

Early Identification and Diagnosis of Axial Spondyloarthritis



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Early Identification
and Diagnosis of
Axial Spondyloarthritis

Spondyloarthritis Research & Treatment Network

The learning objectives for individuals participating in this program are:

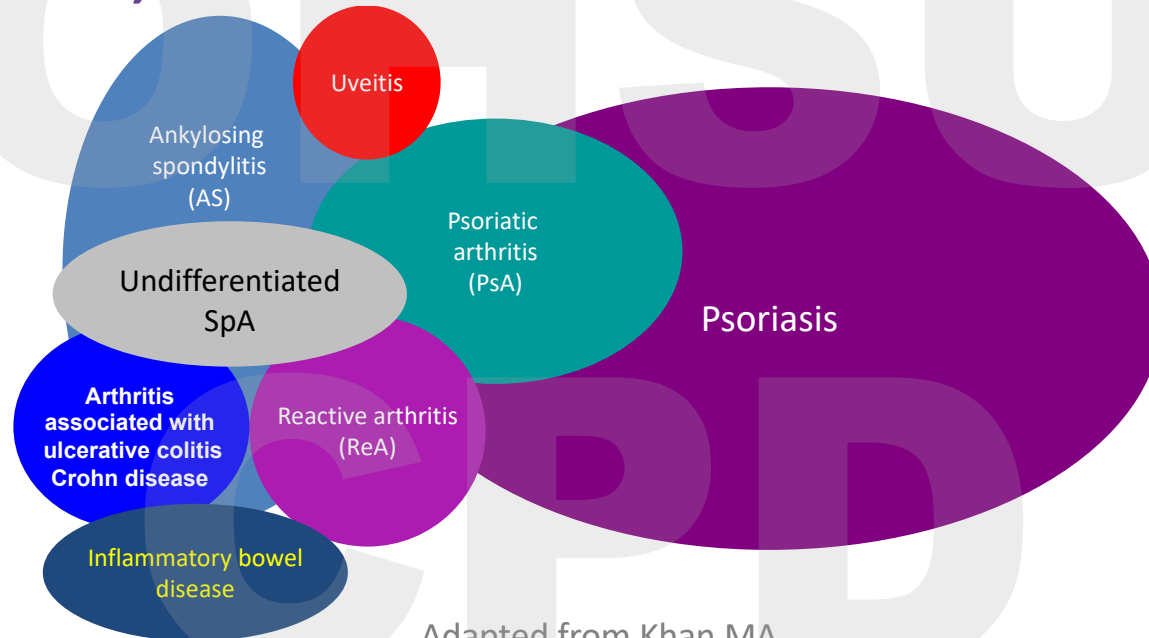
1. Develop an awareness of axSpA as treatable cause of back pain
2. Recognize an inflammatory back pain pattern as a typical presentation of axSpA
3. Identify other common clinical features of axSpA that occur outside the spine
4. Understand appropriate testing for a patient with chronic back pain suspected of axSpA
5. Discuss basic principles of diagnosis and treatment of axSpA as applied by rheumatologists.

AS: Clinical and Radiographic Characteristics

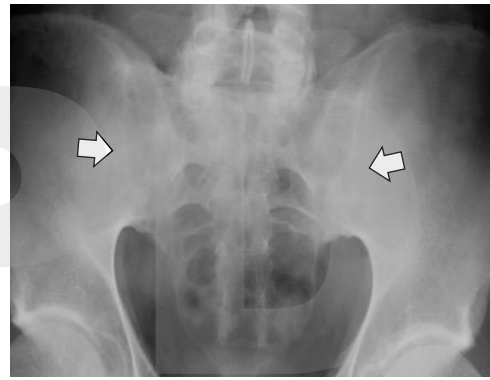
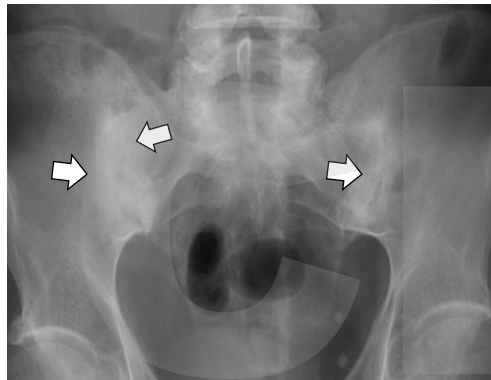
- Chronic inflammatory disease
- Sites affected
 - Axial skeleton
 - Peripheral joints
 - Extra-articular organs
- Clinical signs/symptoms
 - Chronic inflammatory back pain
 - Impaired spinal mobility
 - Diminished chest expansion
 - Enthesitis
 - Uveitis, IBD, psoriasis
- Radiographic hallmark: sacroiliitis



Historical Categorization of Spondyloarthritis (SpA) and Closely Associated Conditions - Psoriasis, Inflammatory Bowel Disease, and Uveitis



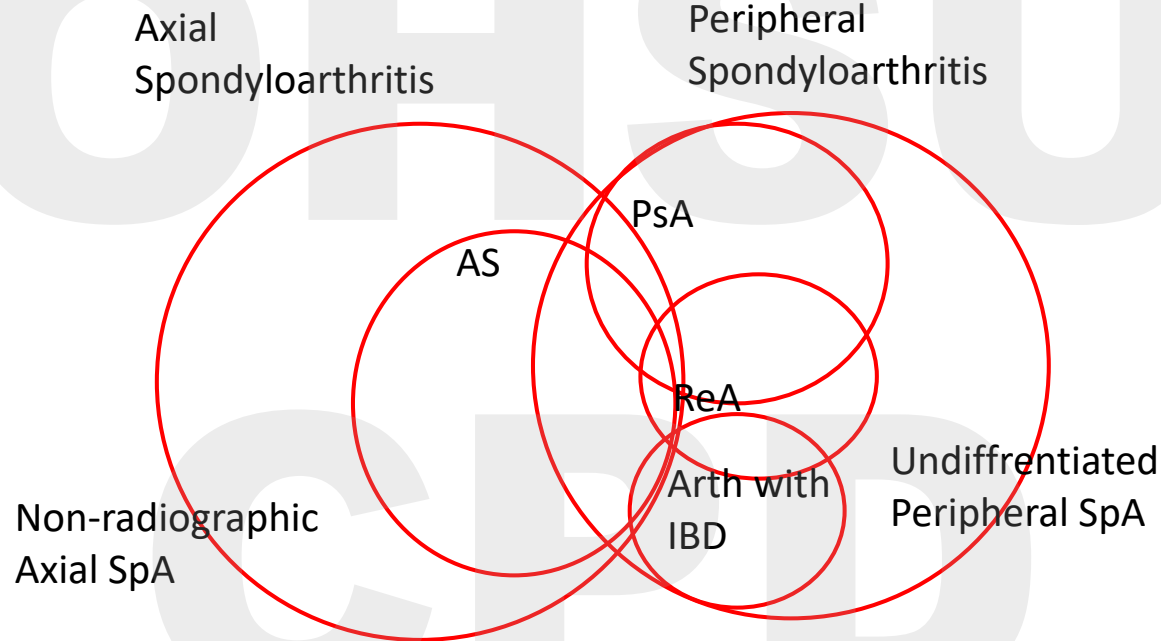
The Four Grades of Sacroiliitis



Imaging: MRI sacrum/pelvis

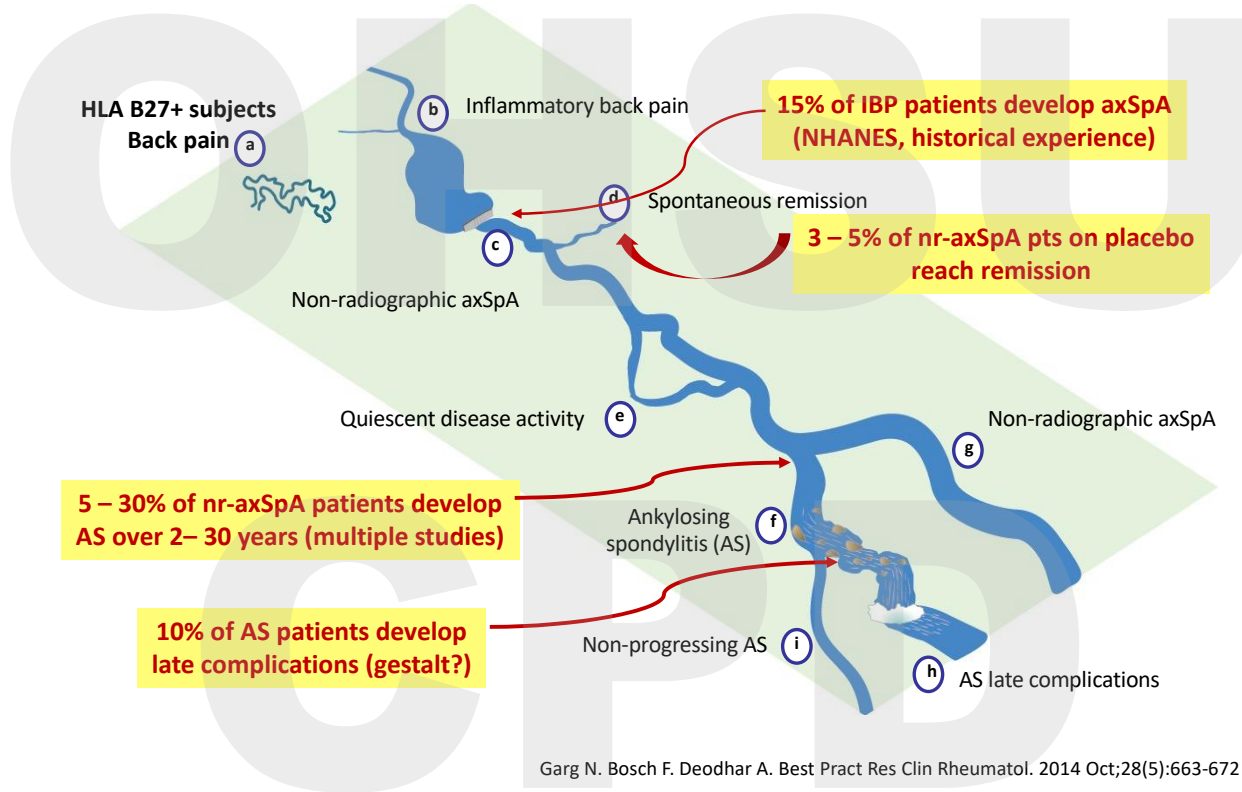


Spectrum of Spondyloarthritis: Current Concept

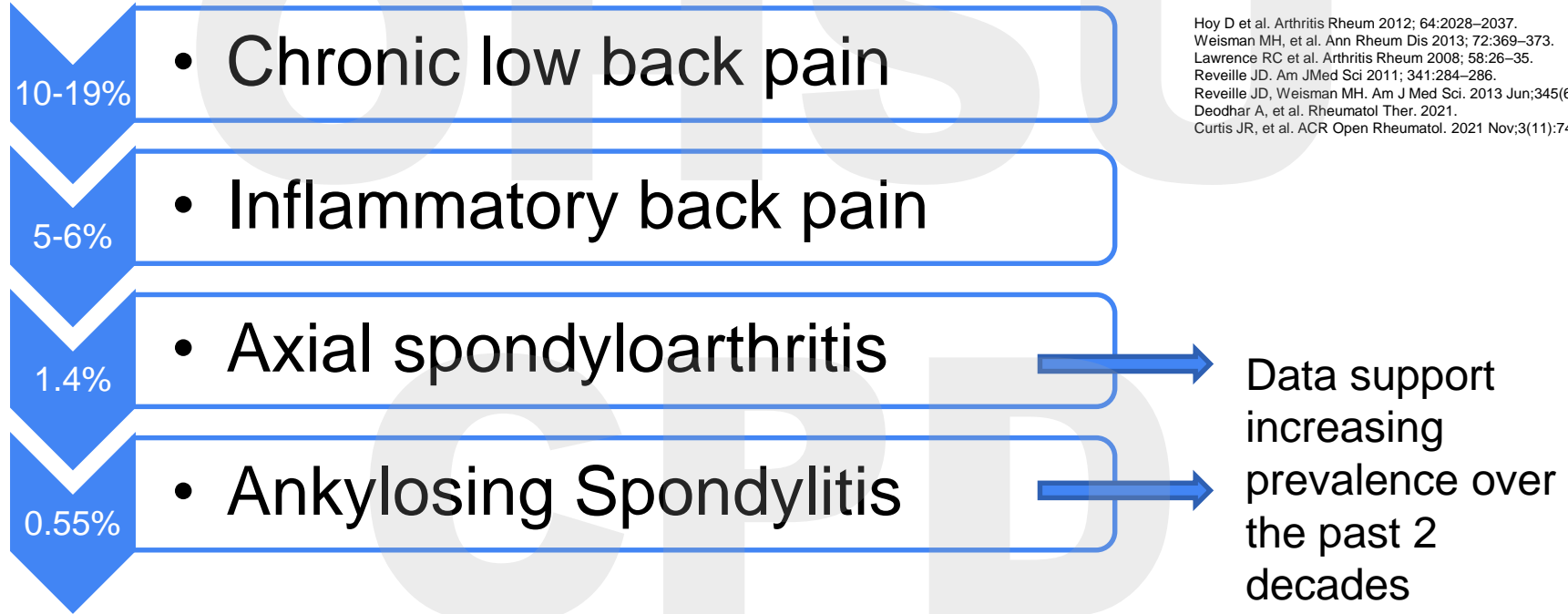


Slide Courtesy of Atul Deodhar MD

Axial Spondyloarthritis: Patient's Journey



Axial Spondyloarthritis: Epidemiology



Hoy D et al. Arthritis Rheum 2012; 64:2028–2037.
Weisman MH, et al. Ann Rheum Dis 2013; 72:369–373.
Lawrence RC et al. Arthritis Rheum 2008; 58:26–35.
Reveille JD. Am JMed Sci 2011; 341:284–286.
Reveille JD, Weisman MH. Am J Med Sci. 2013 Jun;345(6):431-6.
Deodhar A, et al. Rheumatol Ther. 2021.
Curtis JR, et al. ACR Open Rheumatol. 2021 Nov;3(11):743-752.

Inflammatory Back Pain

Calin et al

4/5 needed

- Age at onset <40 years
- Duration > 3 months
- Insidious onset
- Morning stiffness
- Improvement with exercise

Calin A, et al. JAMA
1977;237:261;

Rudwaleit et al

2/4 needed

- Alternating buttock pain
- Awakening at second half of the night because of pain
- AM stiffness > 30 mins
- Improvement with exercise, not with rest

Rudwaleit M, et al. Arthritis
Rheum 2006;54:569-78;

ASAS

4/5 needed

- Age at onset <40 years
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night

Sieper J, et al. Ann Rheum Dis.
2009, 68:784-788

Delay in diagnosis: Factors

- Lack of familiarity with features of IBP and non radiographic disease:
 - Study: 40% of general practitioners were not aware there was a difference between mechanical and inflammatory back pain patterns.
 - Study: only 5% of PCPs were able to identify all features of IBP
 - Study: 75% of chiropractors and osteopaths were not aware of nr-axSpA
- Females have longer delay in diagnosis compared to males (8.8 vs 6.5 years)
- African Americans and Hispanic Americans are less likely to be evaluated with advanced imaging, less likely to be referred to physical therapy

Kumthekar A, Bittar M, Dubreuil M. *Curr Opin Rheumatol*. 2021 Jul 1;33(4):313-318.
van Onna M, et al. *J Rheumatol*. 2014 May;41(5):897-901.
Yong CY, et al. *Rheumatol Adv Pract*. 2019 Sep 30;3(2)
Mathieson HR, et al. *Clin Rheumatol*. 2016 Oct;35(10):2627-8.
Milani CJ, et al. *Spine (Phila Pa 1976)*. 2018 Jul 15;43(14):1007-1017.
Ly DP. *Pain Med*. 2019 Feb 1;20(2):223-232.
Slobodin G, et al. *Clin Rheumatol*. 2011 Aug;30(8):1075-80.

Delay in diagnosis: Factors

- Absence of extra-articular manifestations
- Absence of peripheral involvement
- Younger age of onset
- Limitations of physical examination
- A prior diagnosis of mechanical back pain

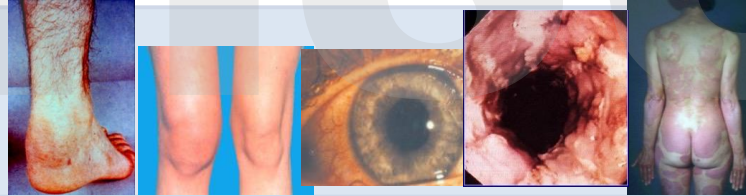
Zhao SS, et al. *Rheumatology (Oxford)*. 2021 Apr 6;60(4):1620-1628.
Danve A, Deodhar A. *Clin Rheumatol*. 2019 Mar;38(3):625-634.
Deodhar A, et al. *Arthritis Rheumatol*. 2016 Jul;68(7):1669-76.
Redeker I, et al. *Rheumatology (Oxford)*. 2019 Sep 1;58(9):1634-1638.
Poddubnyy D, Sieper J. *Curr Opin Rheumatol*. 2021 Jul 1;33(4):307-312.
Garrido-Cumbrera M, et al. *Rheumatology (Oxford)*. 2021 Apr 28;369.
Dube CE, et al. *Rheumatol Ther*. 2021 Jun;8(2):1015-1030.

AxSpA Pattern Recognition used for Diagnosis

Patient History

- Inflammatory back pain
- Good response to NSAIDs
- Positive family history for SpA

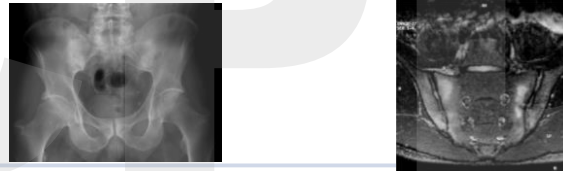
Physical Examination



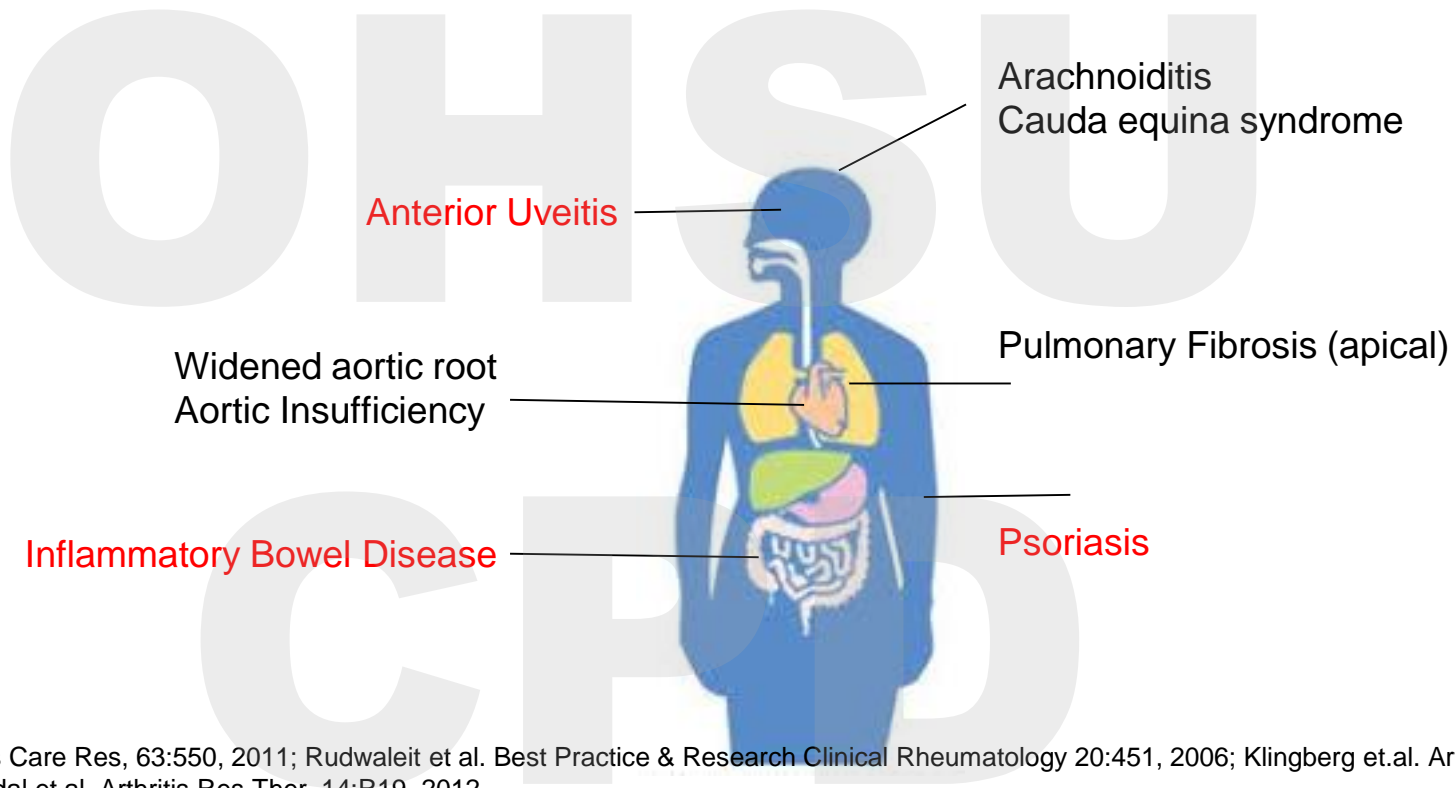
Laboratory

- HLA-B27
- CRP/ESR

Imaging



Extra Musculoskeletal Manifestations



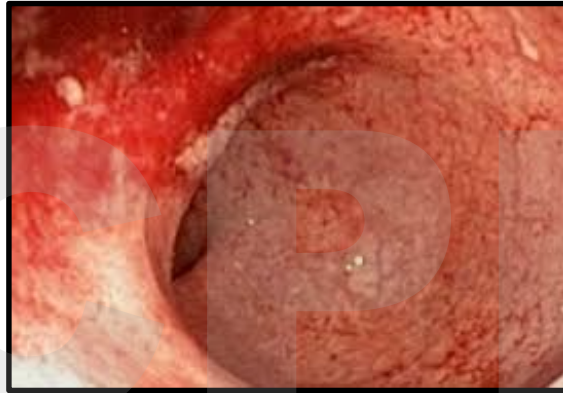
Bremander et.al., Arthritis Care Res, 63:550, 2011; Rudwaleit et al. Best Practice & Research Clinical Rheumatology 20:451, 2006; Klingberg et.al. Arthritis Res Ther, 14:R108, 2012; Berdal et.al. Arthritis Res Ther, 14:R19, 2012.

Extra Musculoskeletal Manifestations



Acute Anterior Uveitis

Inflammatory Bowel Disease



Psoriasis

ASAS Classification Criteria for Axial SpA

In patients with chronic (>3 months) back pain, age at onset <45 years

Sacroiliitis plus
≥ 1 clinical parameter***

or

**HLA-B27 plus
≥ 2 other clinical
parameters***

**Sacroiliitis (x-rays or MRI):

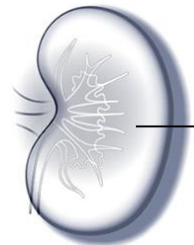
- Definite **radiographic** sacroiliitis (grade 2 bilat or grade 3-4 unilat; according to modified NY criteria 1984)
- or
- Active (acute) inflammation of sacroiliac joints on **MRI**, highly suggestive of sacroiliitis associated with SpA

*Clinical parameters:

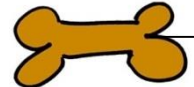
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease /Ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- Elevated CRP
- HLA-B*27

Rudwaleit M, et al. *Ann Rheum Dis.* 2009; 68(6):777-83.

Comorbidities



IgA nephropathy
Amyloidosis
Nephrolithiasis

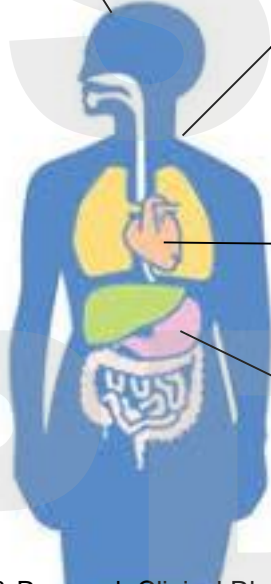


Osteoporosis
Vertebral fractures &
pseudo-fractures

NAFLD, obesity, metabolic syndrome (PsA > AxSpA)

Depression

Restrictive lung disease
Sleep apnea

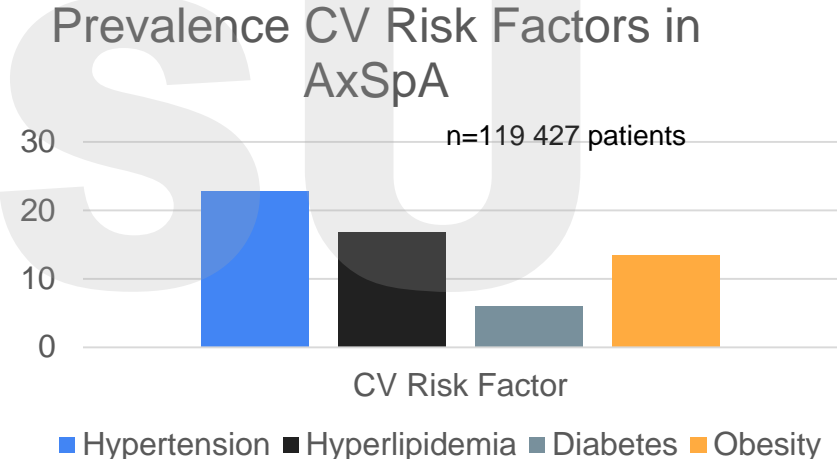
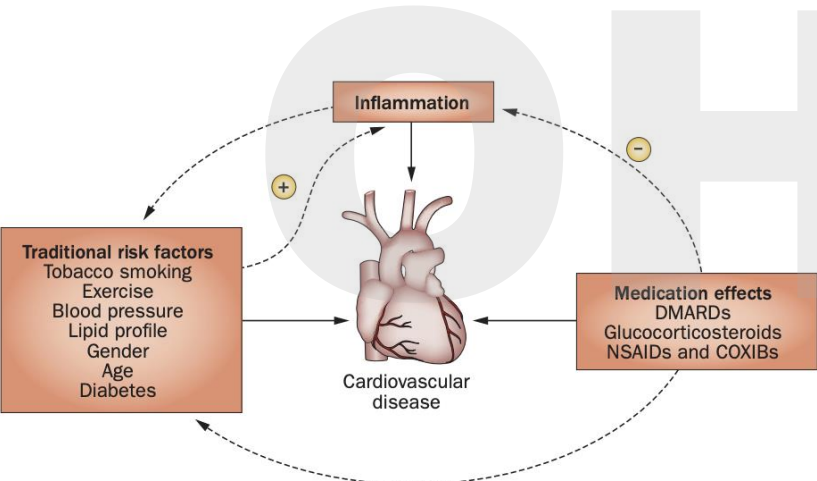


Cardiac risk factors (HTN)
Cardiac events
First Degree AVB

Peptic Ulcer Disease

Bremander et.al., Arthritis Care Res, 63:550, 2011; Rudwaleit et al. Best Practice & Research Clinical Rheumatology 20:451, 2006; Klingberg et.al. Arthritis Res Ther, 14:R108, 2012; Berdal et.al. Arthritis Res Ther, 14:R19, 2012.

Cardiovascular Risk Factors in Axial Spondyloarthritis



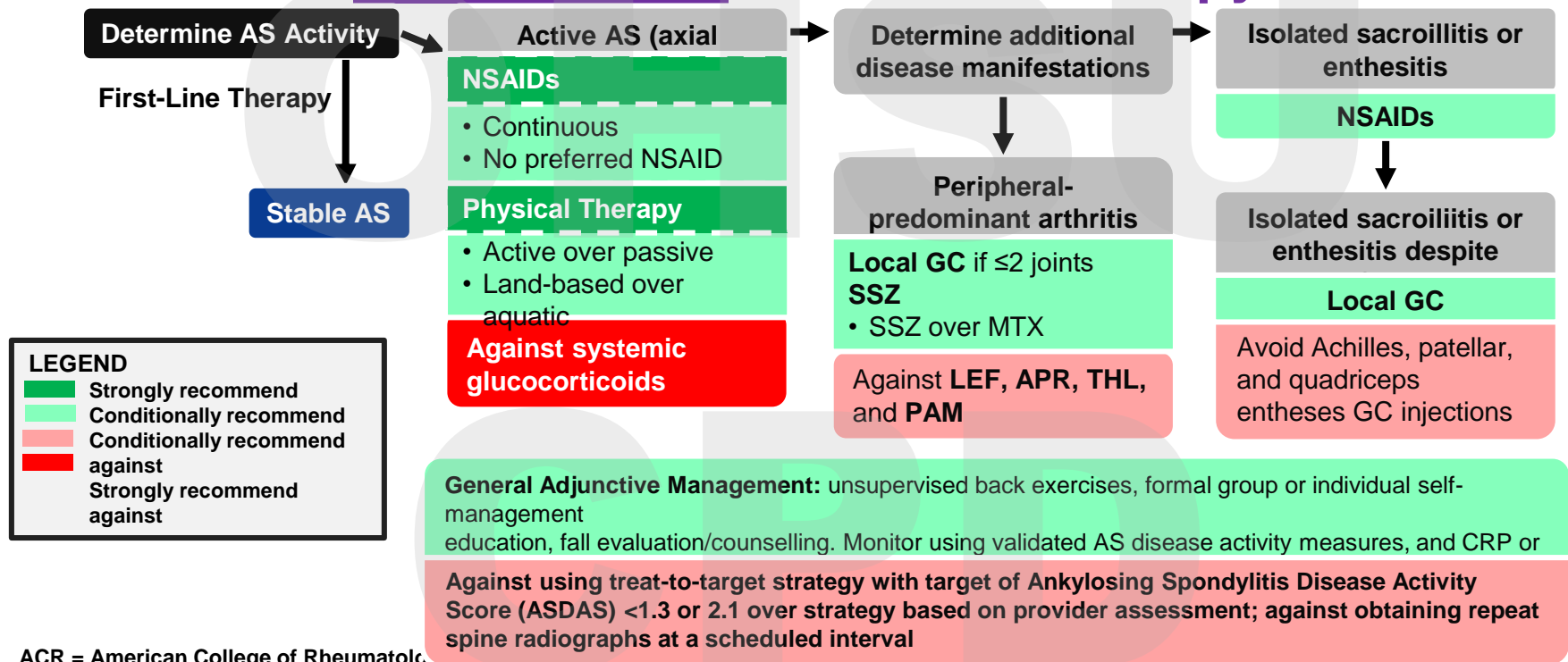
Risk Factor	No. Studies	Pooled OR	95%CI
Hypertension	9	1.58	1.29, 2.92
Hyperlipidemia	5	1.18	1.01, 1.39
Diabetes	8	1.14	1.001, 1.30



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Treatment

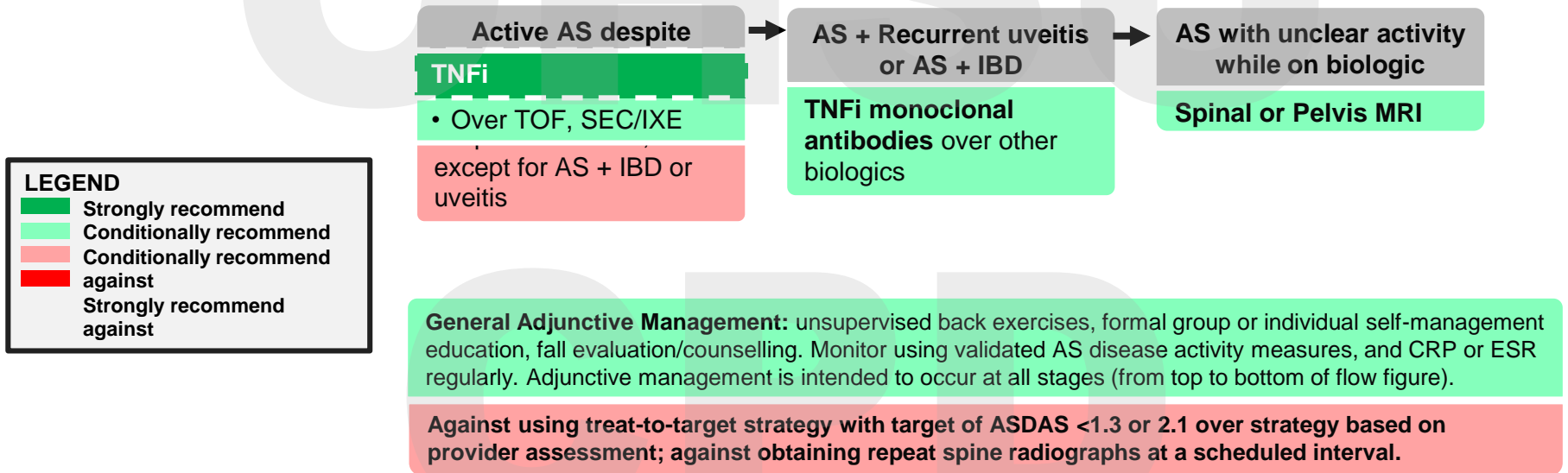
2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: First-Line Therapy



ACR = American College of Rheumatology; SAA = Spondylitis Association of America; SPARTAN = Spondyloarthritis Research and Treatment Network; SSZ = sulfasalazine; THL = thalidomide.

Ward MM, et al. *Arthritis Care Res (Hoboken)*. 2019;71:1285-1299.

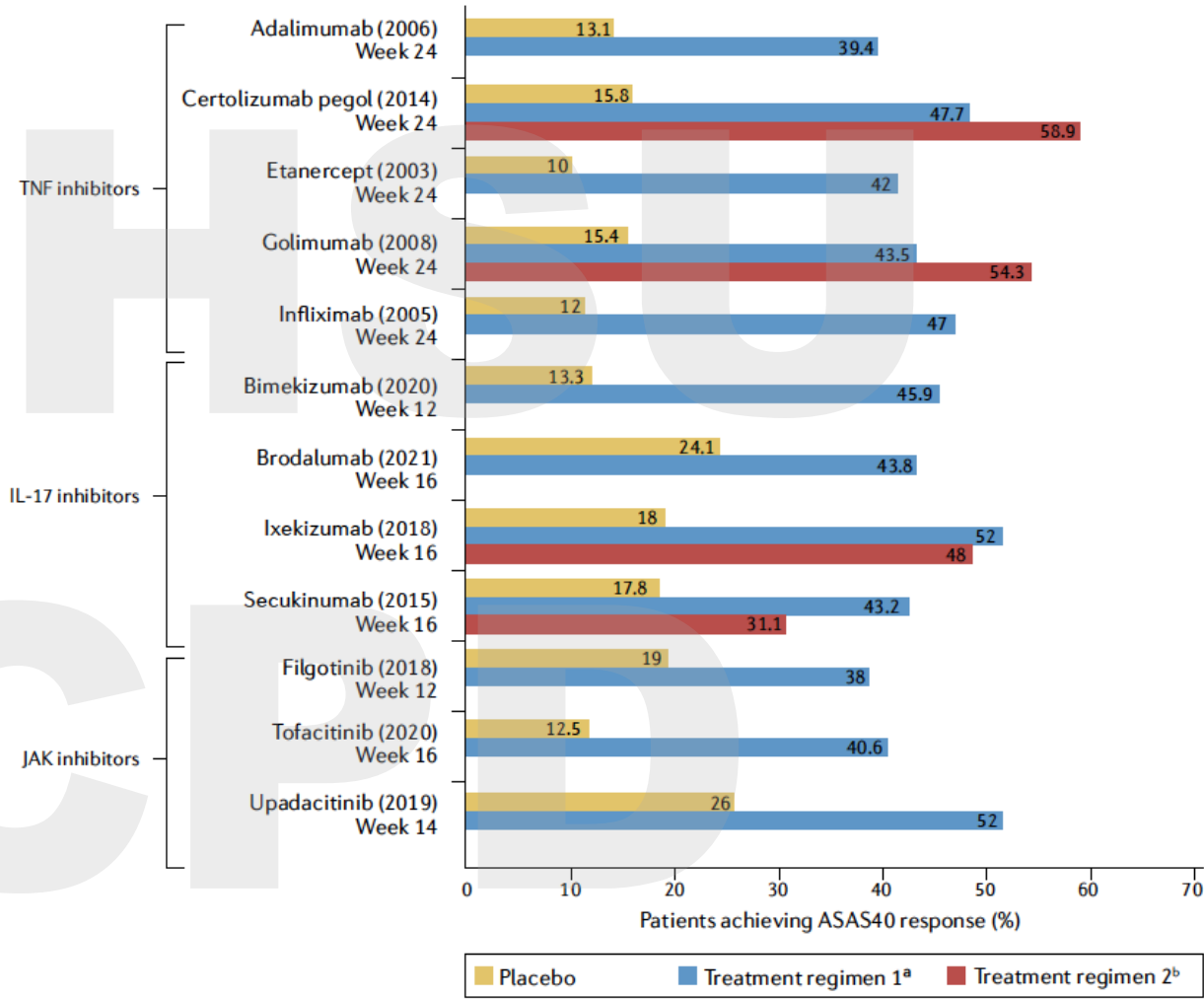
2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: Second-Line Therapy



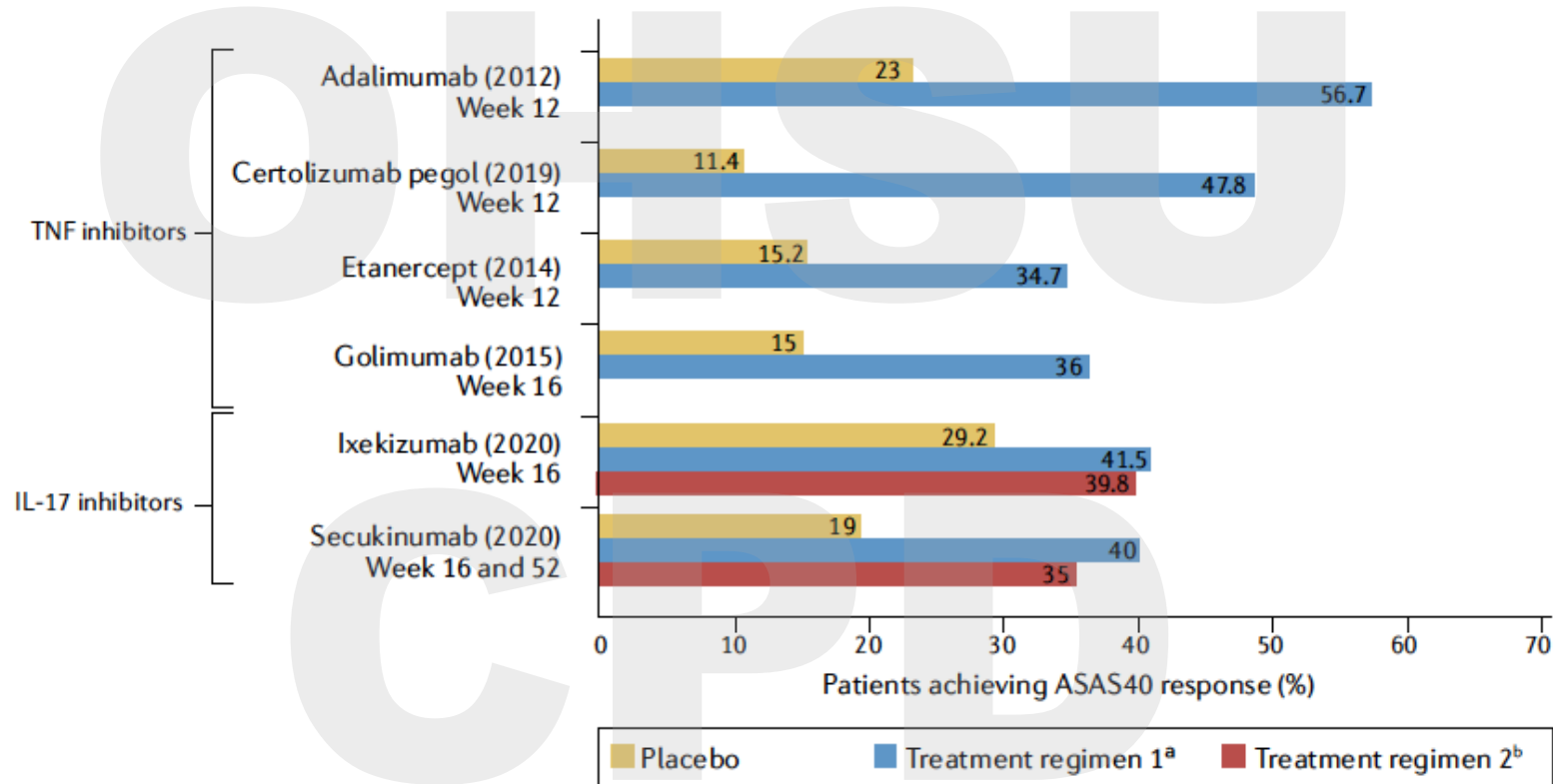
TNFi = tumor factor necrosis inhibitor; TOF = tofacitinib; SEC = secukinumab; IXE = ixekizumab.

Ward MM, et al. *Arthritis Care Res (Hoboken)*. 2019;71:1285-1299.

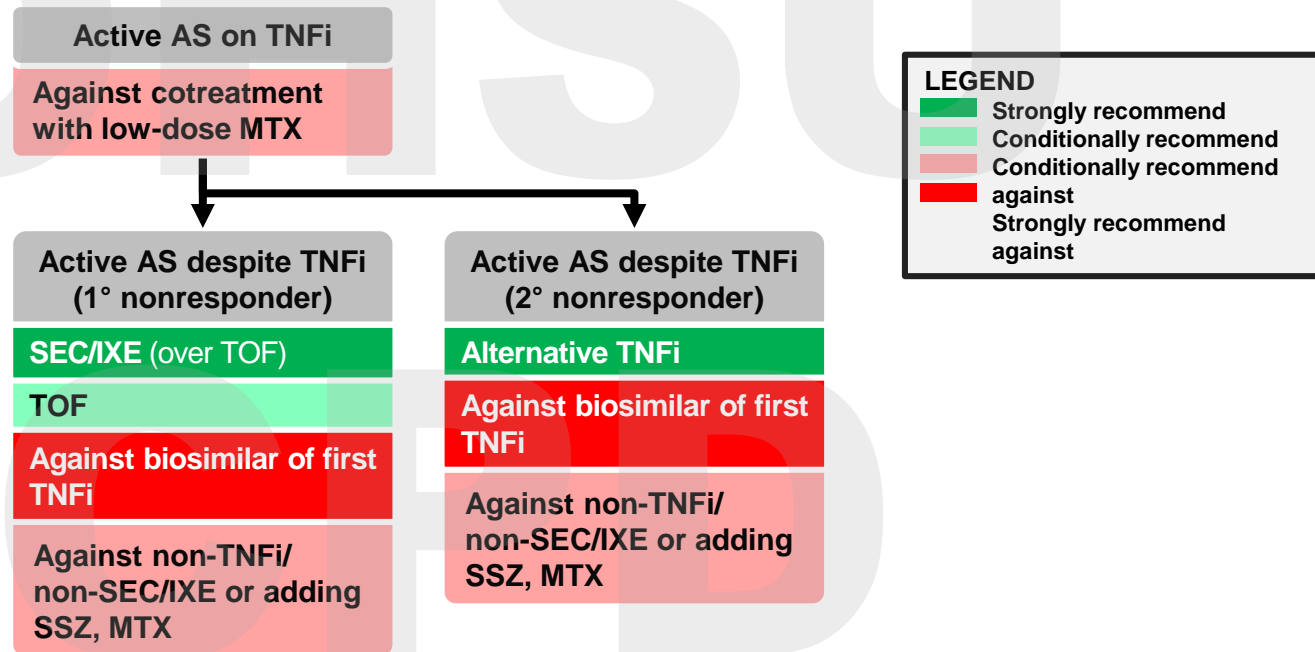
ASAS40 Responses in bDMARD Trials in AS



ASAS40 Responses in bDMARD Trials in nr-axSpA

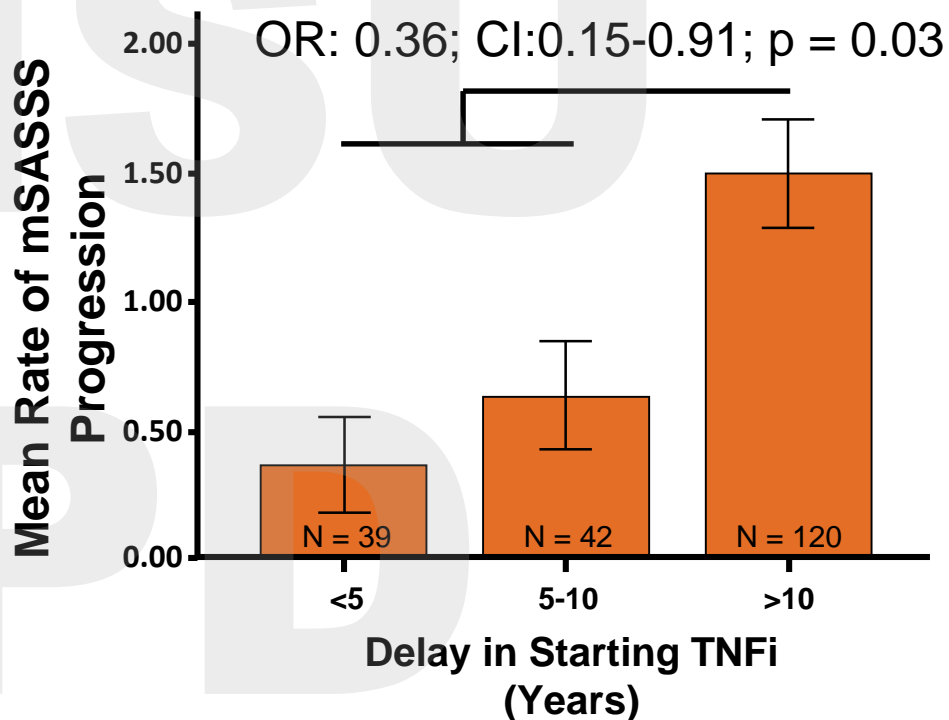


2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: Third-Line Therapy



Early Use of TNFi May Reduce Rate of Radiographic Progression

- Prospective Study Of Ankylosing Spondylitis (PSOAS) cohort
- N = 334 with 2 x-rays at least 1.5 years apart (mean = 2.8 years); mean disease duration 16.5 years; 75% male; 83% HLA-B27+
- Baseline ESR, mSASSS, and smoking associated with radiographic progression
- TNFi treatment associated with 50% reduction in the odds of progression (OR 0.52, 95% CI 0.30-0.88, $P = 0.02$)



EIDA
SPARTAN

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Cases

Case

A 33-year-old Hispanic female presents to her primary care provider for the evaluation of low back pain (LBP). Patient reports LBP for the past 1 year. Patient denied any triggers or traumas.

What questions should we ask this patient?

Case

It gets worse with rest and improves with activity. Patient reports 1 hour of morning stiffness. She sometimes wakes up in the middle of the night because of LBP. Patient tried Ibuprofen 400mg over-the-counter, which provided good relief but did not resolve her symptoms completely. No other joint pains reported. Patient denied any fevers. No unintentional weight loss.

Review of systems: no skin rashes, no gastrointestinal symptoms. Patient reported a history of two episodes of “painful red eye” that required Ophthalmology evaluation. It resolved with ocular drops. No respiratory or neurologic symptoms reported.

Case

Past medical/surgical history: previously healthy. No previous surgical procedures. Non-smoker.

Medications: Ibuprofen 400mg BID PRN.

Family history: mother has psoriasis. Father has diabetes and hypertension.

Physical exam: vital signs are within normal limits. Eyes: PERRLA, no erythema. Neck: no lymphadenopathy. Heart: RRR, no murmurs. Lungs: CTAB. MSK: no synovitis or joint effusions throughout. Tender to palpation over the sacroiliac (SI) joints bilaterally. Full range of motion of the hips, low back and neck.

Case

Labs: CBC, CMP within normal limits.
ESR 38 mm/hr (0-20 mm/hr), CRP 2.4 mg/dL (0.0-0.5 mg/dL)

Imaging: Sacroiliac joint xrays were performed and read as: “Sacroiliac joints are symmetric and well-maintained. No displaced fracture or dislocation is seen. No focal erosions. Soft tissues are unremarkable.”



What is the next step in this patient's workup/management?

- A. Gabapentin 300mg TID
- B. Cyclobenzaprine 10mg QHS PRN
- C. Sulfasalazine 500mg BID
- D. MRI Lumbar spine without contrast
- E. Rheumatology referral for further evaluation
- F. Pain clinic referral for a nerve block

Answer: E, Rheumatology referral for further evaluation

Patient is having features of inflammatory back pain (IBP), chronic duration with age of onset <45 years. Patient also has good response to NSAIDs, elevated CRP/ESR, possible history of uveitis, family history of psoriasis. No clinical evidence to suggest “red flags” such as malignancy, infection or fracture. While SI joint xrays were read as “unremarkable”, this does not exclude a diagnosis of non-radiographic axial spondyloarthritis. This patient needs further evaluation by a Rheumatologist.

Per ASAS endorsed recommendations for the early referral of patients with a suspicion of axial spondyloarthritis, “Patients with chronic back pain (duration ≥ 3 months) and back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present: Inflammatory back pain; human leucocyte antigen-B27; Sacroiliitis on imaging if available (X-rays or magnetic resonance imaging); Peripheral manifestations (arthritis, enthesitis, dactylitis); Extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis); Positive family history for spondyloarthritis; Good response to non-steroidal anti-inflammatory drugs; Elevated acute phase reactant.” (1)

A, B, and F would not be correct as patient is not currently having radicular symptoms and needs further evaluation to rule out inflammatory spondylitis. C is not correct. Even if patient has a confirmed diagnosis of axSpA, SSZ is not shown to benefit axial disease and this patient does not currently have peripheral manifestations. D is not correct. After Rheumatology referral, it is appropriate to check MRI pelvis without contrast as the physical exam findings are localized to the SI joints.

1. Poddubnyy D, van Tubergen A, Landewé R, Sieper J, van der Heijde D; Assessment of SpondyloArthritis international Society (ASAS). Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis*. 2015 Aug;74(8):1483-7. doi: 10.1136/annrheumdis-2014-207151. Epub 2015 May 19. PMID: 25990288.

Case History

- 44-year old male, lawyer, very healthy & active lifestyle – completed Ironman Canada in July 2017
- Post Ironman, C/O pain in the left buttock, thought to be related to hamstring tendon injury
- Rested for 8 weeks and then tried to run again, but pain returned
- Tried prolonged physical therapy, acupuncture, massage, with some relief, but couldn't continue lifestyle of running, swimming, strength training
- April 2018: Seen at family practice sports medicine clinic, diagnosis confirmed: left Hamstring strain & treated with US guided triamcinolone injection

Case History

- June 2018: MRI Pelvis: “Minimal tendinopathy of the origin of the left conjoint Hamstring tendon, no tear, left SI joint normal”
- July 2018: FU at Family Practice Sports Medicine: since he had limited relief, treated with US guided ‘prolotherapy’ (5 CC autologous blood injection)
- Oct 2018: Seen at IM Sports Medicine clinic. Further history revealed multiple joints & tendons aches and complaints, “I have autoimmune disease in my family”
- O/E: Tender on bilateral SI joints, left ischial tuberosity and piriformis, reduced Hamstring flexibility on left compared to right
- HLA B27+, Referral to rheumatology

Case History

- Nov 2018: Seen in OHSU rheumatology clinic
- Rheum Fellow's note:
 - “Developed low back & left buttock pain in mid 20's, pain would awaken him at night, rest would worsen the pain & activity would improve it. Ibuprofen & naproxen relived the pain completely. Morning stiffness 30 minutes, also suffered from chronic bilateral Achilles tendon pains without swelling
 - No uveitis, psoriasis, IBD
 - Family H/O Celiac disease & gout in dad, ALS in maternal grandfather & RA+OA in brother
 - O/E: Tender on bilateral Achilles tendon insertions, tender on bilateral SI joints & on left ischial tuberosity & piriformis area

Case History

- We diagnosed him with axial spondyloarthritis based on
 - Inflammatory back pain starting at age of 20
 - Multiple episodes of verifiable enthesitis (Achilles tendon, hamstrings tendon – MRI proven)
 - History of very good response to NSAIDs
 - HLA B27+
- X-ray SI Joints: No sacroiliitis, hence he did not have AS, but had “non-radiographic axial SpA”
- He entered the clinical trial on adalimumab in nr-axSpA and underwent a repeat pelvic MRI scan that showed right sided sacroiliitis
- He was symptom-free within a month in the trial

Early Identification & Diagnosis of Axial Spondyloarthritis

Summary

- Axial Spondyloarthritis is more common than you think (1% prevalence)
- Suspect axSpA in patient with chronic back pain starting before age of 45, and presenting with
 - inflammatory back pain
 - History of peripheral inflammatory arthritis
 - Psoriasis, IBD, Uveitis
 - HLA-B27
- Early referral to rheumatology is the key
- Apart from PT & NSAIDs, new treatments include TNF, IL-17, & JAK inhibitors