University of Colorado **Anschutz Medical Campus**

Inflammatory Bowel Disease-Related Arthritis

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Disclosures

- I have the following relevant financial relationship(s) to disclose:

  Consultant, speaker: UCB, Grant/Research Support: Pfizer. All of the relevant financial relationships listed for these individuals have been mitigated.

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The American College of Rheumatology thanks Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC for supporting the Winter Rheumatology Symposium 2024 with an independent medical education grant.

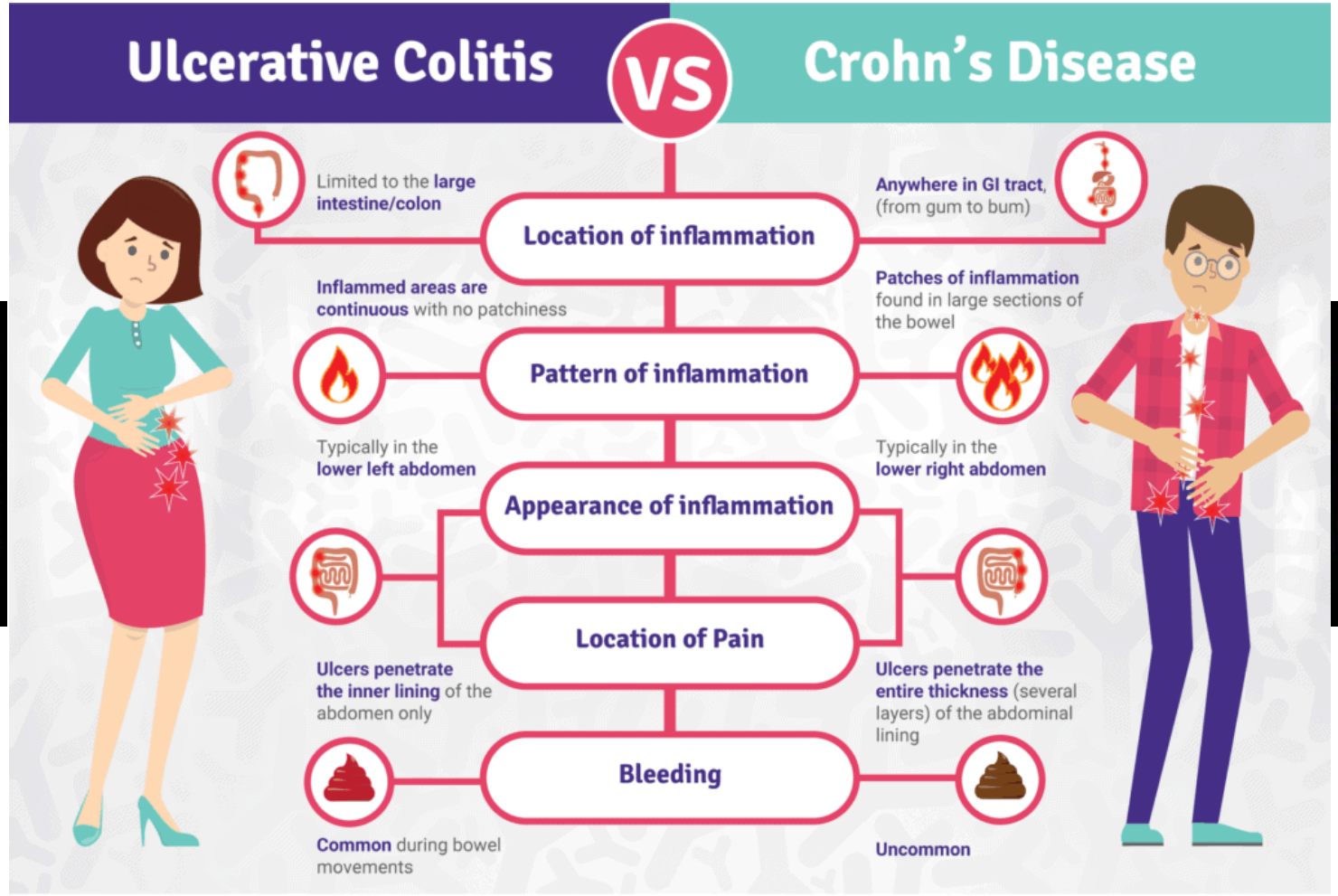
Evidence Based Medicine & Key References

- References are embedded in slides.

Learning Objectives

- Identify comorbid inflammatory bowel diseases (IBD) and spondyloarthritis (SpA)
- Evaluate the latest evidence and guidelines for the treatment and management of patients with IBD and SpA
- Apply interdisciplinary strategies to streamline the collaboration, communication, and referral of patients between rheumatology and GI teams

Inflammatory Bowel Disease (IBD) 101 refresher

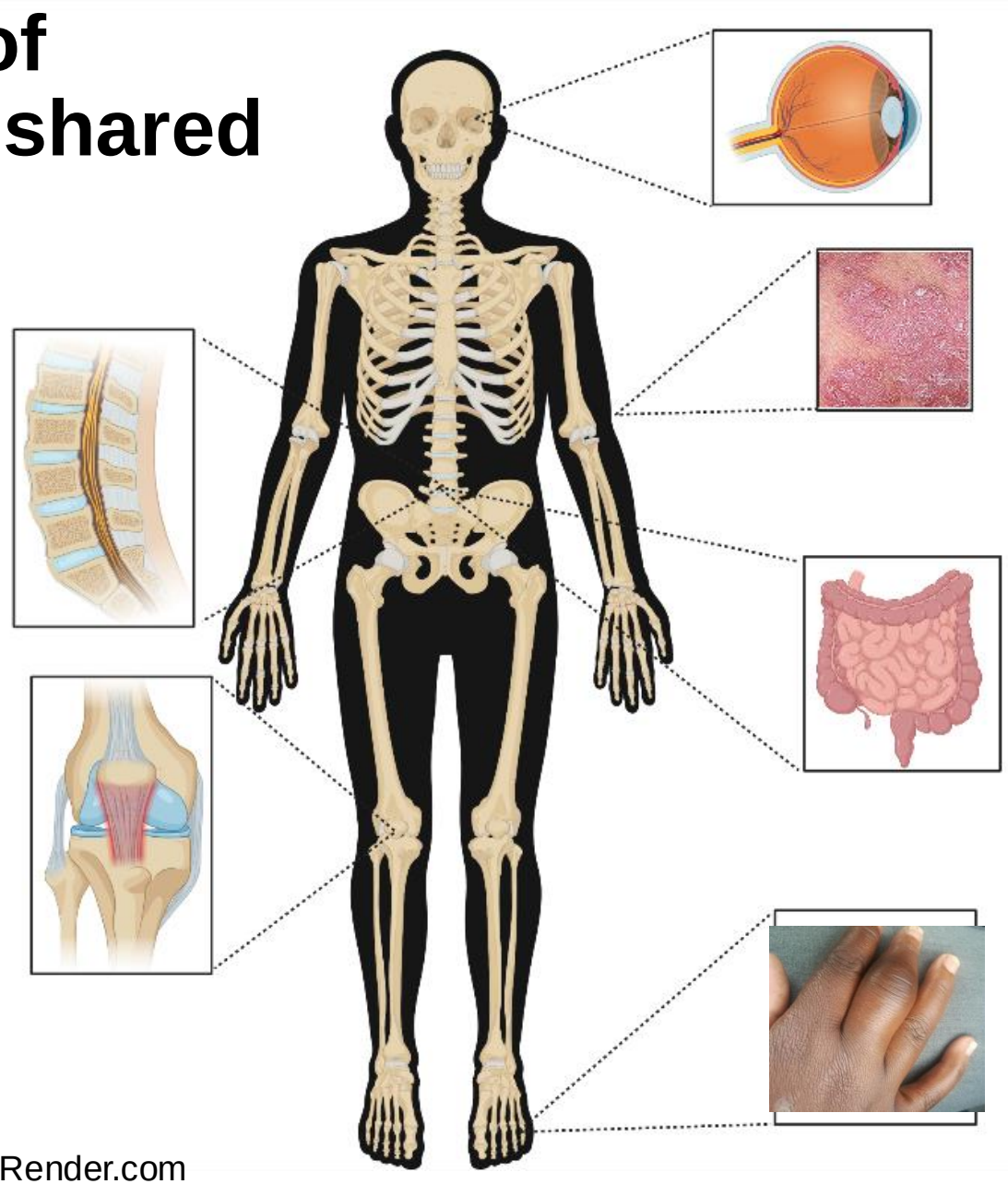


IBD belongs to a spectrum of inflammatory diseases with shared pathophysiology

IBD, uveitis, psoriasis, and **spondyloarthris**

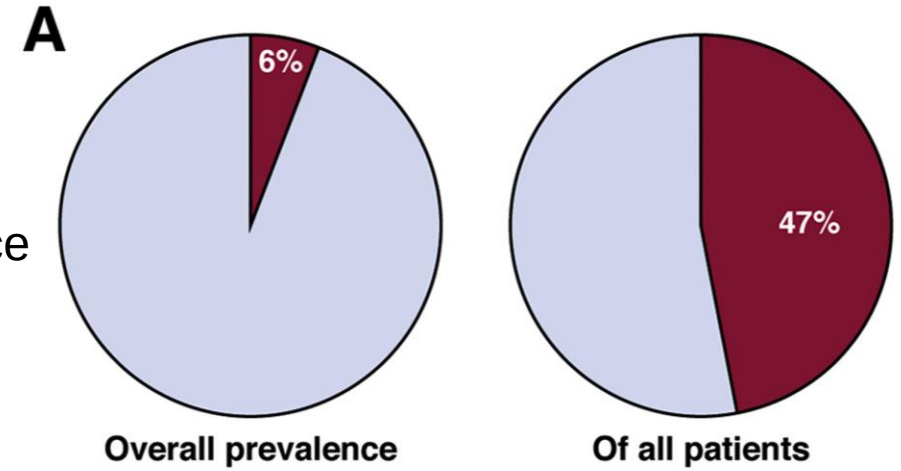
Shared genetic risks: e.g. IL-23R, STAT3, NFkB1, IL2RA

Elevations of key inflammatory cytokines: TNF, IL-12, IL-17, IL-23

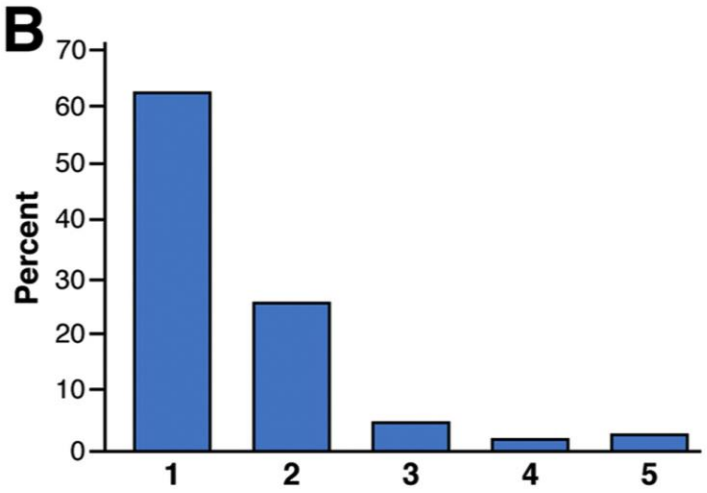


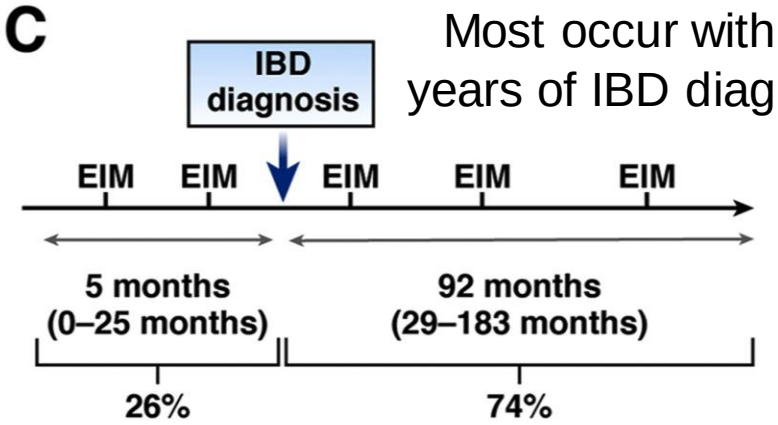
Half of patients with IBD will develop extra-intestinal manifestations (EIMs)

Prevalence



Number of EIMs per patient





Most occur within 5 years of IBD diagnosis

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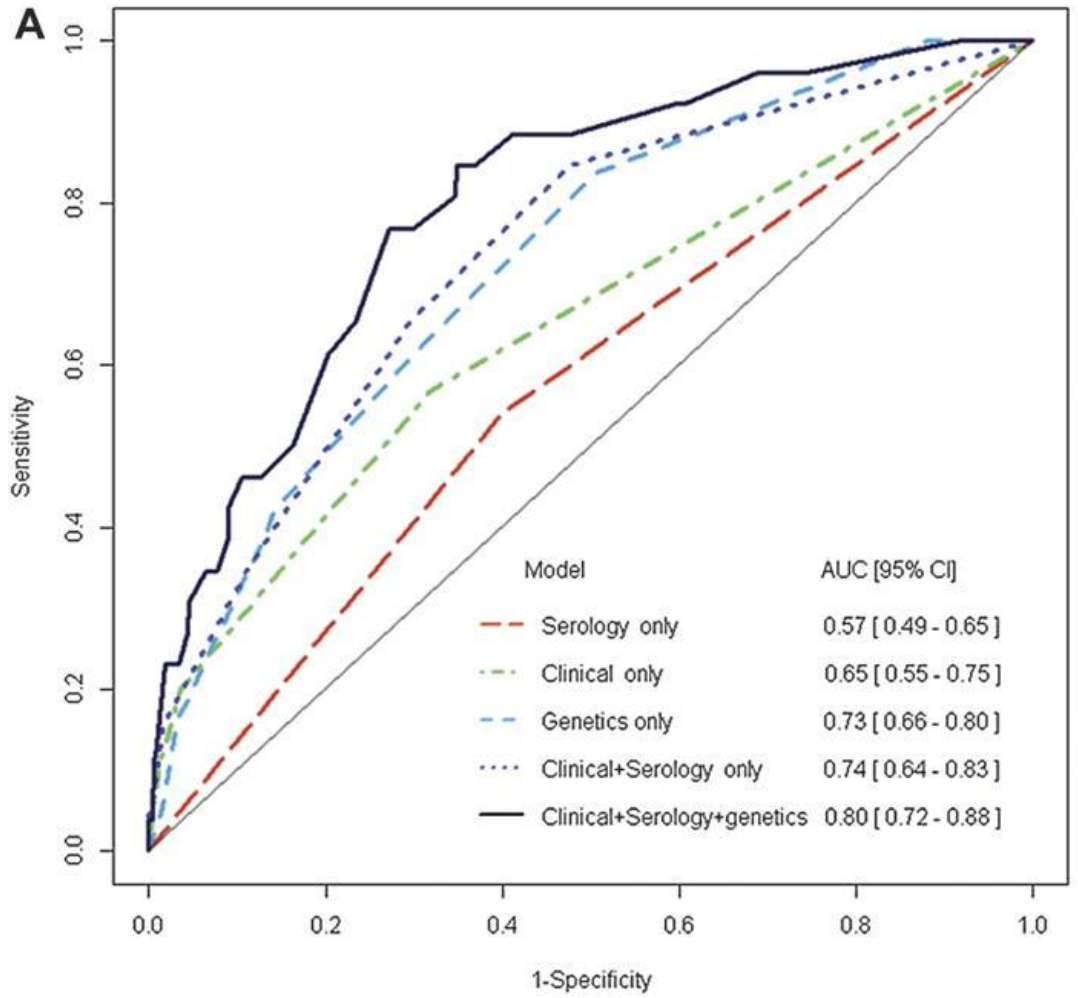
Rogler G et al. Gastroenterology 2021.

Who develops EIMs?

- Pyoderma Gangrenosum
  - Colonic disease, previous IBD-related surgery, other EMs
  - ANCA+
  - IL8RA, PRDM1, USP15, and TIMP3

- Arthritis
  - Genetic markers? IL23R?
  - Clinical features?
  - Serologic markers?



Weizman et al. Inflammatory Bowel Diseases 2014.
Rogler G et al. Gastroenterology 2021.

Clinical features of IBD that associate with likelihood of spondyloarthritis

	Univariate Analysis		Multivariate Analysis[a]	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.04)	0.01
Female sex	1.80 (1.27-2.55)	<0.001	2.03 (1.41-2.93)	<0.001
History of smoking	1.83 (1.23-2.71)	<0.01	1.70 (1.11-2.59)	0.01
Crohn's disease (vs. UC)	1.19 (0.86-1.64)	0.30	–	–
Extensive UC	1.12 (0.65-1.93)	0.67	–	–
Ileocolonic CD	1.14 (0.74-1.78)	0.55	–	–
Penetrating or stricturing CD	0.88 (0.57-1.37)	0.58	–	–
History of prior IBD surgery	1.60 (1.13-2.26)	<0.01	1.36 (0.94-1.97)	0.11
Any history of biologic or targeted small molecule	1.93 (1.19-3.14)	<0.01	2.27 (1.34-3.84)	<0.01
Current biologic use	1.10 (0.75-1.62)	0.64	–	–
Duration of disease (years)	1.01 (0.99-1.02)	0.49		
Onset before age 40	0.69 (0.44-1.06)	0.09	0.99 (0.56-1.73)	0.96

Hong, Jan, Davis, Ermann, Weisman, Kuhn et al., unpublished

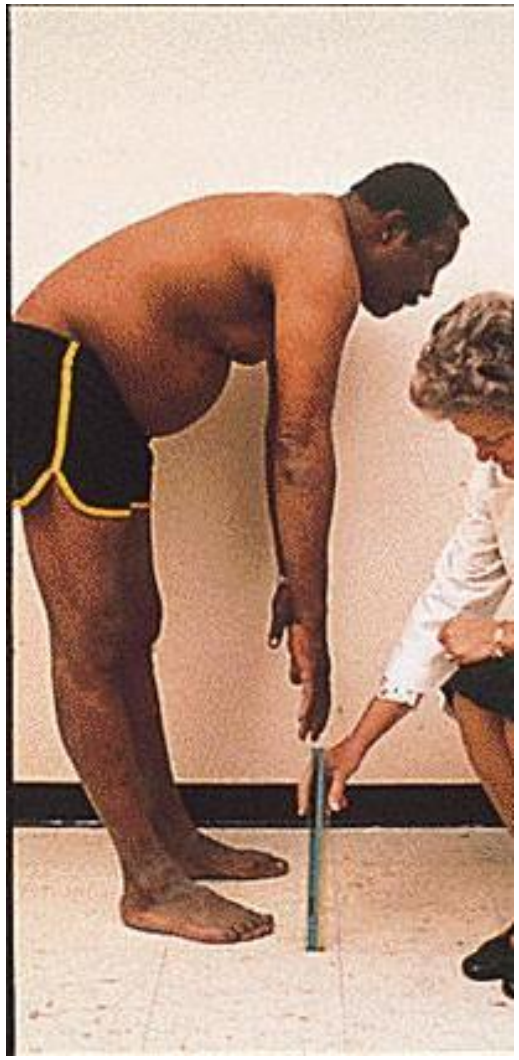
Interrelationship between risk of these diseases

UC

CD

~33% of patients with IBD have spondyloarthritis

~50% of patients with spondyloarthritis have intestinal inflammation



Rheumatology Image Library © American College of Rheumatology

Case 1: When to suspect IBD in a patient with spondyloarthritis

- 32 year-old woman with psoriatic arthritis controlled on MTX
  - Fatigue
  - Weight loss of ~20 lbs over the last 6 months
  - Diarrhea off and on
- Exam
  - No psoriatic plaques or joint abnormalities
  - Abdomen TTP
- Labs
  - Iron deficient anemia
  - CRP elevated

Fecal calprotectin as a biomarker of IBD in patients with SpA

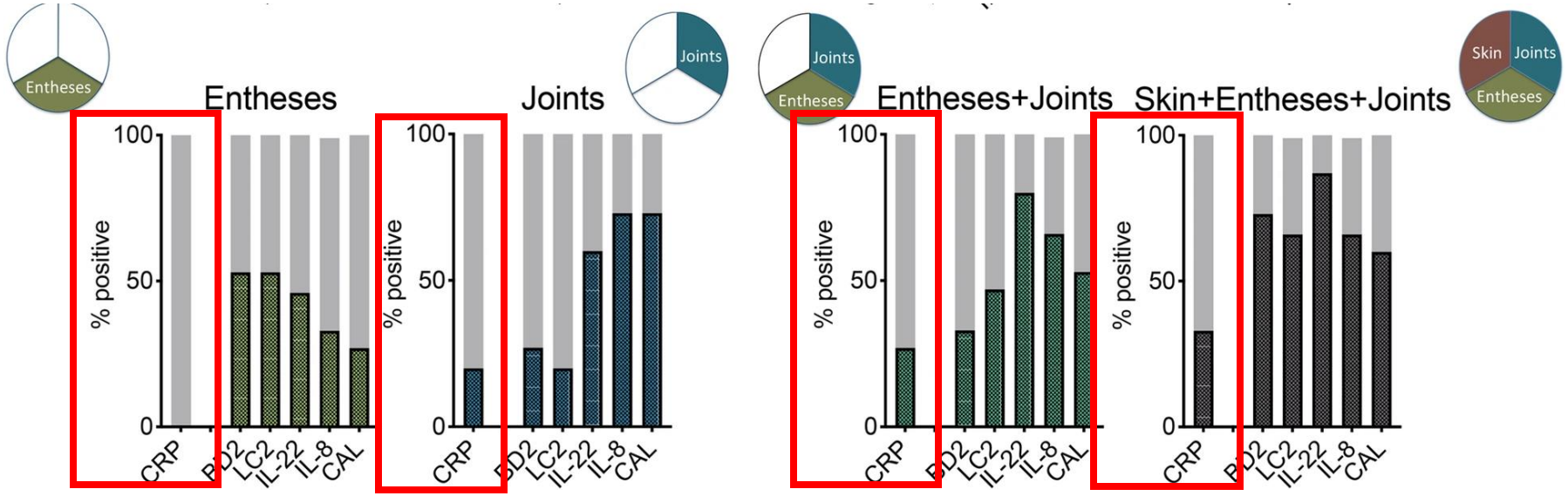
Study	FC cut-off	Microscopic inflammation	Macroscopic inflammation	NSAIDs
Klingberg E	266 mg/kg Predicts Crohn's disease	10/24 patients [41.7%]	5/24 patients [20.8%]	Increase in FC levels [p <0.05]
Klingberg E	NS	5/8 patients [62.5%]	5/8 patients [62.5%]	Increase in FC levels [p >0.05]
Cypers H	85 mg/kg Predicts bowel inflammation	53/125 patients [42.4%]	39/125 patients [31%]	Increase in FC levels [p <0.05]
Matzkies FG	NS	NS	NS	No difference in FC levels
Ostgard RD	100 mg/kg Predicts bowel inflammation	NS	12/15 patients [80%]	NS
Kopylov U	132 mg/kg Predicts Crohn's disease	NS	7/64 patients [11%]	NS
Simioni J	NS	39/39 patients [100%]	13/39 patients [33.3%]	No difference in FC levels

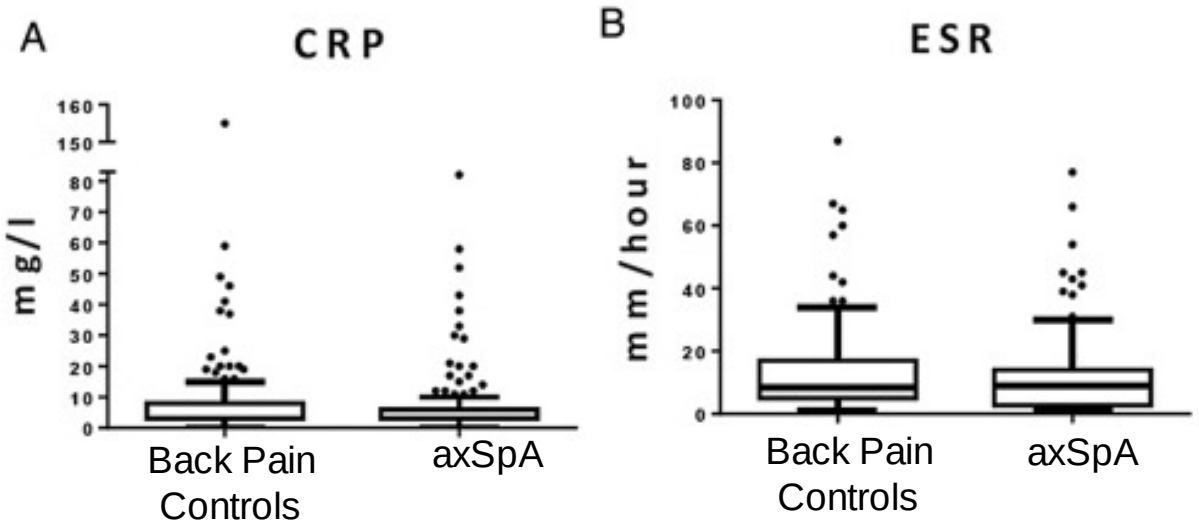
Fauny M et al. Journal of Crohn's and Colitis, 2020

Case 2: When to suspect SpA in a patient with IBD?

- 54 year-old-woman
- Ulcerative Colitis for 10 years
  - Well managed with mesalamine
  - No complications
- Arthralgias have been present through this time
  - Bilateral wrists and hands with “swelling”
  - Right knee will swell during which she is unable to ambulate
  - 30 minutes of morning stiffness in the lower back
- No exam findings on day of visit to rheumatology

Inflammatory markers often are not elevated

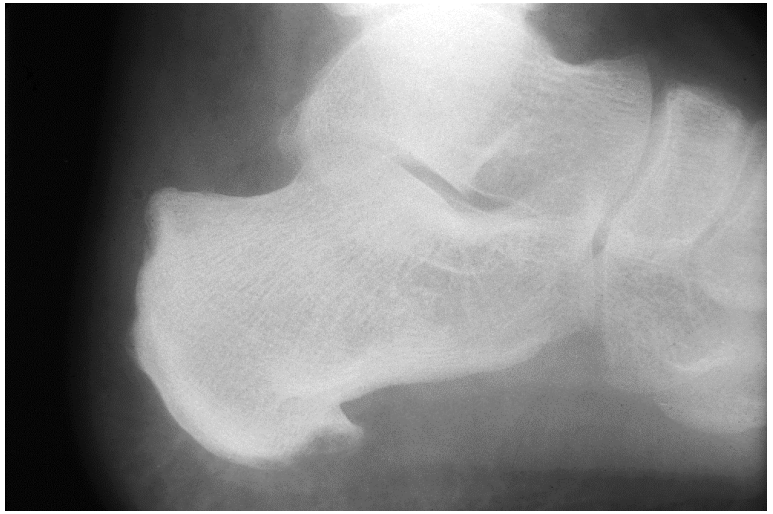


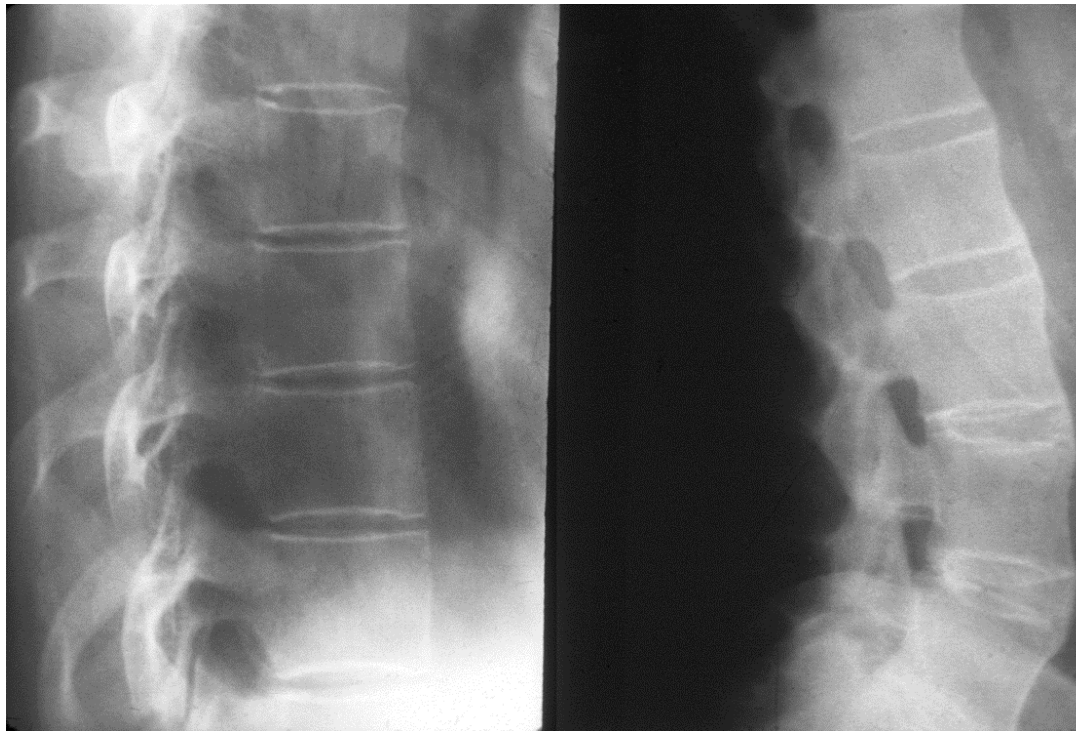


Sololova et al. Arthritis Res Ther 2020
Turina et al. *RMD Open* 2017
De Vries et al *Arthritis Rheum* 2009

Radiography

- Peripheral arthritis generally non-erosive
- Axial arthritis like ankylosing spondylitis
  - Always examine pelvic imaging first!

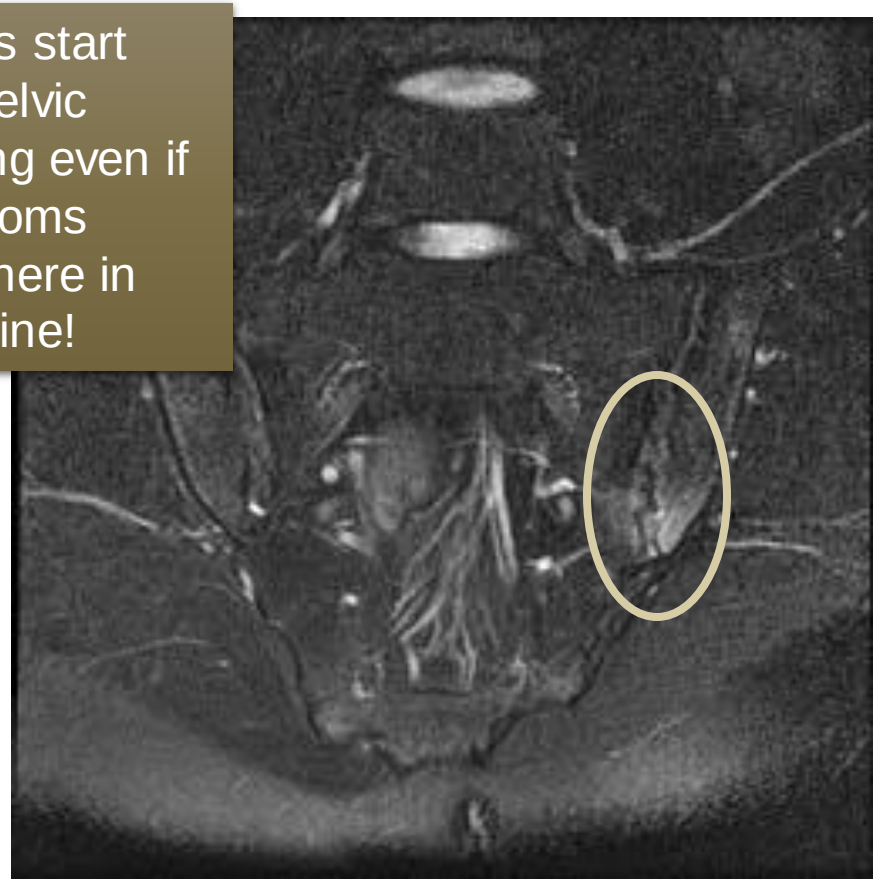




MRI is more sensitive for active inflammation

Semi-coronal STIR of pelvis with unilateral osteitis

Always start with pelvic imaging even if symptoms elsewhere in the spine!



Rheumatology Image Library
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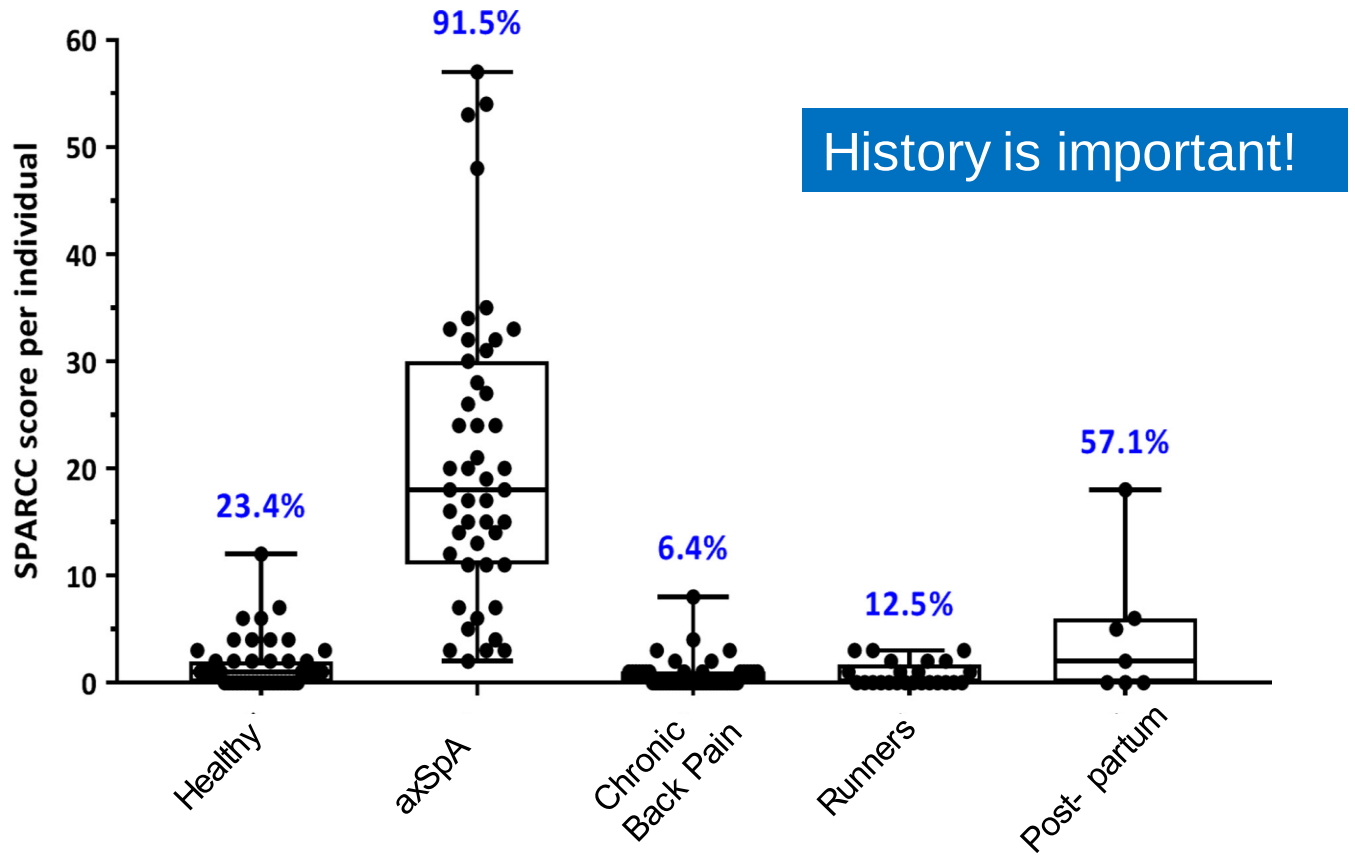
Saggital T2 of L-spine with “shiny corners”

Case courtesy of Dr Hani Al Salam, Radiopaedia.org, rID: 29896

MRI is very sensitive for sacroiliitis and false positives occur



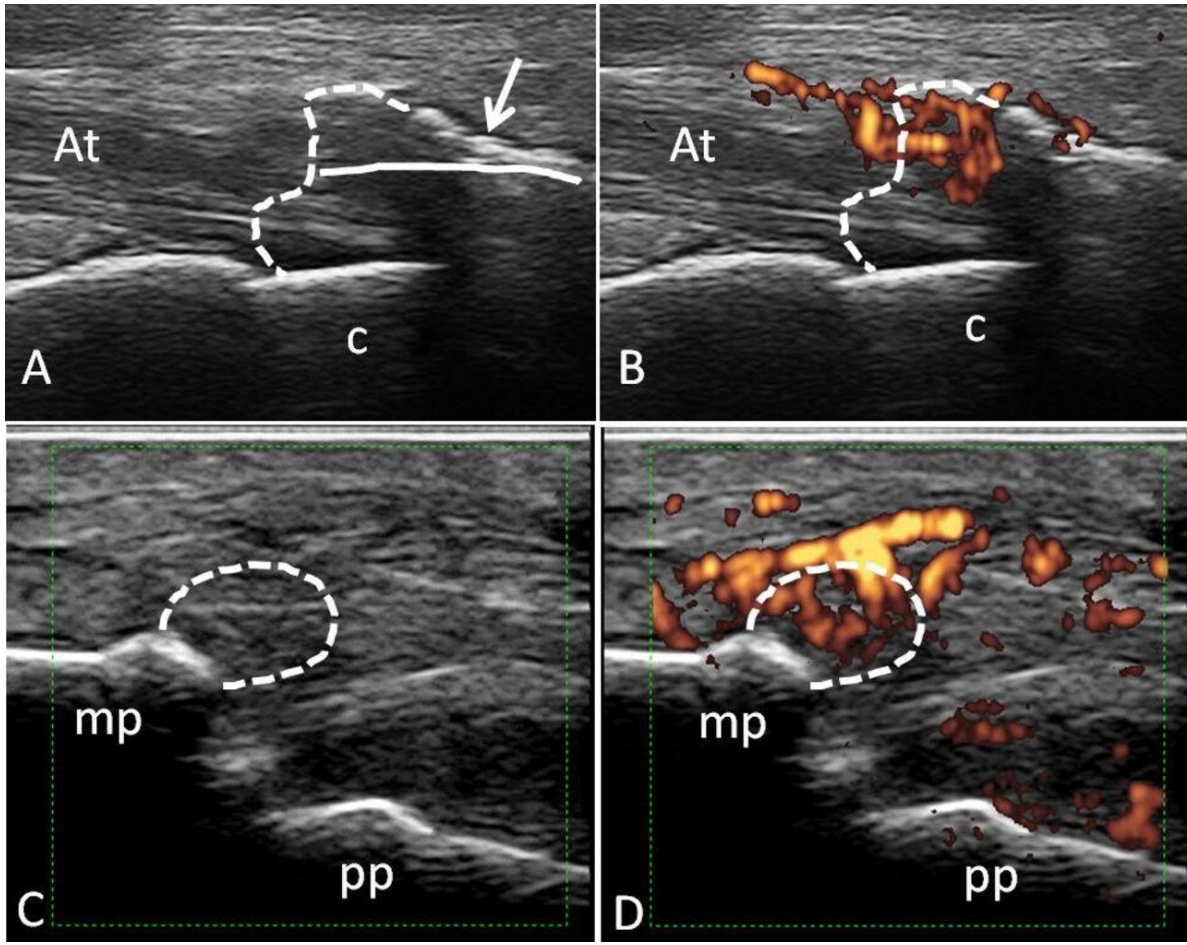
History is important!

De Winter J et al. *Arthritis & Rheumatology* 2018

Peripheral joint disease may be better appreciated by ultrasound

- More sensitive at identifying enthesitis compared to physical exam
- Enables differentiation from tenderness due to fibromyalgia

Dubash et al. Front Med 2020
Aydin et al. J Rheumatol 2020
Polachek et al. Ann Rheum Dis 2021



Filippucci et al. Ann Rheum Dis 2021

But… is it enthesitis or fibromyalgia?!?!

Enthesitis

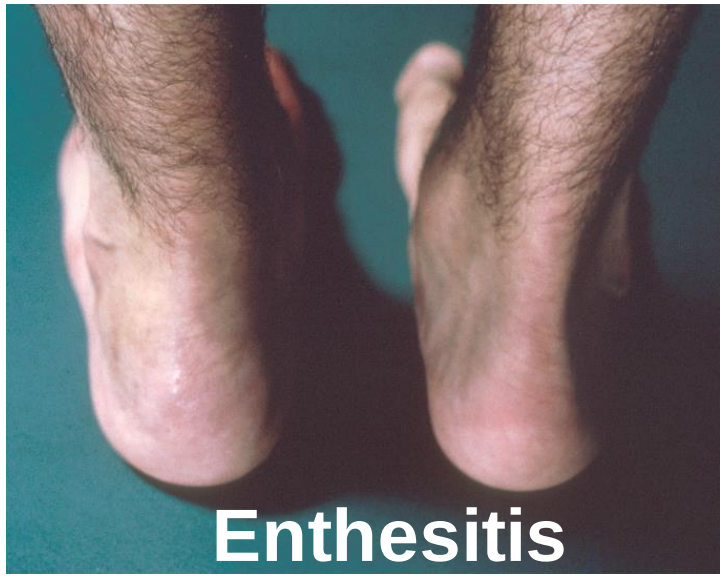
Not mutually exclusive
Frequent reassessment

Fibromyalgia

Additional objective findings:
Psoriasis or other SpA-features
Swelling, warmth, erythema

Qualitative Features:
Improvement with mobility
And worsen with immobility

Therapeutic trial:
Scheduled NSAIDs
Steroid injection



Additional symptoms:
Sleep disturbance
Mood symptoms/associations

Qualitative Features:
Worsens with mobility or stress

Failed therapeutic trial:
Scheduled NSAIDs
Steroid injection

Marchesoni et al. *Rheumatology* 2018

Case 3: How do we manage SpA in the setting of IBD?

- 60-year-old woman
- Crohn's disease for 30+ years
  - Complicated by multiple bowel resections (strictures)
  - Has ileostomy
  - Disease currently controlled on TNFi
- Right wrist is swollen and painful
- Exam notable for right wrist effusion, tenderness and warmth

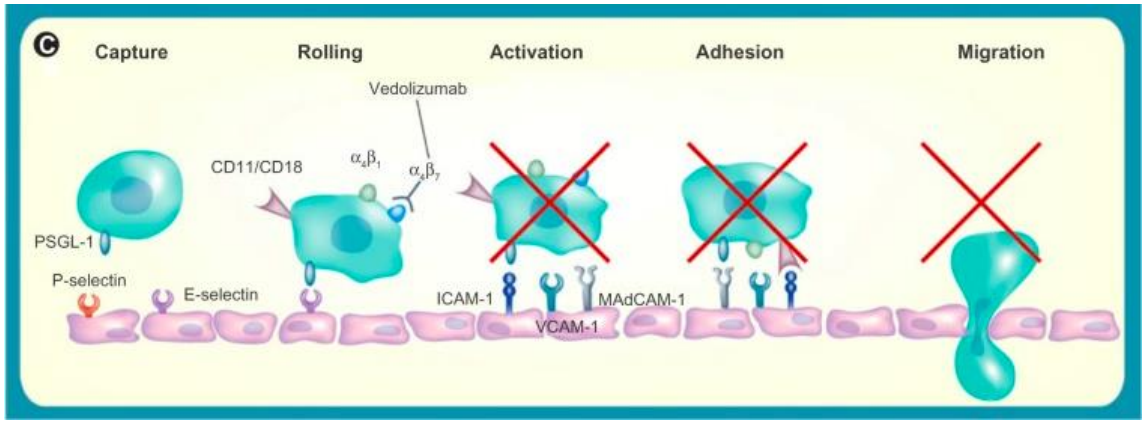
Rheumatology Image Library © American College of Rheumatology

Medication efficacy in the setting of IBD-SpA

Agent	IBD	Axial SpA	Peripheral SpA
NSAIDs	Contraindicated (Celecoxib?)	Y	Y
Oral DMARDs	Some (SSZ, AZA)	N	Some (MTX, SSZ)
TNFi	Y	Y	Y
IL-17 inhibitors	Worsens active disease	Y	Y
IL-12/23	Y	N	Maybe
Vedolizumab	Y	N	N
JAKi	Y	Y	Y

Vedolizumab

- Blocks α4β7 on leukocytes
  - Unable to bind MAd-CAM
  - No transmigration into gut



- Mad-CAM selective to gut
  - Not in joints -- α4β7 blockade of no benefit to SpA?

Feagan et al. NEJM 2013
Feagan et al. J Crohns Colitis 2019

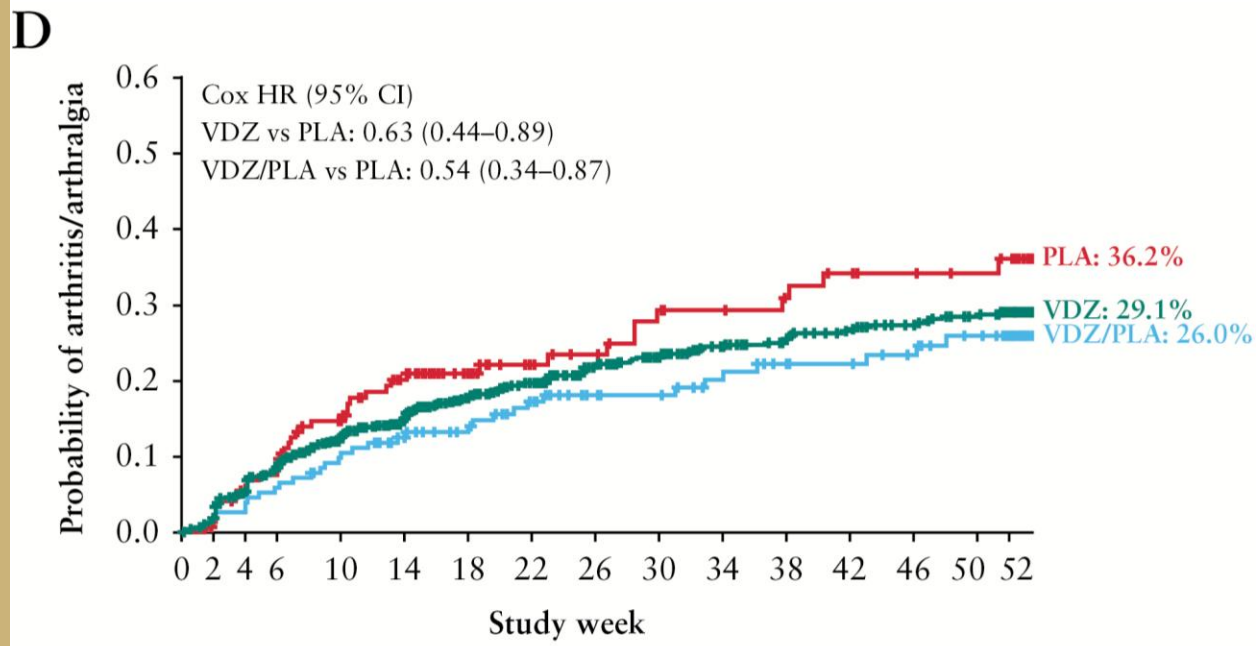
Case series of arthritis development/flare with vedolizumab

Sex	Age	Concomitant medication	IBD	Response of gut inflammation	Prior Dx of SpA	TTF (days)	SpA feature
F	50	Mesalazine	CD	Good HBI 0 at week 14	No	60	Sacroiliitis
F	28	AZA	UC	Good Mayo 0 at week 10	No	58	Arthritis
M	30	AZA	CD	Good HBI 0 at week 28	Yes (axial disease)	14	Sacroiliitis
F	47	Mesalazine	CD	Good HBI 2 at week 20 HBI 1 at week 32	No	114	Sacroiliitis
F	26	None	UC	Poor Mayo 3 at week 10	No	73	Arthritis

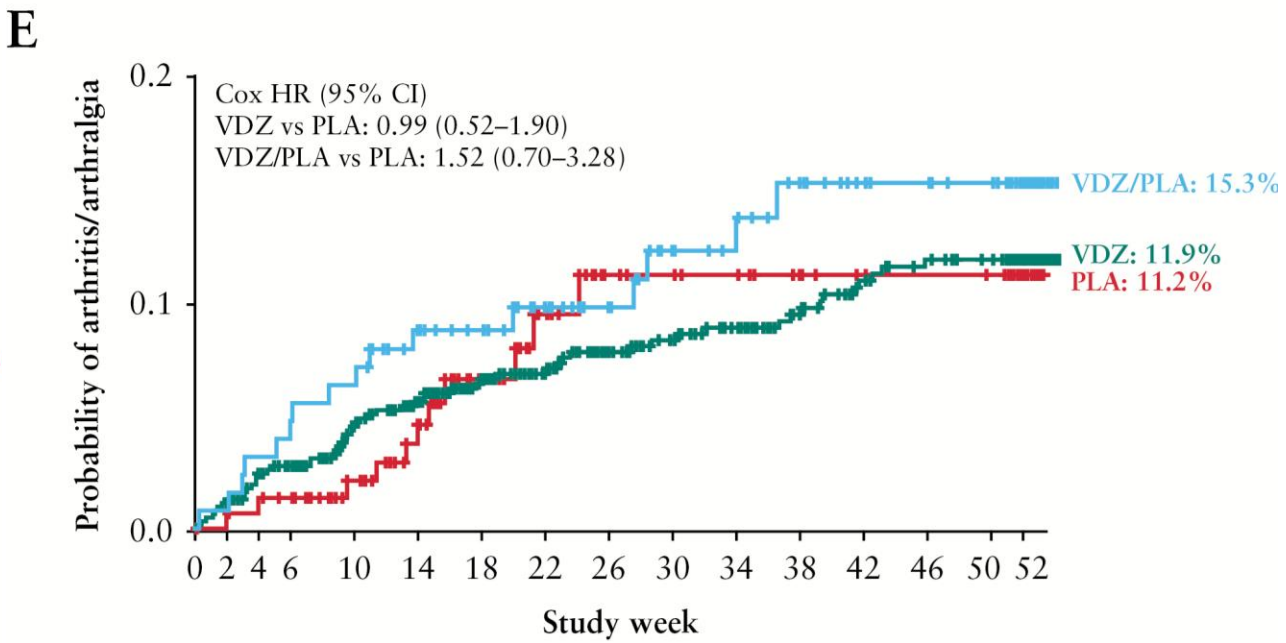
Varkas G et al. Annals of the Rheumatic Diseases 2016.

No significant increases in arthritis in post hoc analysis of Gemini trial

Crohn's Disease



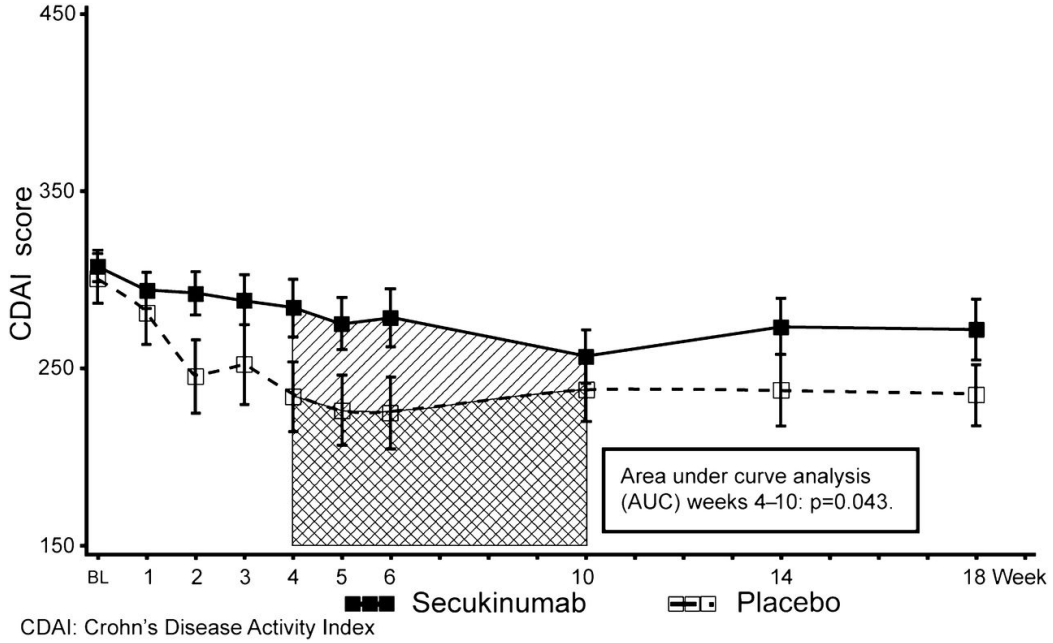
Ulcerative Colitis



Feagan et al. J Crohns Colitis 2019

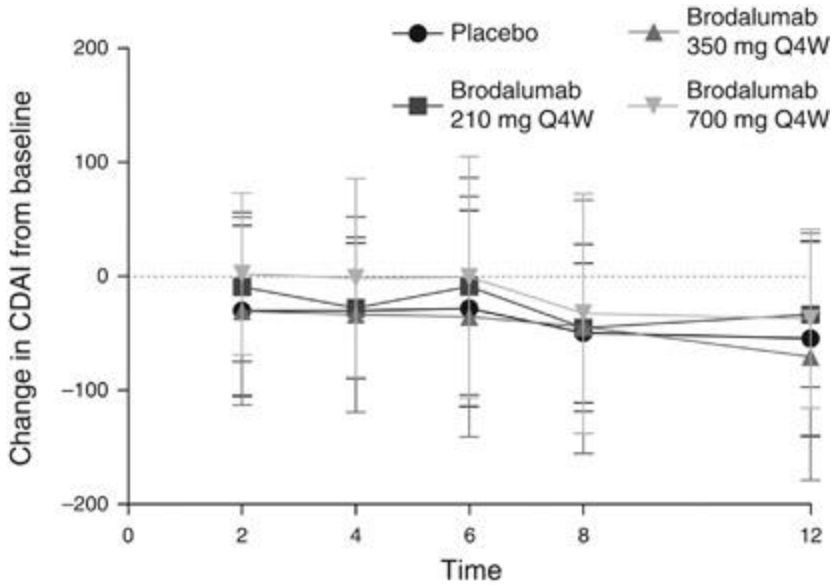
IL-17 inhibitors and IBD

Secukinummab in Crohn's



Hueber W et al. Gut 2012.

Brodalumab



Targan et al. Am J Gastroenterol 2016

Risk of developing IBD in the setting of IL-17 inhibition is small

- French National Health Data System
- 2016–2019
- 16,793 new IL-17i users
- 10,294 new ETN users

	PsO exclusively	PsA or AS exclusively	PsO or PsA	Biologic-naive
No. of IBD events/no. of individuals at risk				
New IL-17i user	7/1,658	21/4,835	19/5,884	13/4,394
New ETN user	0/466	31/6,033	18/3,795	37/7,464
Risk of IBD in new IL-17i users, weighted HR (95% CI)				
	4.1 (0.2–89.5)	0.8 (0.5–1.5)	0.7 (0.3–1.3)	0.6 (0.3–1.1)

Penso et al Arthritis & Rheum 2021

Case 4: Joint Pains while on IBD Therapy

- 45-year-old man
- UC, active with 8 bloody BM/day
- Infliximab initiated 5mg/kg at 0, 2 weeks and then increased to 10mg/kg at week 6 due to partial response
- At week 8 develops F/C, rash, wrist, shoulder, and knee pain, swelling and limited ROM
- HR 101, RR 18, BP 130/63

JM Martin et al Lupus 2008

Anti-TNF Induced Lupus (ATIL)

Incidence ~1-5% based on study/definition

ANA positive 100% and dsDNA positive ~75%

- Arthritis (87%), fatigue (41%), mucocutaneous symptom (29%), myalgia (24%), cytopenia (16%), fever (12%), cytopenias (10%), renal (9%)

Resolution 1-6 months after withdrawal of TNFi

- Corticosteroids, NSIADs, HCQ, AZA, MTX, mycophenolate
- Switch to another TNFi considered safe

Dai C et al. International Immunopharmacology, 2022

Case 5: Arthritis despite IBD in remission

- 27-year-old man diagnosed with AS in 2008
  - 2007-2013 taking naproxen and methotrexate
  - 2013 had flare and turned 18 so switch to adalimumab (ADA)
- CD diagnosed 2013
  - Moderate inflammation on endoscopy but didn't follow with GI as was already on ADA
  - 2020 ADA wasn't helping CD so switched to infliximab - effective for AS but not CD
  - June 2020 did not respond to tofacitinib
    - Rapid decline requiring hospitalization - prednisone taper
    - Temporary ileostomy
  - Oct 2020 started ustekinumab for CD but AS uncontrolled

Dual biologics for recalcitrant disease

IBD most common combinations

- TNFi & anti-integrins (48%)
- Ustekinumab & anti-integrins (19%)

RA combinations included

- TNFi, abatacept, anakinra, rituximab, and tocilizumab

Ahmed W et al. Clinical Gastroenterology and Hepatology, 2022
Boleto G et al. Seminars in Arthritis and Rheumatism, 2019

Use of dual biologics in IBD

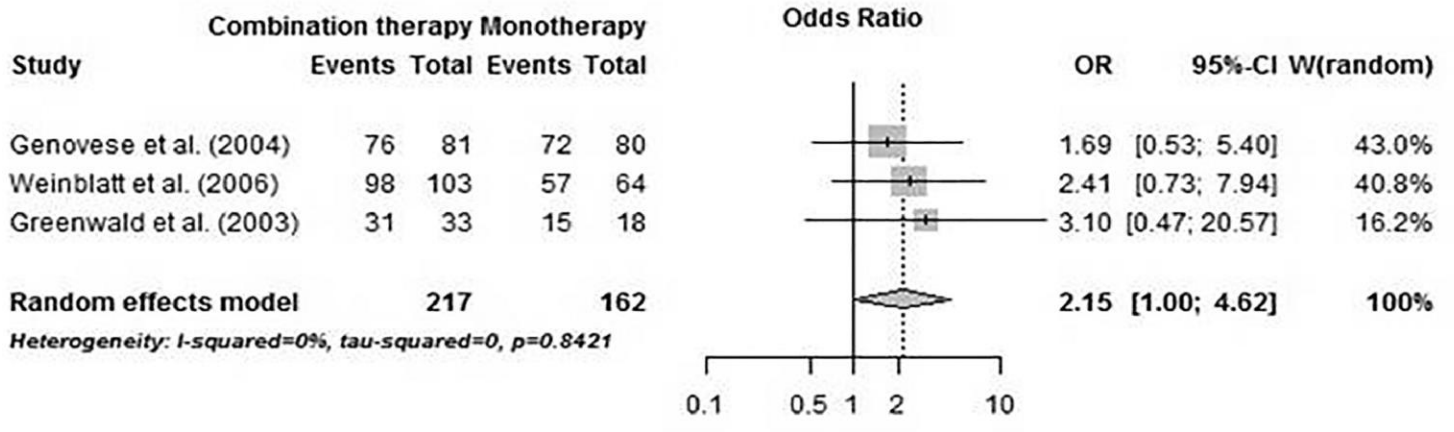
Study	Year	Type of Review	Findings
Ahmed et al	2021	Systematic review with meta-analysis	This review included **30 studies with 288 patients** on dual biologic therapy. The review also included combination therapy with a small molecule and a biologic. **No severe safety concerns** were identified. The authors concluded that dual biologic or other combination therapy may be an option for patients with severe, refractory IBD.
Ribaldone et al	2019	Systematic review with pool analysis	This review included **7 studies (18 patients) with a combination of TNF inhibitors and VDZ as well as VDZ with UST**. Clinical improvement was seen in all patients, and endoscopic improvement was reported in 93% of patients. **No safety concerns** were identified.

VDZ = vedolizumab; UST = Ustekinumab

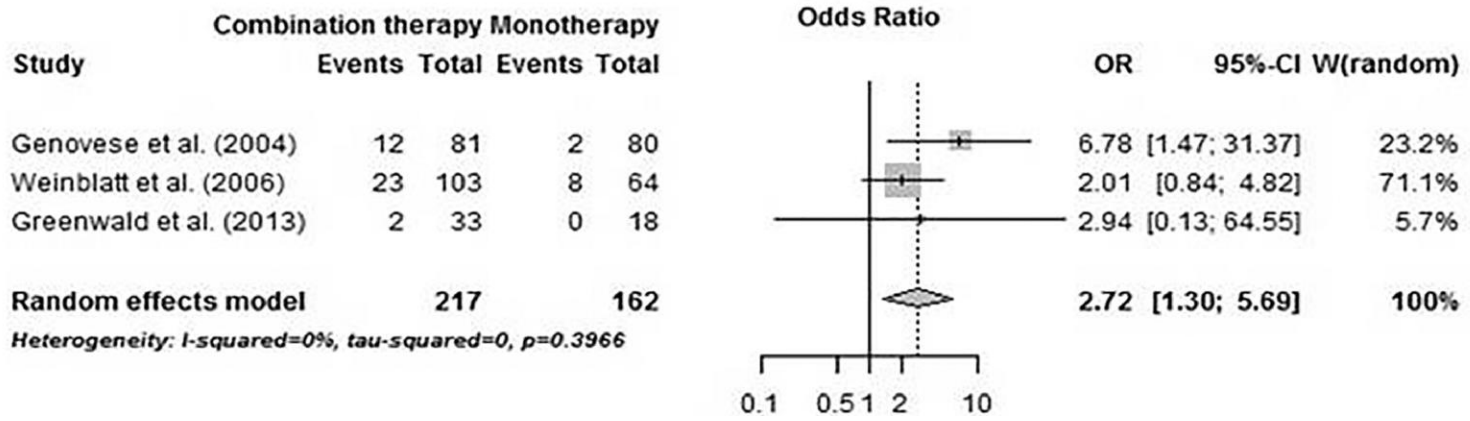
Gold & Steinlauf. Gastroenterol Hepatol (N Y) 2021

Use of dual biologics in RA

A Overall adverse events



B Serious adverse events

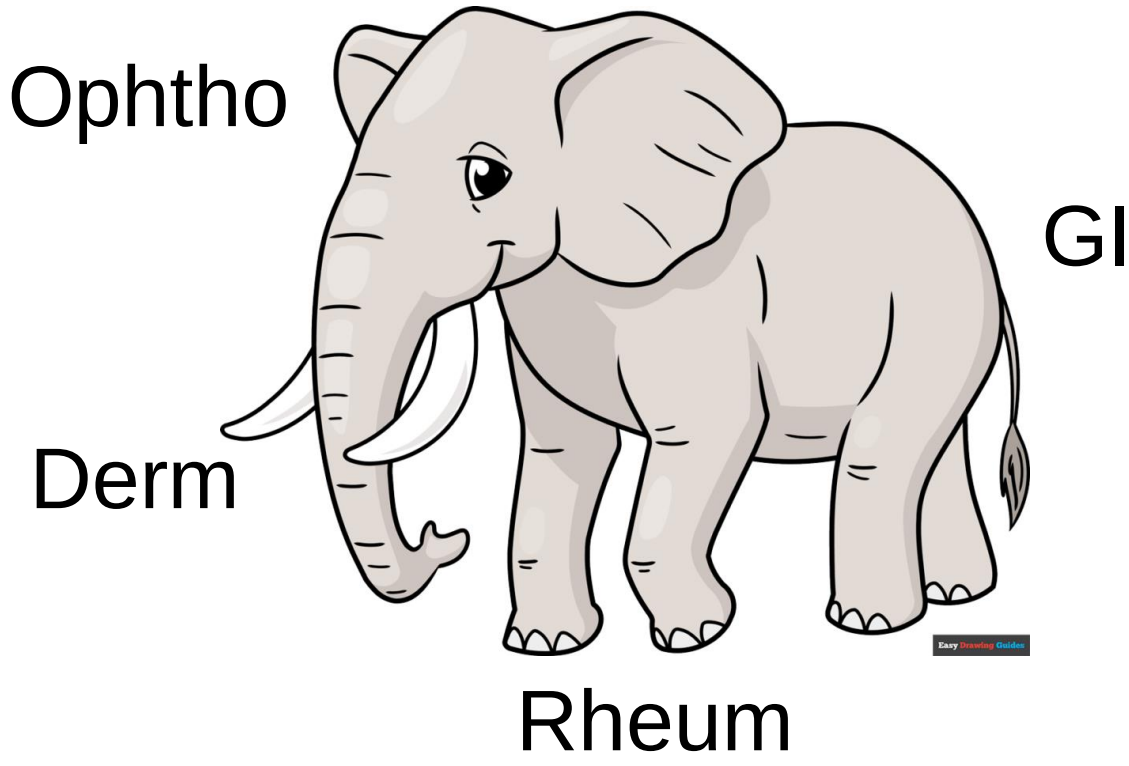


Tapered doses reduced the risk of adverse effects

Boleto G et al. Seminars in Arthritis and Rheumatism, 2019

Importance of bi-directional communication

- Patients with concomitant IBD and SpA are complex!
- Improved outcomes with multidisciplinary care teams



Key Takeaway Points

- IBD and SpA co-exist and one can precede the other
  - Ask the patient about extra-intestinal/articular symptoms
- Choose therapies that can put both disorders in remission
  - In some instances, dual biologic/Jaki therapy is needed
- Joint pains can be a complication of IBD therapies
  - TNFi-induced lupus, steroid withdrawal
- Effective communication and collaborative care are key to improving the care of patients with IBD-SpA


THANK YOU!
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