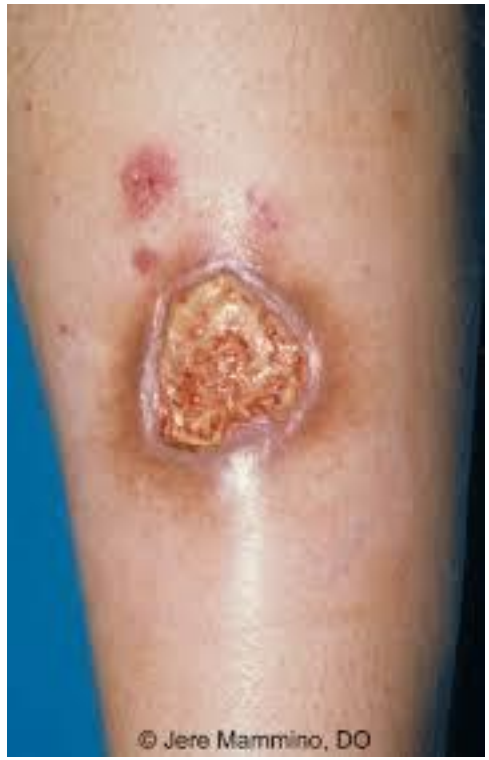
Table 3. Musculoskeletal Conditions Associated With Inflammatory Bowel Disease: Therapy of Peripheral and Axial Arthritis in Inflammatory Bowel Disease

Variable	Prevalence	Diagnosis	Therapy
Peripheral arthritis (peripheral SpA)	5%–14% in UC 10%–20% in CD	Clinical (and US or MRI)	Treatment of intestinal inflammation COX-2 inhibitors Corticosteroids (short term) Sulfasalazine (especially in UC) Methotrexate Anti-TNF
Axial arthritis/ axSpA	Up to 50 % in CD symptomatic in up to 8%	Clinical and MRI	Anti-TNF

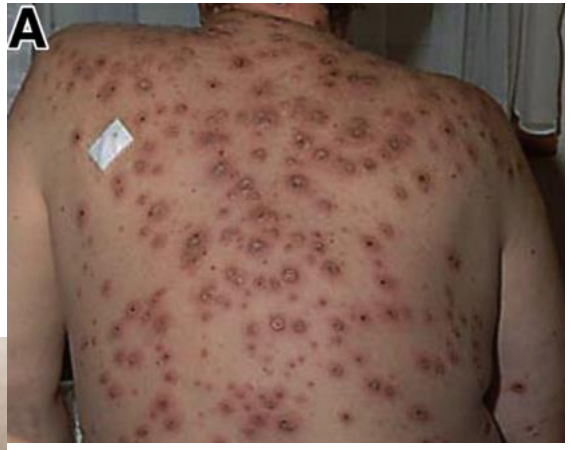
Skin

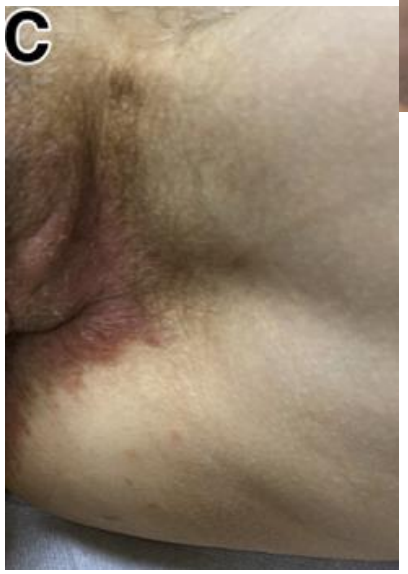


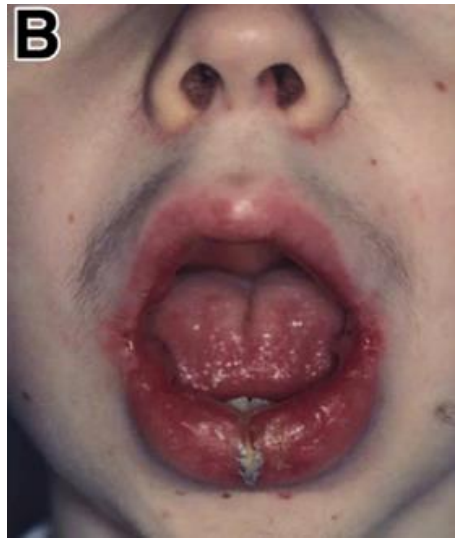
- 5-15% of IBD pts, EN and PG most frequent
- **EN:**
  - Tender, red/violet, raised, subcutaneous nodules, 1-5cm
  - Typically extensor surfaces of lower extremities
  - 5-15% CD, 2-10% UC, can be associated with active IBD
  - If Rx of intestinal inflammation insufficient, then steroids or anti-TNF
- **PG:**
  - Pustule/nodule -> deep ulcers with irregular violaceous edges
  - Mainly legs, also H&N, trunk
  - Ulcers solitary or multiple, uni- or bilateral, cms to entire limb
  - Not commonly associated with IBD activity
  - Clinical dx; Skin biopsy should be avoided
  - Rx: oral steroids, cyclosporine, tacrolimus, anti-TNF



- Sweet Syndrome:
  - ‘acute febrile neutrophilic dermatitis’ – rare
  - Painful, erythematous lesions
  - Dx on biopsy
  - Usually parallels intestinal activity
  - Also reported as AE of azathioprine
  - Rx: steroids, IMs, treat intestinal inflammation
- ‘Metastatic Crohn’s disease’:
  - Skin lesions show granulomas (biopsy)
  - Anywhere on integumentum
  - Does not parallel intestinal activity
  - Rx: steroids, IMs, anti-TNFs (case reports)
- Oral:
  - Aphthous ulcers and stomatitis, periodontitis, orofacial granulomatosis
  - Usually parallels intestinal disease
  - Rx: topical or oral steroids, anaesthetics, anti-TNF, treat intestinal inflammation

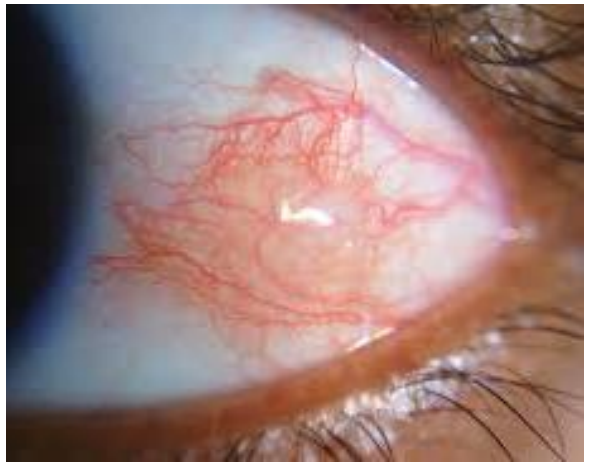




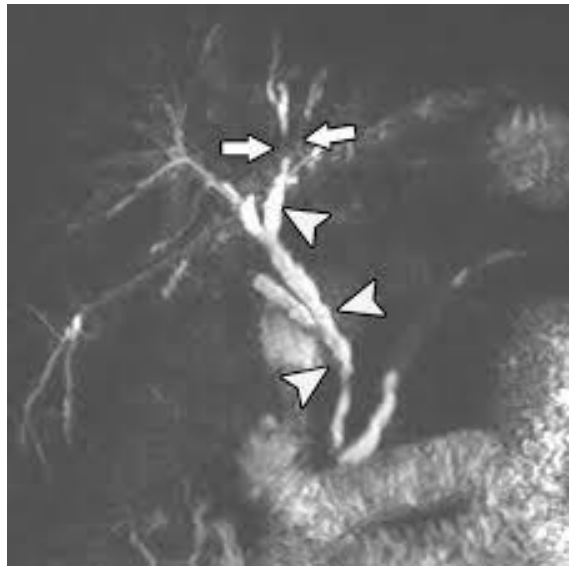


Ocular

- 2-7% of IBD pts, CD>UC, often associated with skin & joint EIMs
- **Episcleritis**: most common, moderate discomfort, active IBD and flares. Rx: treat underlying IBD, topical steroids (can have AE such as increased IOP and cataracts)
- **Scleritis**: can progress to permanent vision loss, anterior/posterior, requires aggressive Rx, steroids early, immunosuppressive therapy (IFX)
- **Uveitis**: less associated with intestinal inflammation, steroid eye drops -> systemic steroids, IM, anti-TNFs
- Retinal vasculitis, papillitis, corneal infiltrates, optic neuritis



Hepatobiliary



- **PSC**:
  - Most NB HB EIM
  - In 60-80% of PSC , underlying IBD diagnosed
  - UC mainly, if CD mainly colonic
  - RFs: male, pancolitis, nonsmoker, appendicectomy
  - Elevated ALP or GGT
  - Lymphocyte infiltration in the intra- and extrahepatic biliary tree -> inflammation -> fibrosis -> strictures of small or large bile ducts -> cirrhosis / ESLD / cholangioCa
  - 10X fold increased risk of CRC in IBD pts
  - Median survival without LTx 10-12 years
  - Dominant stricture -> ERCP and dilatation
  - Small duct PSC better outcomes and longer median survival
  - Ursodeoxycholic acid frequently prescribed – no significant benefit for survival
  - Rx of intestinal inflammation does not change course of PSC
- **Hepatitis:**
  - AIH, IgG4-related cholangitis, granulomatous inflammation

- Vascular: increased risk VTE, increases with severity of inflammation and highest in hospitalized pts with ASUC
- Pancreatitis: acute idiopathic, autoimmune type 2
- Bronchopulmonary: ILD (mainly UC), granulomatous lung disease (mainly CD)
- Other: GN, amyloidosis, nephrolithiasis, pericarditis / myocarditis, osteoporosis/osteopenia
- Systemic: fatigue, pain, anaemia
  - Very frequently reported by IBD pts

	Peripheral arthritis	Axial arthropaty	Uveitis	Pyoderma gangrenosum	PSC
Mesalazine					
Sulfasalazine					
Azathioprine					
Mercaptopurine					
Methotrexate					
Infliximab					
Adalimumab	Although evidence supports the benefit of antiTNF on certain EIMS the best characterized are infliximab and adalimumab in this setting				
Golimumab					

Certolizumab			
Vedolizumab	Observational data shows improvement in some patients*		
Ustekinumab			
Risankizumab			
Mirikizumab			
Tofacitinib		Observational data shows improvement in some patients	
Filgotinib		As per JAK family?	
Upadacitinib		Observational data shows improvement in some patients	
Ozanimod			
Etrasimod			