Brigham and Women's Hospital
Founding Member, Mass General Brigham

Spondyloarthritis

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Clinical focus: Lyme arthritis, rheumatoid arthritis, psoriatic arthritis, dermatology-rheumatology overlap, quality and safety

DISCLOSURES

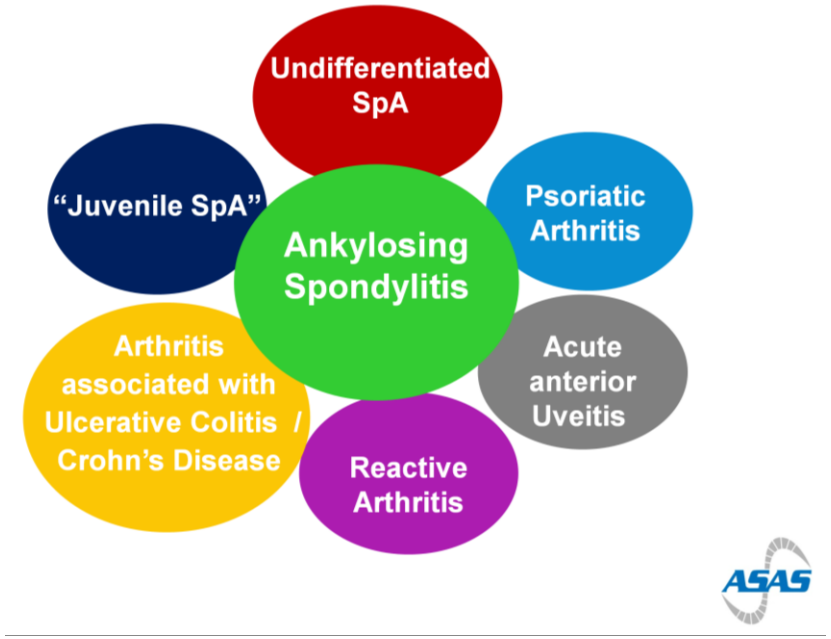
I have no relevant financial relationships with ineligible companies.

OBJECTIVES

- Provide an overview of clinical and epidemiologic features of spondyloarthropathy (SpA)
- Review physical, laboratory and imaging findings and diagnostic criteria
- Highlight mechanisms of pathogenesis
- Discuss treatment strategies

What is Spondyloarthritis (SpA)?

- Also known as spondyloarthropathy or seronegative spondyloarthropathy
- Group of inflammatory arthritides
  - Psoriatic arthritis, ankylosing spondylitis, IBD-associated, reactive arthritis, undifferentiated, juvenile
- Seronegative for ANA, RF
- *Associated* with HLA-B27
- All can affect the spine
- All can have GI, eye, and skin involvement



From Greek, Spondylo=vertebrae

Assessment for Spondylo-Arthritis International Society (ASAS)

Musculoskeletal Involvement in SpA

Axial (Spine, sacroiliac joints),

--inflammatory back pain

--new bone formation, ankylosis

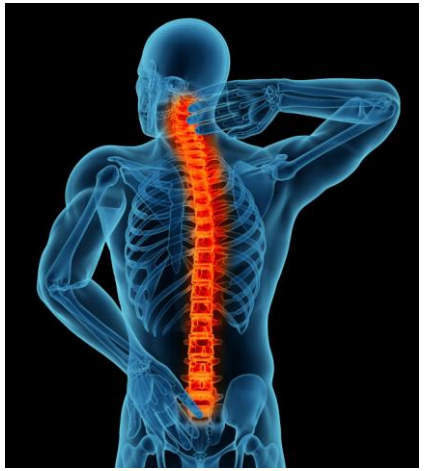
Peripheral

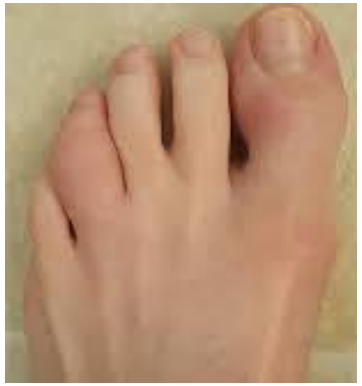
--peripheral arthritis

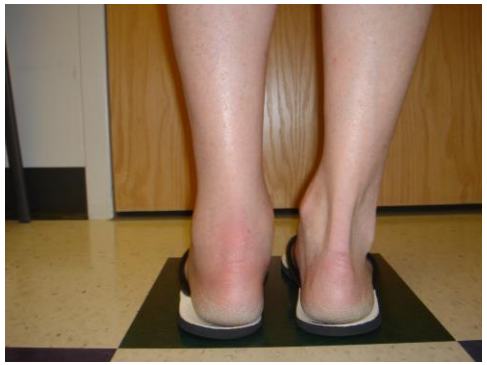
--enthesitis

--dactylitis

May have mix of both features

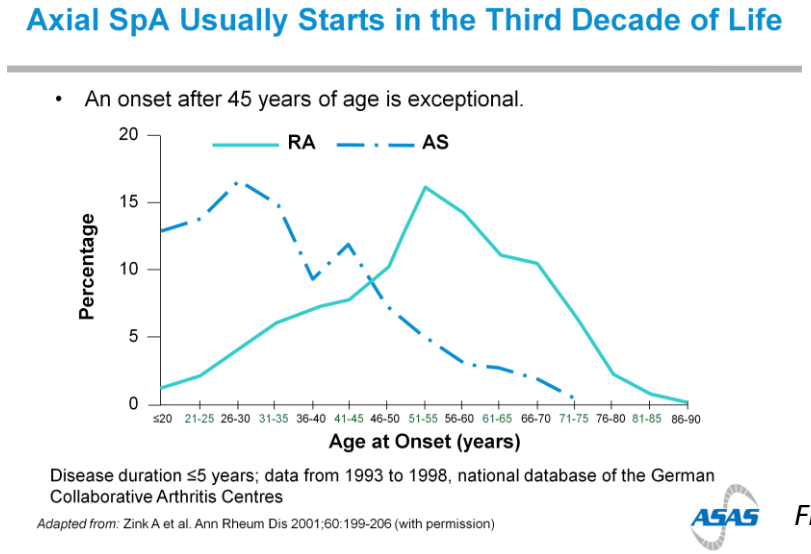






Epidemiology

- Age <40 (particularly AS)
- M=F (PsA, IBD), M>F (AS, ReA)
  - Gender differences less strong than previously thought in AS
- Global prevalence ~1%
- Correlates with HLA-B27 prevalence



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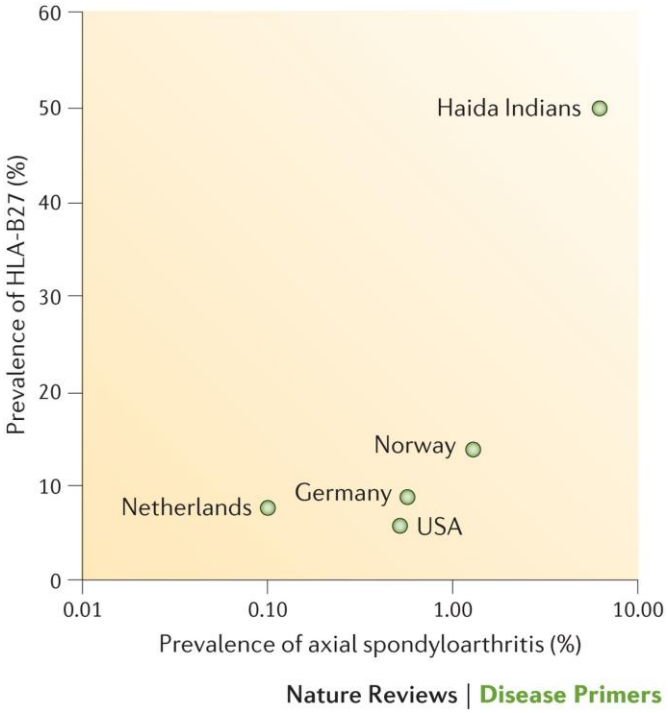


Sieper, J., *et al.* Axial spondyloarthritis. *Nat Rev Dis Primers* , 2015

Deodhar *et al.* Geographic Variations in Diagnosis and Treatment of Ankylosing Spondylitis in the United States: A Real-World Study. *Rheumatol Ther* **9**, 447–463 (2022).

Case 1

29 yo F medical student in USOH until about 2 years ago, when she developed acute R sided low back pain while training for marathon. She was treated with NSAIDs and improved after a few weeks. She had a similar occurrence 4 mos later however at this time was not exercising intensively, improved with PT. Then the pain recurred, became more persistent and bilateral. Has pain daily which waxes and wanes. Pain is worse in am when she wakes, may last about an hour. She denies much stiffness but has pain after prolonged sitting. No peripheral joint pain or swelling. She takes NSAID 2-3X/week which helps. PT also has helped but she is still symptomatic and not doing as much as activity as she would like.

Studies: ANA1:160, negative RF, CCP, HLA-B27, CRP 0.5, ESR 5.
X-rays of lumbar spine, SI joints normal

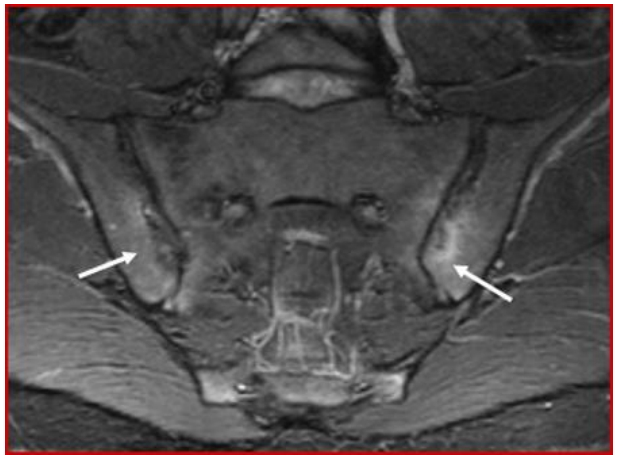
What would you do next?

A. Trial of prescription, standing NSAID
B. Trial of cyclobenzaprine
C. Obtain MRI of sacrum
D. Refer to physiatry

Case 1-Answer

C. MRI of sacrum

Patient was found to have sacroiliitis on MRI, further history also revealed psoriasis.



Delayed diagnosis in axSpA remains an extensive worldwide problem; recent estimates of the median diagnostic delay suggesting that an individual with axSpA will likely wait between 2 and 6 years for a diagnosis

Inflammatory tests may be normal in inflammatory arthritis!
HLAB27 may be negative in spondyloarthropathy
Advanced imaging may be needed to make the diagnosis

Barnett R et al. Diagnostic delay in axial spondylarthritis: A lost battle? Best Pract Res Clin Rheumatol. 2023 Sep;37(3):101870

Diagnosis--Historical Features

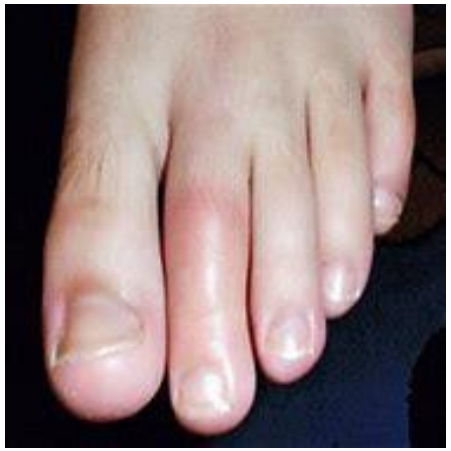
- Insidious onset (AS especially, reactive arthritis more acute)
- Pain and stiffness in back and/or peripheral joints, buttock pain
- Achilles tendinitis/enthesitis, plantar fasciitis, dactylitis
- Inflammatory features
  - Better with exercise
  - No improvement with rest
  - ***Night pain, as well as morning pain***
- Extraarticular features (psoriasis, eye inflammation, GI symptoms)
- Family History (40% psoriatic arthritis)

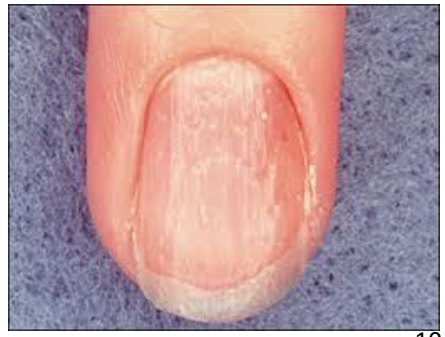
Fallahi S, Jamshidi AR, Arch Rheumatol. 2015 Aug 16;31(1):24-30.

Inflammatory Back Pain (IBP) According to Various Criteria

Calin et al.[1]	Rudwaleit et al.[2]	IBP experts (ASAS)[3]
• age at onset < 40 yrs • duration of back pain > 3 months • insidious onset • morning stiffness • improvement with exercise	• morn. stiffness > 30 min • improvement with exercise, not with rest • awakening at 2. half of the night because of pain • alternating buttock pain	• age at onset < 40 yrs • insidious onset • improvement with exercise • no improvement with rest • pain at night (with improvement upon getting up)
IBP if 4 / 5 are present.	**IBP if 2 / 4 are present.**	**IBP if 4 / 5 are present.**

1 Calin A et al. JAMA 1977;237:261; 2 Rudwaleit M et al. Arthritis Rheum 2006;54:569-78; 3 Sieper J et al. Ann Rheum Dis. 2009; 68: 784-788





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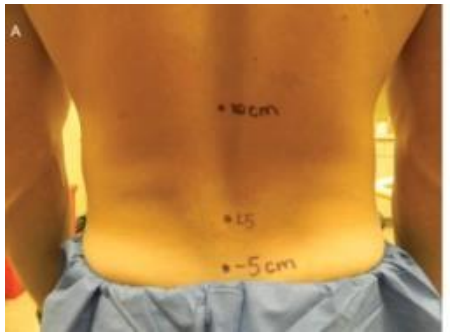
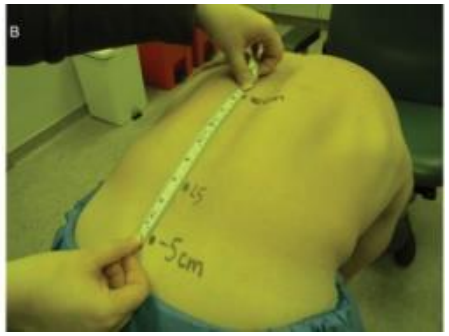
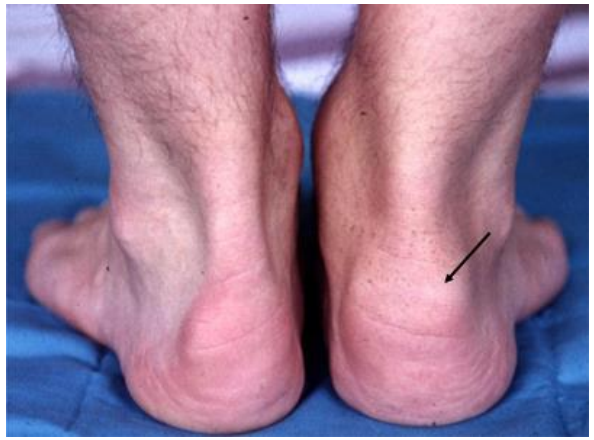
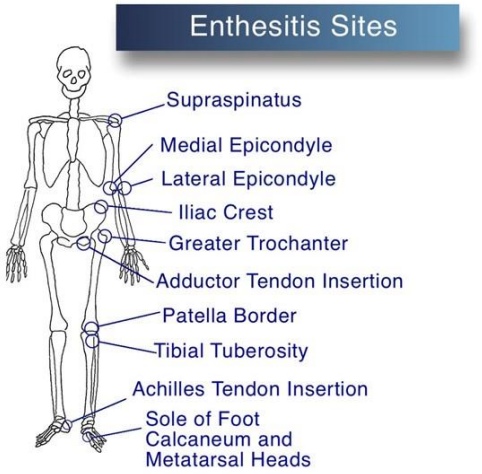
Diagnosis--Physical Exam





- Swollen and Tender Joints
- Enthesitis
  - (Achille's, plantar fascia insertions, epicondyles, femoral condyles
- Tenderness of SIJ
  + FABER testing
- Altered mobility
  --occiput to wall distance
  --Schober (≥5 cm nl)
  --chest wall expansion





Physical exam findings can be subtle with early and axial disease

From ASAS slide library

Diagnosis-Laboratory Features

Blood tests

- ESR/CRP--*may be normal*
- HLA-B27—variable depending on SpA type (ie 90% in AS vs 15% PsA) and ethnicity
- Lack of RF, ANA

Joint fluid analysis

- inflammatory, but non-specific, helps rule out other etiologies

Clinical Associations With HLA-B27

Disorder	HLA-B27 (%)
Ankylosing spondylitis	90
Reactive arthritis (Reiter's syndrome)	40-80
Juvenile SpA	70
Inflammatory bowel disease	35-75
Psoriatic arthritis	
With spondylitis	50
With peripheral arthritis	15
Undifferentiated SpA	70
Acute anterior uveitis	50
Aortic insufficiency, heart block	80

Kahn MA. *Ann Intern Med.* 2002;136:896-907.

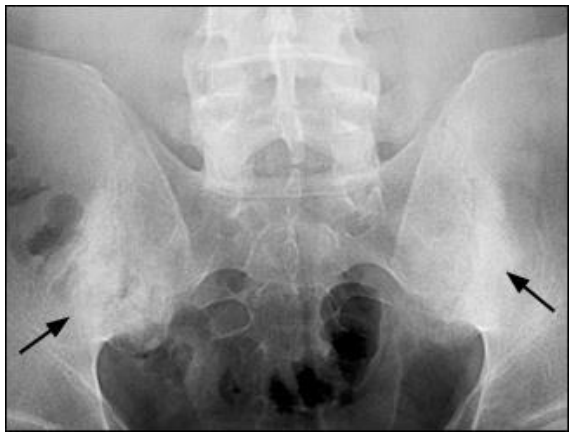
Diagnosis-Imaging

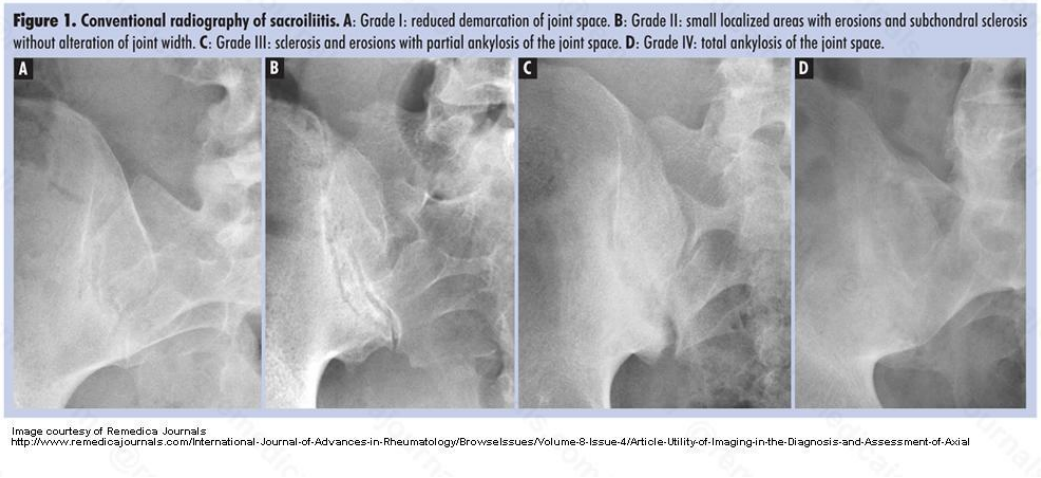
Obtain baseline X-rays
- Spine, SIJ

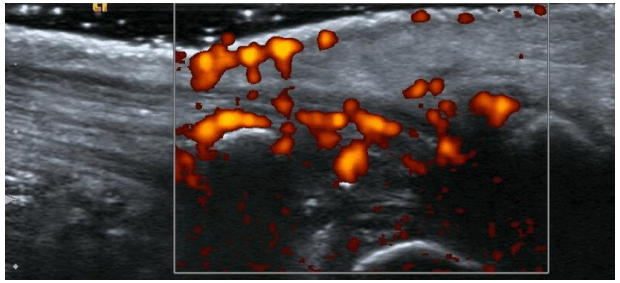
X-ray Findings
- *May be normal in early disease*
- Destruction/Erosions
- Periosteal Reaction
- New bone formation

"Non-radiographic Axial SpA"
Moe of a historical term, now that MRI widely used

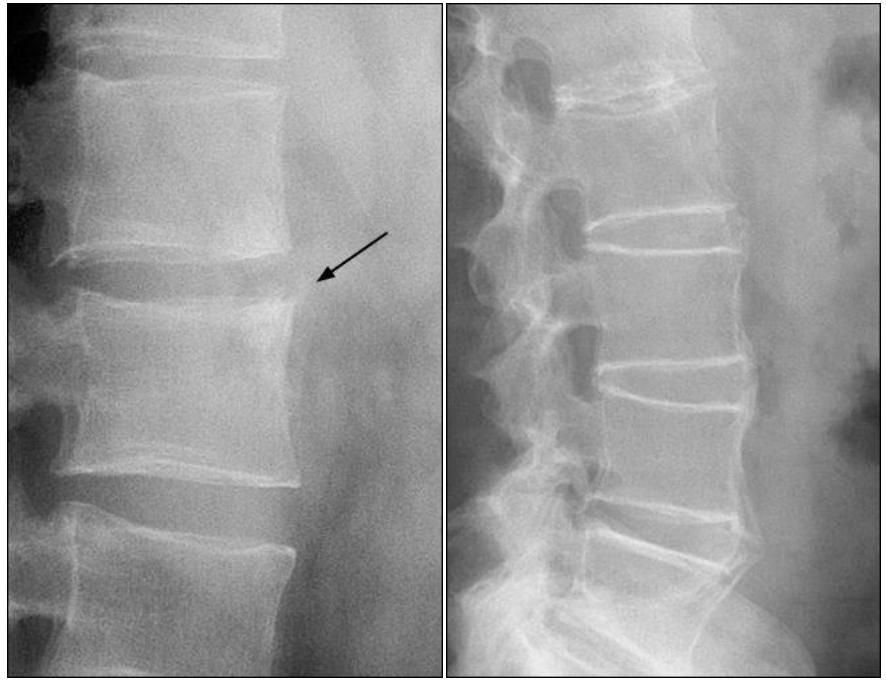
Axial disease such as sacroiliitis is particularly hard to diagnosis and MRI may be needed, MSK ultrasound can be helpful for peripheral enthesitis/synovitis







Early Late



Consider advanced imaging when suspicion for inflammatory arthritis is high but labs/exam normal

Subtypes of SpA

Ankylosing Spondylitis

Spine/SIJ hallmark sites

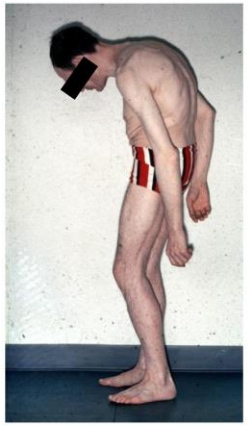
Peripheral Arthritis
- Hip and Shoulder involvement (25-30%)
- Enthesitis (40-70%)
- Peripheral joint arthritis (35-50%)

Complications
- Postural changes
- Limited spinal mobility, limited chest wall expansion
- Spinal cord injury
- Atlantoaxial subluxation
- Cauda equina syndrome
- Osteopenia
  - DEXA more difficult to interpret, Vertebral fracture (OR: 3.3)

AS Patient with Disappearance of the Lordosis of the Lumbar Spine

Final Stage of AS with Severe Kyphosis of Thoracic and Cervical Spine

Unable to look ahead while walking ('patient cannot see the sun')



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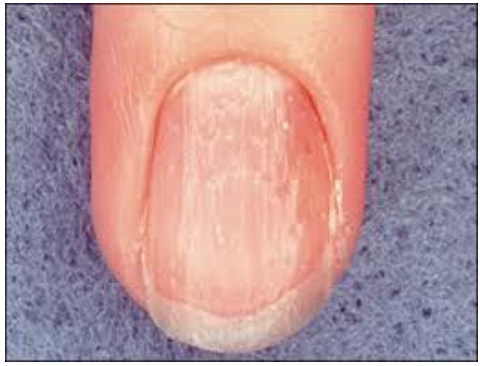
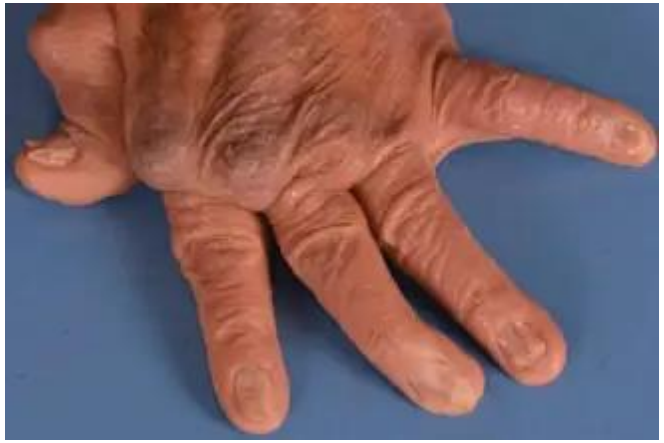
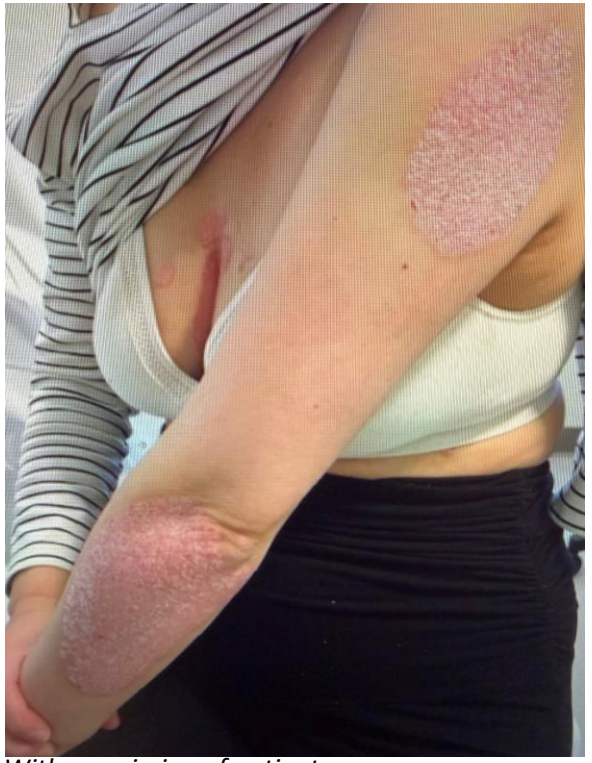
Psoriatic Arthritis





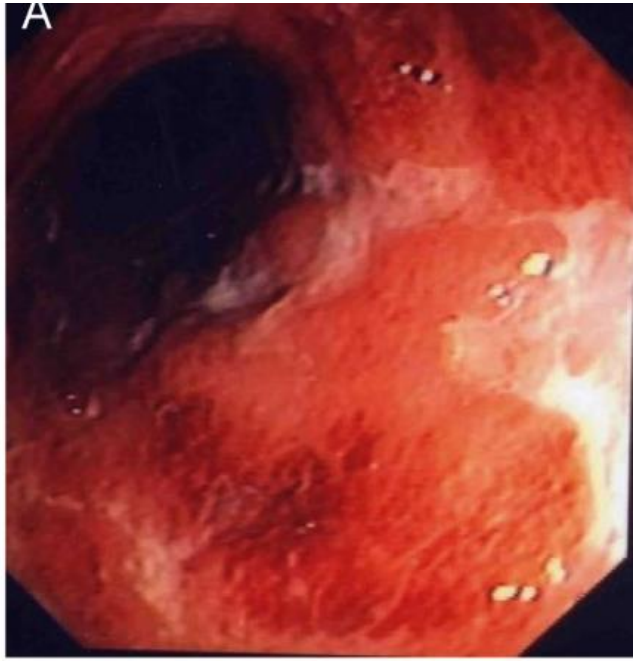
- ~30% of patients with psoriasis
- Risk Factors
  - Nail involvement (pitting, onycholysis) may be risk factor
  - Scalp disease
  - Intergluteal disease
- Oligoarticular (70%), polyarticular, predominant distal interphalangeal (DIP) joint involvement; arthritis mutilans, and psoriatic spondylitis

Psoriatic arthritis does not correlate with skin disease severity, skin disease may be subtle, nail and scalp involvement are PsA risk factors



With permission of patient

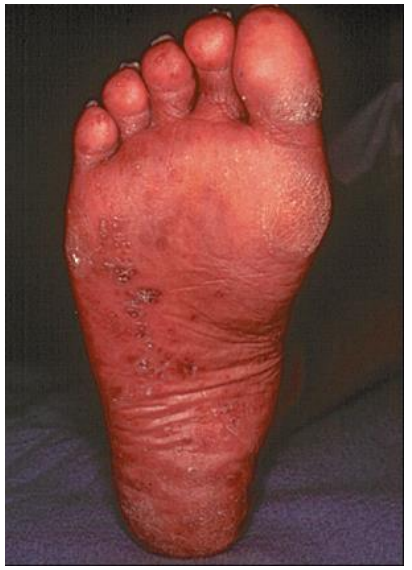
IBD-associated Arthritis



- Most common extraintestinal manifestation
  - 20-30% of IBD patients
- Peripheral arthritis is non-erosive, often tracks with GI disease
- Axial disease less likely to correlate with intestinal activity
- Treatment of IBD not always sufficient for control of arthritis

Reactive Arthritis

- Sterile inflammatory arthritis, onset within days to weeks of GI or GU infection
  - 10-25% cases no identifiable cause
    - Chlamydia most common cause (4-8% develop ReA after chlamydia)
- Asymmetric mono or oligoarthritis affecting lower extremities, associated with enthesitis and dactylitis
- Small subset have Reiter's (arthritis, conjunctivitis, urethritis)
- Extraarticular manifestations (cutaneous, ocular, CV)
- Many patients have resolution by 6 months, but can become chronic arthritis
  - HLA-B27 positivity or the triad of arthritis, conjunctivitis and urethritis may be at risk for developing a chronic spondyloarthritis.
  - First-line treatment is NSAIDs, followed by steroids and non-biologic DMARDs
  - Antibiotic therapy is not of clear benefit once infection has resolved, may have more of a role in *Chlamydia*-induced arthritis*.

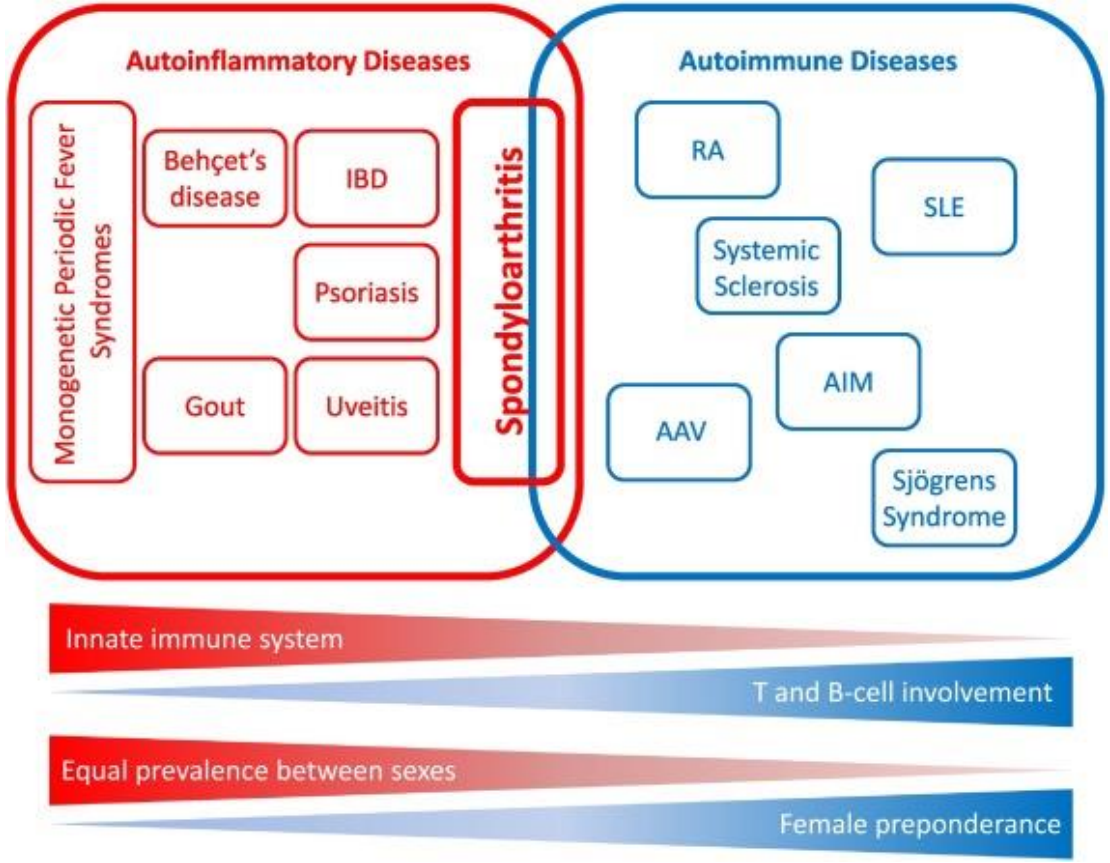


*Carter JD, et al. *Arthritis Rheum*. 62: 1298-307, 2010.

Pathogenesis

Autoimmune vs. Autoinflammatory

M=F prevalence
No detectable autoantibodies
Respond to IL-17/IL-23 blockade
Not as responsive to steroids
No IL-1 association



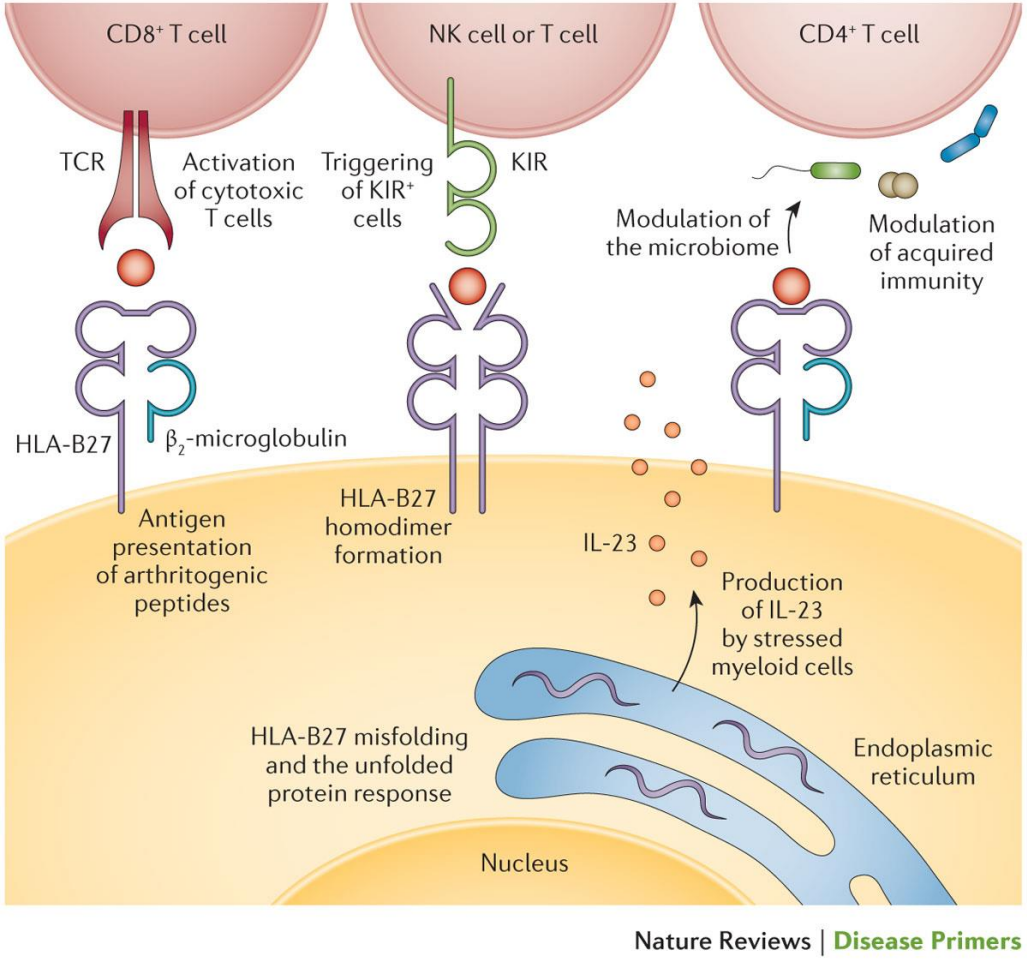
Generali, E et al, Nature versus nurture in the spectrum of rheumatic diseases: Classification of spondyloarthritis as autoimmune or autoinflammatory, Autoimmunity Reviews, 2018

Pathogenesis-Genetics

Genetics-HLA-B27-MHC class 1 molecule
Overall accounts for 40% genetic risk for SpA
Other important polymorphisms: TNF, IL-23, ERAP 1 and 2 (trims peptides prior to HLA-1 presentation)

Multiple potential B27 mechanisms

- Present peptides to cytotoxic T cells
- Homodimers activate NK/Tcell
- Protein misfolding leads to accumulation of protein in ER, increases inflammation and IL-23
- Modify microbiome, polarize toward Th17 cells

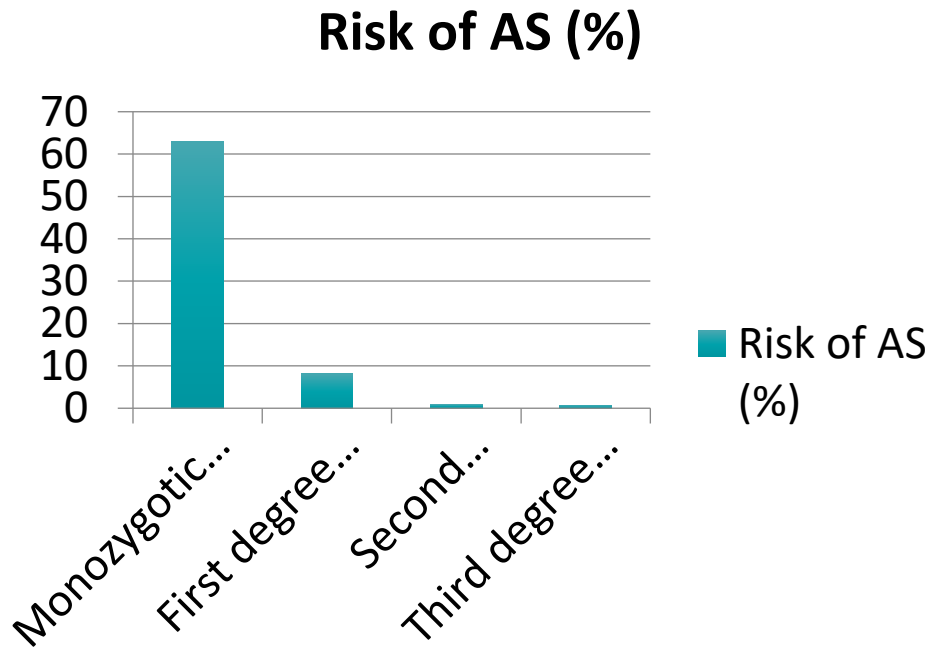


*Sieper, J., et al. Axial spondyloarthritis. Nat Rev Dis Primers **1**, 2015*

Pathogenesis-Environment

Smoking
Infections
- known triggers in ReA
- not well characterized in others

HIV associated with SpA
Gut Microbiome
- 5-10% of patients with AS have overt inflammation on endoscopy
- 70% with occult inflammation on endoscopy
- IL23 secreted by gut epithelium, and markedly elevated in terminal ileum of patients with AS
- IL23→ IL17 production
- Dysbiosis seen in AS/SpA patients, B27 transgenic rat
- Numerous SpA animal models show amelioration/abrogation in germ-free environment

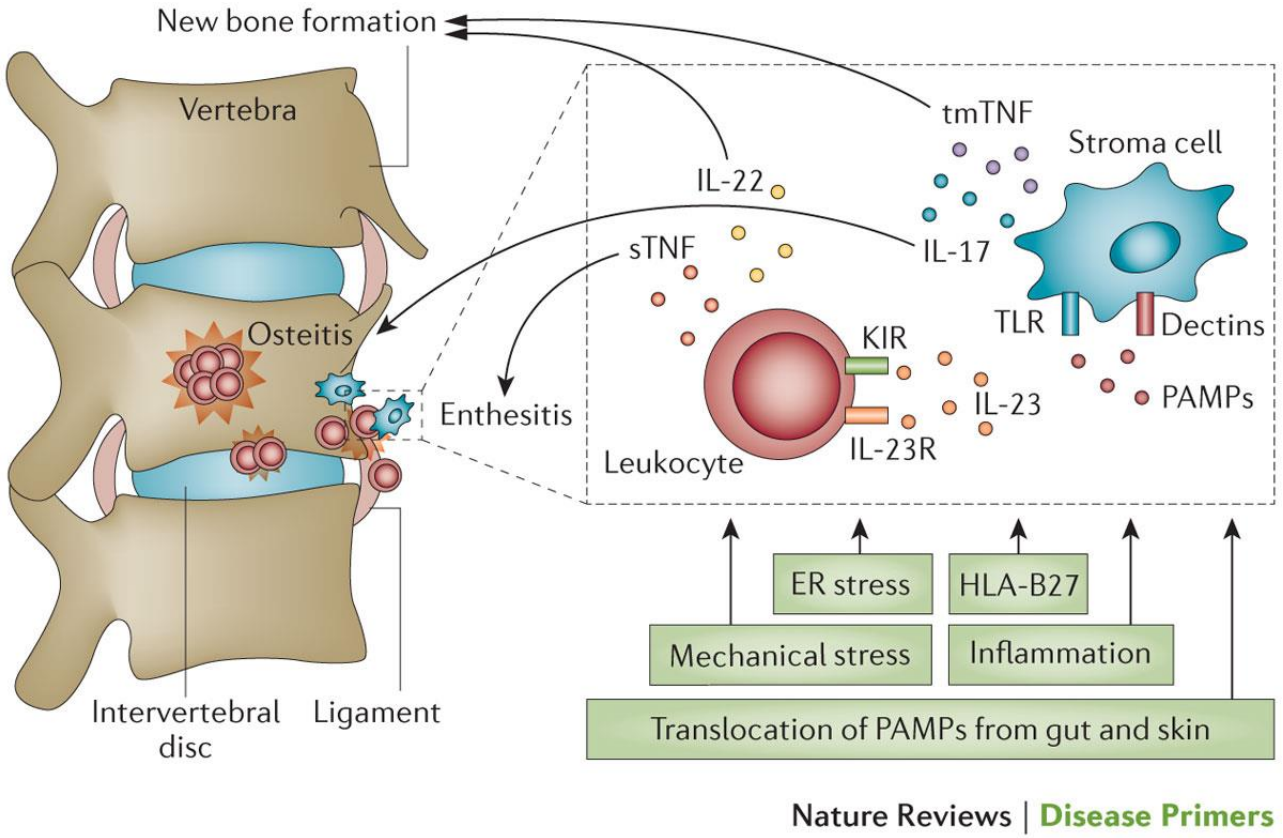


Costello et al, Arthritis and Rheum, 2015 , Gill T, et al, Arth Rheum 2018, Wen et al, Genome Biol, 2017,

Gill T, Rosenbaum JT. Front Immunol. 2021 Jan 18;11:586494.

Pathogenesis-Inflammation

- Enthesis key site of inflammation
- IL-23 activates leukocytes and stromal cells in entheses and bone marrow
- Soluble TNF , IL-17 important in driving the disease
- Transmembrane TNF and IL-22 may lead to new bone formation



Sieper, J. *et al.* (2015) Axial spondyloarthritis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.13

Treatment Strategies

Treatment-General Principles

NSAIDs, initial treatment for all

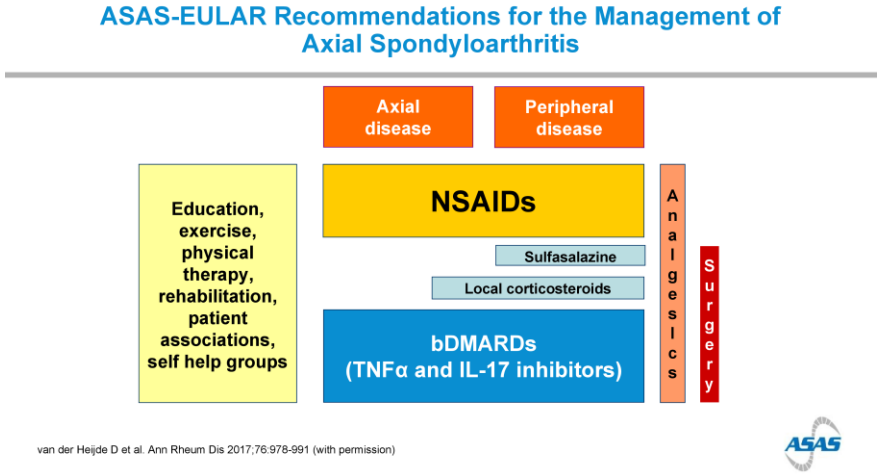
Peripheral disease
- Conventional DMARDs for peripheral disease (although most evidence for PsA)
- Apremilast (PDE4 inhibitor)for PsA
- Local steroid injections
- Biologics if refractory

Axial disease
- If refractory to NSAIDs, Biologics (TNFi, IL-17i, JAKi)
- Axial PsA may respond to IL-23i
- No role for conventional DMARDs

Consider Extraarticular manifestations
- IL-17/23 inhibition better for skin disease
- TNF inhibition better for enthesitis, uveitis
- TNFi, IL23i, JAKi for concomitant IBD

For axial disease, if refractory to NSAIDS, move to biologics. NO role for conventional DMARDs

Spondyloarthritis Treatment



Non-biologic

NSAIDs
Local steroid injections
Conventional DMARDs (i.e. MTX, SSZ) for peripheral disease
Apremilast (PDE4 inhibitor, PsA)

Biologics/Targeted DMARDs

TNF inhibitors

IL-17/IL-23 inhibitors

- Seckukinumab (PsA, AS)
- Ustekinumab (anti-p40 IL-12/23) (PsA, IBD)
- Ixekizumab (PsA)
- Risankizumab (PsA, IBD)
- Bimekizumab (dual IL-17 A/F inhibitor, PsA, AS)

CTLA-4 Ig Abatacept (PsA)

JAK inhibitors (PsA, IBD, AS)

- Tyk-2 inhibitor (PsA)

For axial disease, if refractory to NSAIDS, move to biologics. NO role for conventional DMARDs

Principles of Treatment—unanswered ?s

"Treat to target" and early aggressive strategies used for RA less studied in SpA

- Ongoing studies of "window period"

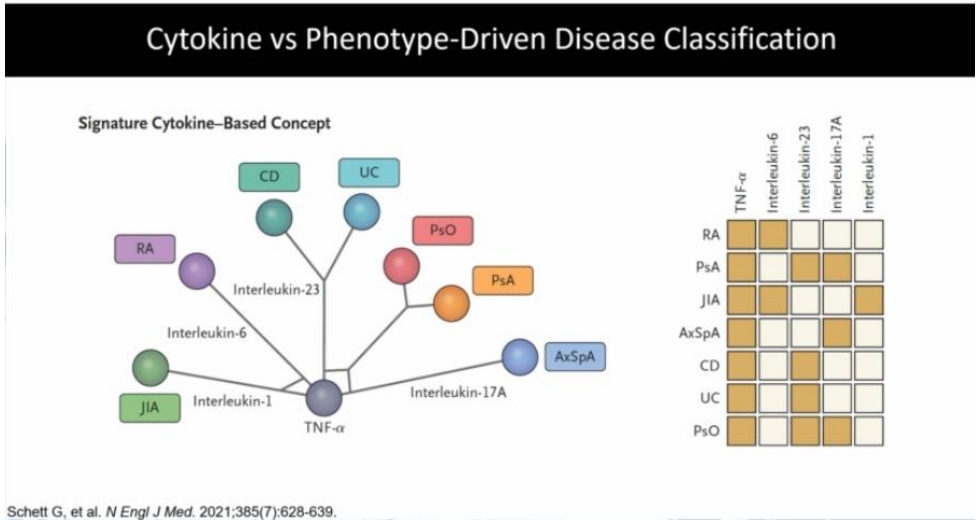
No biomarkers to guide treatment

- Personalized medicine approach in future?

No "cure" at present time

- < 20% AxSpA and <30% PsA achieve remission
- Medications usually needed long-term, although doses can be lowered and drug "holidays" achieved
- Novel treatments, combination treatments, bispecific antibodies in development

Smolen J, et al. Annals of Rheumatic Disease 2010; 69:631-7



Non-Pharmacologic Interventions

- Surgery—less common in biologic era
- Smoking Cessation
  - decrease CVD, progression of disease
- Physical Therapy
- Diet/weight loss

  ? Mediterranean diet

Case 2

38 yo F (BMI 27, no DM) with history of psoriasis and psoriatic arthritis on apremilast with some benefit, but residual psoriasis and joint pain. She is reluctant to try a biologic recommended by rheumatology. She asks you, her PCP, about adding a GLP-1 agonist as she heard on a podcast that this may benefit her symptoms. What do you recommend?

A. Anti-inflammatory diet and exercise, no indication for GLP-1 medication
B. Start GLP-1 medication
C. Anti-inflammatory diet and exercise first, start GLP-1 if not improving
E. Start metformin

A. Anti-inflammatory diet and exercise, no indication for GLP-1 medication

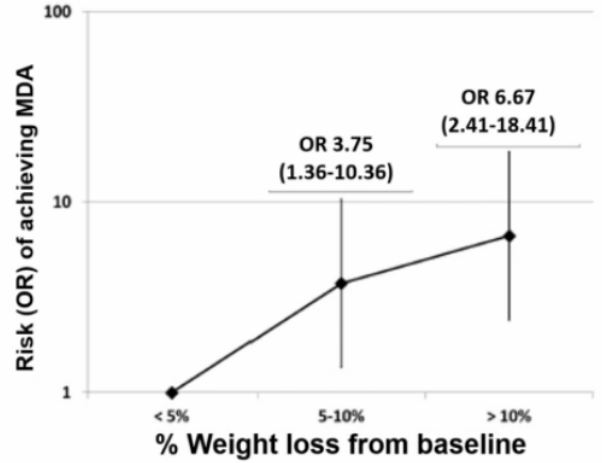
However—GLP-1 medications may have benefit for inflammatory arthritis/psoriasis—stay tuned!

Obesity is major comorbidity in PsO/PsA

- 61% of psoriasis patients are obese or overweight with at least one weight-related comorbidity
- Associated with higher burden of symptoms, lower chance of achieving treatment targets, and biologic response
- Diet-induced weight loss improves response to tx in PsA

- Patients with obesity have **60%** higher risk of failing TNFi therapy
- 1 unit of BMI >> 6.5% higher risk of failure

Weight Loss Improves Therapy Outcomes



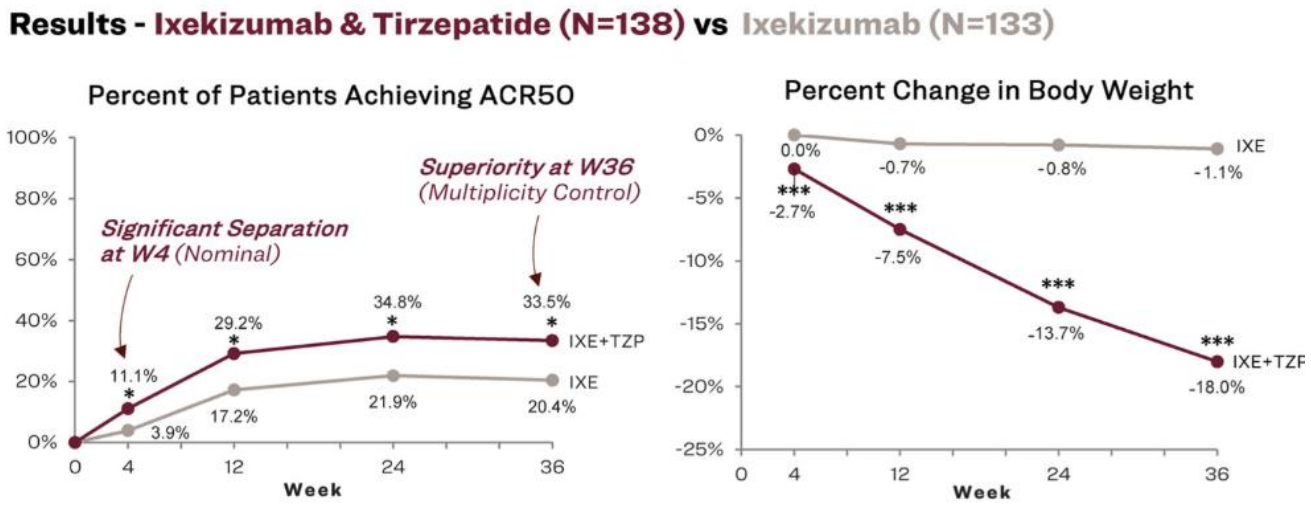
Di Minno MN et al. Ann Rheum Dis 2014

Together-PsA Trial

- Phase 3b, n= 271 average BMI 39

Interim analysis showed superiority of the combination use of ixekizumab (Taltz) and tirzepatide over IXE alone

- Primary endpoint (ACR50 and ≥10% weight loss) favoring combination therapy (31.7%) over IXE (0.8%) at 36 weeks.
- Similar results seen in Together-PsO trial



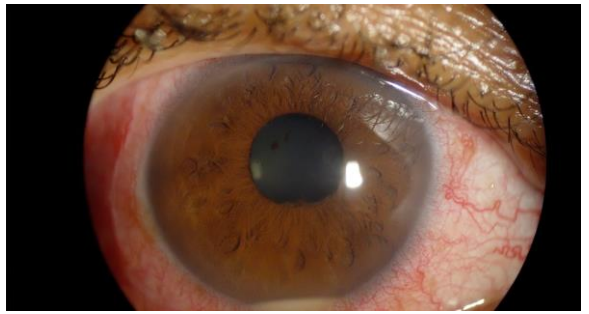
Merola, JF et al Arthritis Rheumatol. 2026 Mar 28. doi: 10.1002/art.70134.

Case 3

58 yo M with long history of psoriasis and psoriatic arthritis incompletely controlled on methotrexate overdue for physical. On exam has multiple swollen and tender joints. He recently had LFTs and CRP checked (16 mg/L) by rheumatology. What additional lab would you prioritize at his primary care appointment?

A. Vitamin D level
B. Lipid panel
C. Hepatitis C antibody
D. TSH

Answer B:
Patients with PsA have high risk of CVD



Extra-Articular Features

Acute Anterior Uveitis (25-40%)
- Usually painful, usually unilateral (may be alternating), with photophobia and blurry vision
- May not correlate with MSK disease
- Can lead to glaucoma via synechiae

Cardiovascular disease
- Sclerosing inflammatory process affecting aortic root and valves (6-10%)
- Conduction issues (3-33%)
- **CVD (OR: approx 1.3)**
- Mortality ratios AS 1.6-1.9 and PsA 0.8-1.6
- PsA High rate of co-morbidities (CVD, DM, obesity)

Renal disease
- Rare, includes IgA nephropathy, renal amyloid

Pulmonary
- Restrictive, due to chest wall involvement
- Apical fibrosis (AS)

Case 4

36 yo M with obesity, psoriasis and severe psoriatic arthritis on Ixekizumab, methotrexate and Celebrex. He also recently started taking ginger root extract which he read online could help with inflammation. Arthritis is currently controlled on current regimen but is presenting to you with several weeks of cramping, diarrhea, feeling feverish. What medication is most likely responsible for the symptoms?

A. Celebrex
B. Ixekizumab
C. Methotrexate
D. Ginger root extract

Answer

B. Ixekizumab

IL-17 inhibitors may exacerbate and trigger IBD

Deng Z, Wang S, Wu C, Wang C. IL-17 inhibitor-associated inflammatory bowel disease: A study based on literature and database analysis. Front Pharmacol. 2023

DMARD side effects

Infection is a side effect of nearly all DMARDs, biologics>conventional

- Exceptions: sulfasalazine, apremilast
- Lower risk with IL-23 inhibition

Biologics/MTX increase risk of non-melanoma skin CA

Conventional DMARDs

- MTX requires frequent (q 3 mos) lab monitoring due to risk of cytopenias and hepatotoxicity

Secukinumab, Ixekizumab (anti-IL17)

- May exacerbate underlying IBD

JAK-inhibitors

- Herpes Zoster risk increased
- cytopenias, hepatotoxcity, hyperlipidemia, bowel/diverticular perforation
- **Potential increased risk of CV events, CA, blood clots** with JAK-I—avoid in >65 yo or those with history of or high risk for CV events, thrombosis, malignancy

Ytterberg, S. R. et al.. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis, *N. Engl. J. Med. 386, 316–326 (2022).*

Take Home Points-Spondyloarthritis (SpA)

Spondylarthritides are a heterogeneous group of diseases that may affect axial, peripheral, and extra-articular structures
- Enthesitis, dactylitis are unique features

Recognition can be challenging in axial SpA, especially in patients without HLA-B27, abnormal ESR/CRP, or x-ray changes
- Imaging with X-rays are not sensitive in early disease
- Historical features are still important in diagnosis
- May need advanced imaging, i.e. MRI especially for early disease, axial disease, enthesitis

Understanding of genetics and pathogenesis has led to advances in treatment
- IL/17-IL23 important pathway and target for treatment in SpA in contrast to RA
- Conventional DMARDs have no benefit for axial disease, but biologics may be disease modifying
- Treatment decisions are influenced by presence of extraarticular manifestations such as psoriasis, uveitis and IBD
- DMARDs have unique side effects (risk of IBD with IL-17 inhibitors, CV risks and thrombosis with JAK inhibitors)

Be aware of extra-articular manifestations and complications
- Ocular, GI, and cutaneous involvement
- Increased risk of CVD in ankylosing spondylitis and psoriatic arthritis
- Musculoskeletal complications such as vertebral fracture with longstanding AS

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