Axial Spondyloarthritis: Disease State

Module 1 | Defining and Diagnosing axSpA

Module 2 | Pathogenesis, Clinical Presentation, and Disease Burden

Module 3 | axSpA Disease Assessments

Module 4 | axSpA Disease Management

AXIAL SPONDYLOARTHRITIS: PATHOGENESIS, CLINICAL PRESENTATION, AND DISEASE BURDEN

Learning Objectives

- Describe the pathophysiology of AS/r-axSpA and nr-axSpA, and role of HLA-B27 in the pathogenesis of axSpA
- Describe the axSpA disease spectrum, natural history, and differentiate AS/r-axSpA and nr-axSpA
- Describe the clinical presentation of AS/r-axSpA vs. nr-axSpA, symptoms, manifestations, and similarities and differences
- Explain how axSpA carries a high disease burden
- Explain the relationship between the delay in diagnosing axSpA and high patient burden

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

Pathophysiology of AS/r-axSpA and nr-axSpA

The IL-23/IL-17 Pathway is Key in axSpA Pathogenesis

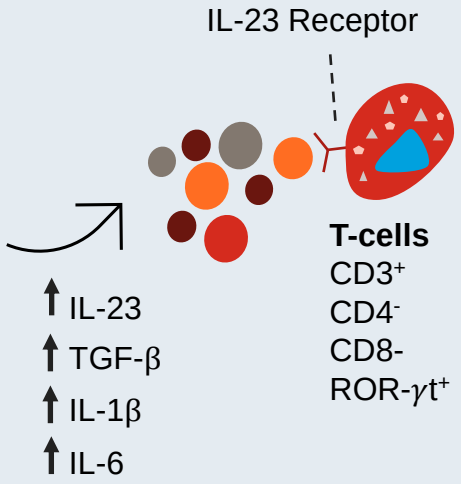
1

Biological factors trigger an immune response.[1-3]

- Biomechanical stress
- Genetic factors, including HLA-B27
- Gut microbiome
- Environmental triggers

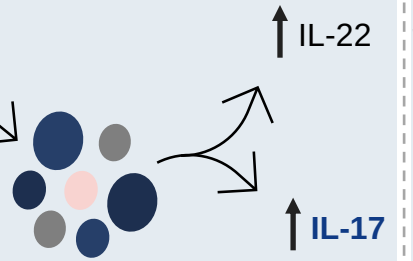
2

This stimulates production of pro-inflammatory cytokines, including IL-23, which bind to resident cells.[1-4]



3

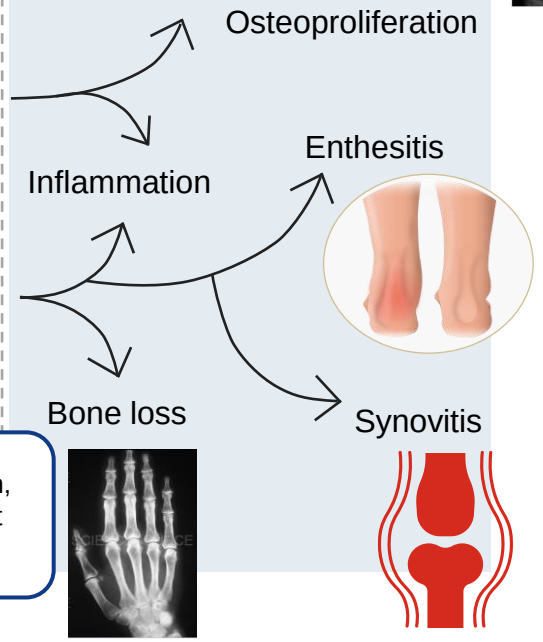
In turn, this triggers production of key inflammatory cytokines, including IL-17, at specific tissue sites.[1-4]



IL-17A has been shown to stimulate RANKL expression, thereby inhibiting osteoblast activity and promoting bone loss.[5]

4

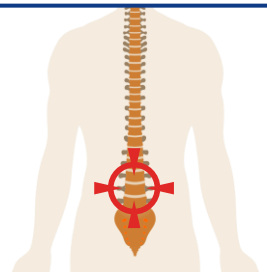
This increase in cytokines has been implicated in the physical manifestations seen in axSpA.[1-5]



IL-22 is thought to contribute to new bone formation,[2,3] simultaneously with tmTNF.[2]

IL-17 can be produced by other pathways independent of IL-23.[6]

Increased IL-17, combined with increased TNF, is thought to drive the inflammatory elements of axSpA.[2,3]

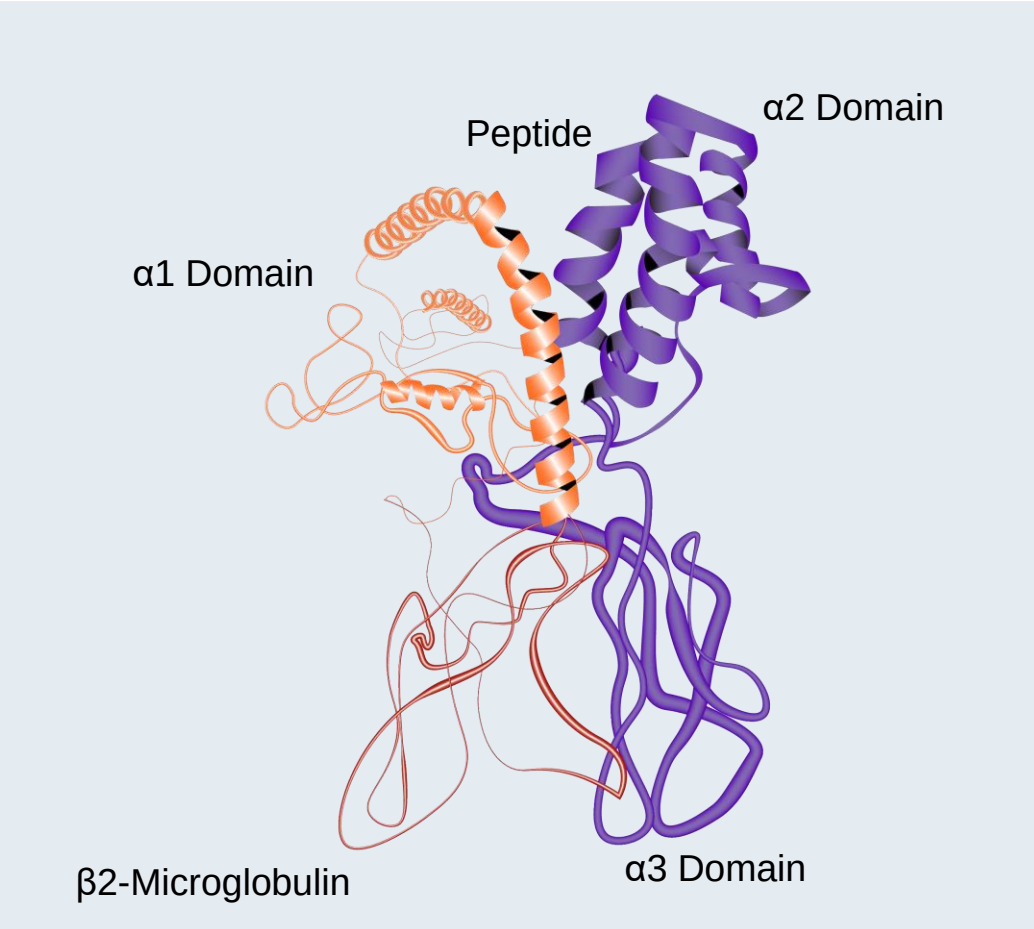


Osteoproliferation image: Image is licensed under CC BY 4.0. Permission has been obtained for reuse. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0204546 (Accessed May 2, 2023).
axSpA=Axial Spondyloarthritis; CD=Cluster of Differentiation; HLA-B27=Human Leukocyte Antigen-B27; IL=Interleukin; RANKL=Receptor Activator of Nuclear Factor-kB Ligand; ROR-γt=Retinoid-Related Orphan Receptor Gamma t; sTNF= Soluble Tumor Necrosis Factor; tmTNF=Transmembrane Tumor Necrosis Factor; TGF-β=Transforming Growth Factor-β.

1. Paine A, Ritchlin CT. *Curr Opin Rheumatol.* 2016;28(4):359-367. 2. Sieper J, et al. *Nat Rev Dis Primers.* 2015;1:15013. 3. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574. 4. Lories RJ, McInnes IB. *Nat Med.* 2012;18(7):1018-1019. 5. McGonagle DG, et al. *Ann Rheum Dis.* 2019;78(9):1167-1178. 6. Navarro-Compán V, et al. *Front Immunol.* 2023;14:1191782.

The Role of HLA-B27 in axSpA

3D Structure of HLA-B27[1]



Prevalence of HLA-B27

<10%

In the general population[2-4]

70%-90%

In White patients with axSpA[2,4,5]

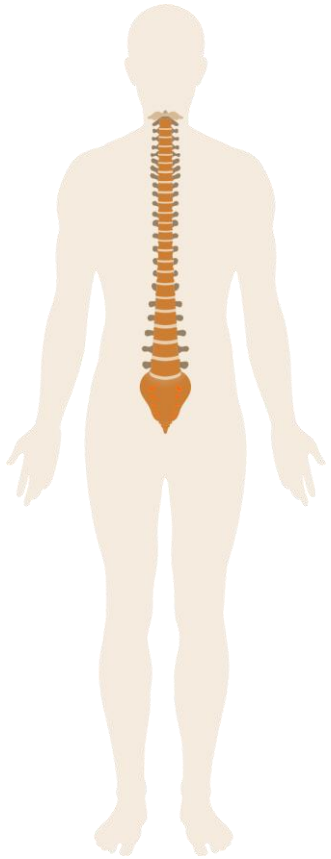
axSpA=Axial Spondyloarthritis; HLA=Human Leukocyte Antigen; RCSB=Research Collaboratory for Structural Bioinformatics.

1. López-Larrea C, et al. *Mol Med Today.* 1998;4(12):540-549. 2. Walsh JA, Magrey M. *J Clin Rheumatol.* 2021;27(8):e547-e560. 3. Reveille JD, et al. *Arthritis Rheumatol.* 2012;64(5):1407-1411. 4. Sieper J, et al. *Nat Rev Dis Primers.* 2015;1:15013. 5. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.

axSpA Disease Overview

axSpA Disease Spectrum

Axial spondyloarthritis (axSpA) refers to the inflammation of the axial skeleton and encompasses two subtypes of the same disease: **AS/r-axSpA and nr-axSpA.**[1,2]



axSpA

- A chronic inflammatory disease of the sacroiliac joint and the axial skeleton.
- May involve peripheral or other joints and entheses.
- May also involve extra-musculoskeletal manifestations including intestines, skin, eyes, lung, and heart.[3,4]

AS/r-axSpA versus nr-axSpA

AS/r-axSpA

Presence of radiographic changes of the sacroiliac joints consistent with sacroiliitis (as defined by the modified New York criteria).[1,5]

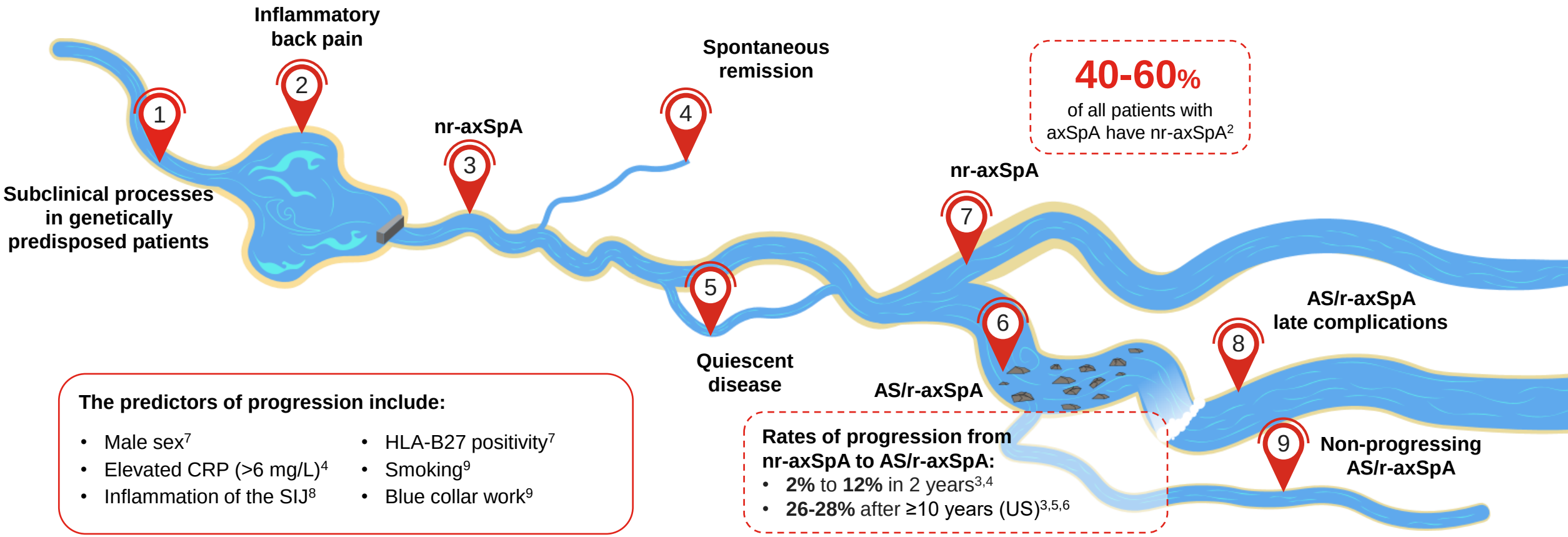
nr-axSpA

Absence of radiographic changes of the sacroiliac joints consistent with sacroiliitis (as defined by the modified New York criteria).[1,5]

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. Taurog JD, et al. *N Engl J Med.* 2016;374:2563-2574. 2. Proft F, Poddubnyy D. *Ther Adv Musculoskel Dis.* 2018;10(5-6):129-139. 3. van der Heijde D. Ankylosing Spondylitis. *In: Primer on the Rheumatic Diseases,* Klippel JH, Stone JH, Crofford LJ, White PH (eds). *Springer New York*. 2008. 4. Navarro-Compán V, et al. *Ann Rheum Dis.* 2021;80(12):1511-1521. 5. van der Linden S, et al. *Arthritis Rheum.*1984;27:361-368.

Natural History of axSpA[1]



The predictors of progression include:

- Male sex[7]
- Elevated CRP (>6 mg/L)[4]
- Inflammation of the SIJ[8]
- HLA-B27 positivity[7]
- Smoking[9]
- Blue collar work[9]

Rates of progression from nr-axSpA to AS/r-axSpA:

- **2%** to **12%** in 2 years[3,4]
- **26-28%** after ≥10 years (US)[3,5,6]

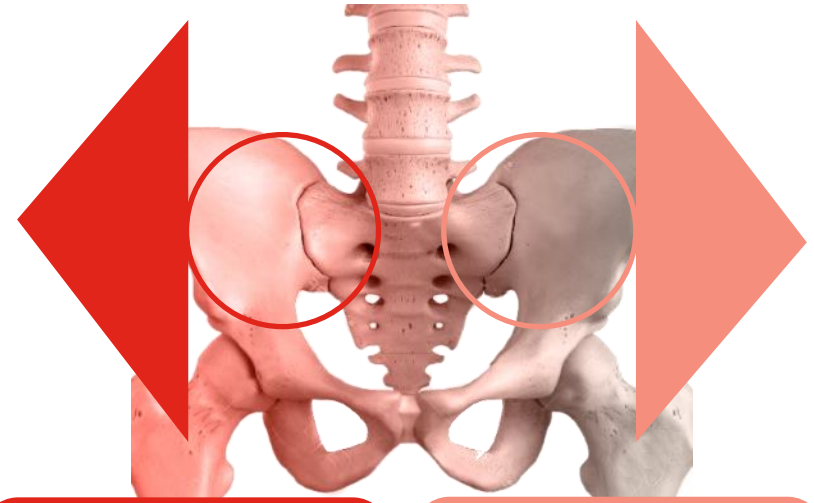
AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; CRP=C-Reactive Protein; HLA-B27=Human Leukocyte Antigen B27; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SIJ=Sacroiliac Joint; US=United States.

1. Garg N, et al. *Best Pract Res Clin Rheumatol.* 2014;28:663-672. 2. Deodhar A, et al. *Lancet.* 2020;395:53-64. 3. Ruderman E, et al. *Arthritis Rheum.* 2013;65:S1052-1053. 4. Poddubnyy D, et al. *Ann Rheum Dis.* 2011;70(8):1369-1374. 5. Ghosh N, Ruderman EM. *Arthritis Res Ther.* 2017;19(1):286. 6. Wang R, et al. *Arthritis Rheumatol.* 2016;68(6):1415-1421 7. Poddubnyy D, et al. *Ann Rheum Dis.* 2022;81:96-97. Abstract OP0149. 8. Molto A, et al. *Ann. Rheum. Dis.* 2024;83(7):858-864. 9. Nikiphorou E, et al. *Arthritis Rheumatol.* 2020;72(11):1855-1862.

Differentiating AS/Radiographic axSpA and Nonradiographic axSpA

Inflammation of the axial skeleton on MRI

Structural SI joint damage[2-4]*



Inflammation of the axial skeleton on MRI

Without* structural SI joint damage[2-4]

AS/r-axSpA | **nr-axSpA**

Clinical features do not differ[1,2,5]

- Pain
- Functional impairment
- SpA features
- Enthesitis
- Elevated CRP

Given the subjective interpretation of the SI joint via x-ray, the distinction between AS/r-axSpA and nr-axSpA is not absolute.[1]

*According to modified New York criteria.[3]

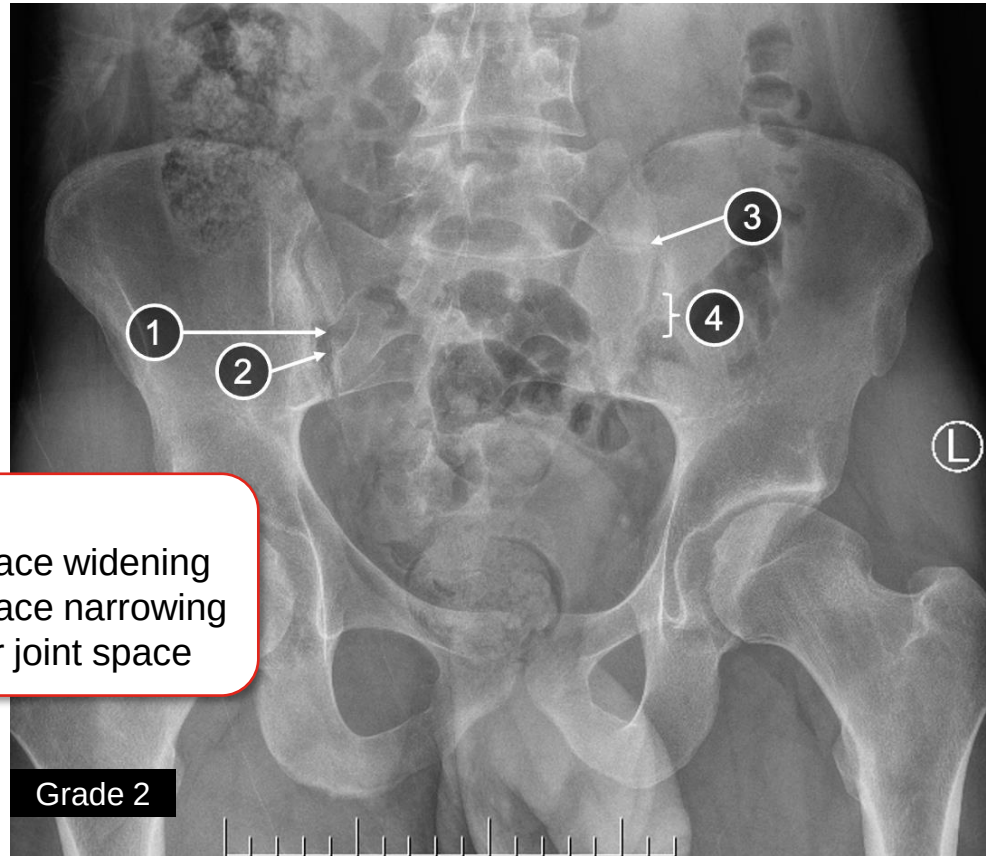
AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SI=Sacroiliac.

1. Deodhar AA. *Am J Managed Care*. 2019;25(17, suppl):S319-S330. 2. Baraliakos X, et al. *RMD Open*. 2015;1:e000053. 3. van der Linden S, et al. *Arthritis Rheum.*1984;27:361-368. 4. Mease PJ, et al. *Arthritis Care Res.* 2018;70(11):1661-1670. 5. Sieper J, et al. *Ann Rheum Dis.* 2009;68 Suppl 2:ii1–44 [page ii23 (Figure 29)and ii6 (Box 10C)].

SIJ Skeletal Changes in Early Versus Late Stage AS/r-axSpA

Radiograph

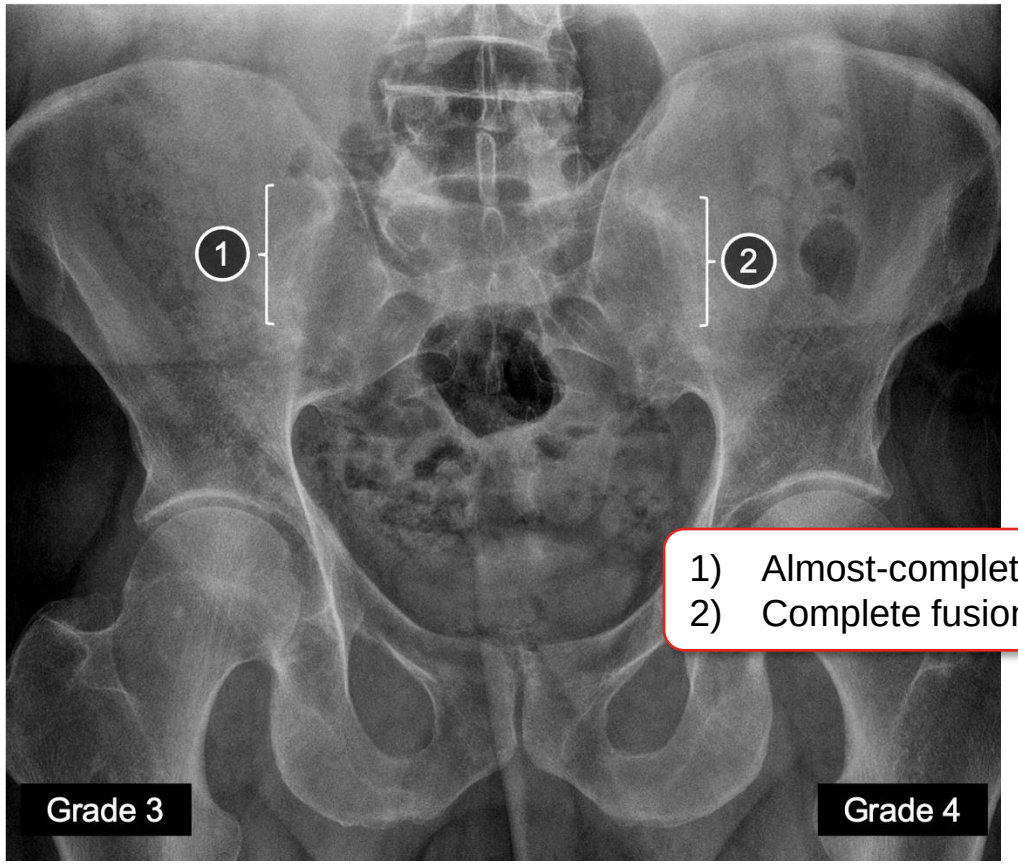
Early



1) Erosion
2) Joint space widening
3) Joint space narrowing
4) Irregular joint space

SIJ Skeletal Changes in early stage AS/r-axSpA: Image courtesy of Dr. R. Inman

Late



1) Almost-complete fusion
2) Complete fusion

SIJ Skeletal Changes in late stage AS/r-axSpA: Image courtesy of Dr. R. Inman

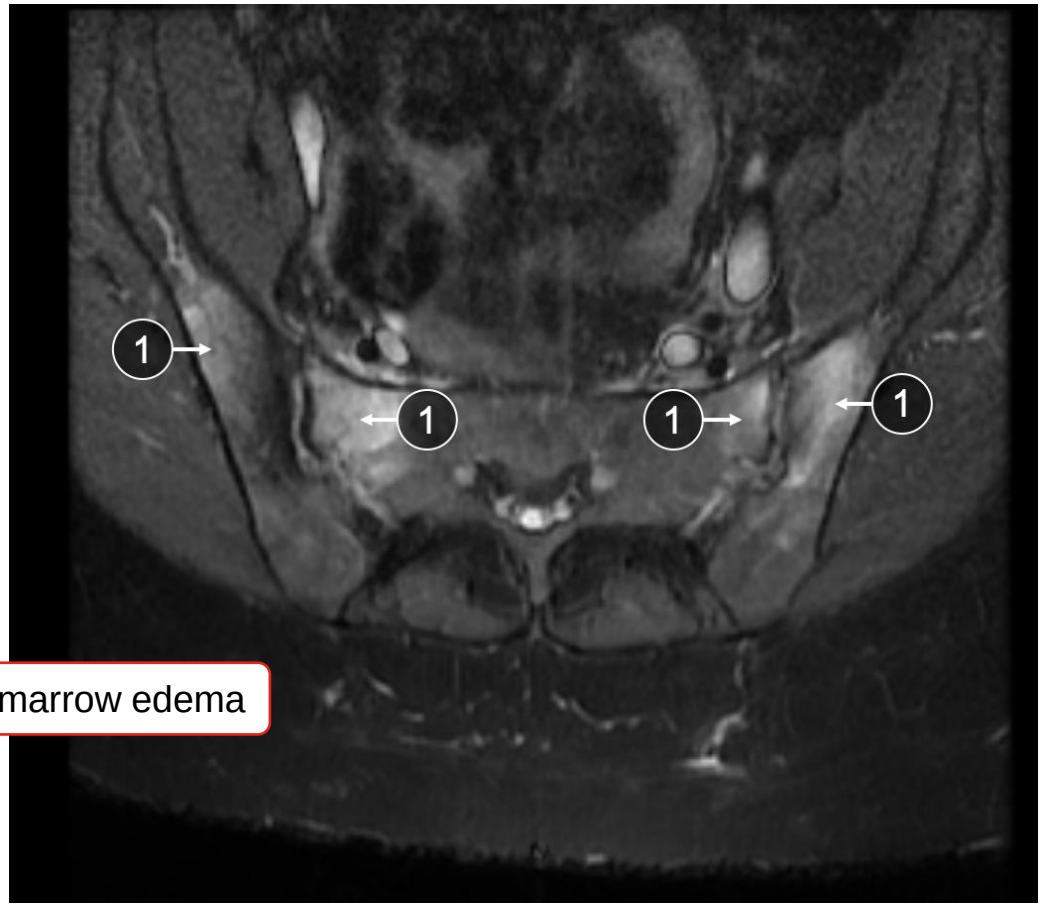
AS=Ankylosing Spondylitis; r-axSpA=Radiographic Axial Spondyloarthritis; SIJ=Sacroiliac Joint.

Lilly AS/r-axSpA nr-axSpA 3D Explorer. https://medical.lilly.com/us/diseases/disease-education-resources/rheumatology/axial-spondyloarthritis/education-resources/axial-spondyloarthritis-as-nr-axspa-3d-explorer-as-r-axspa (Accessed January 30, 2025).

SIJ Inflammation Changes in Early Versus Late Stage AS/r-axSpA

MRI

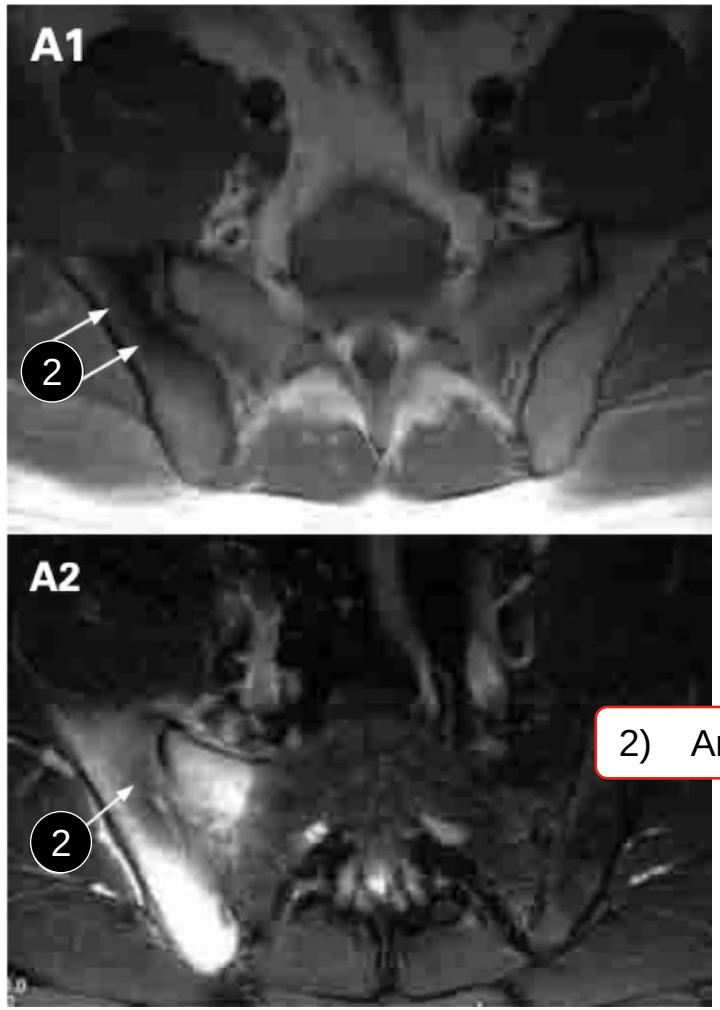
Early[1]



1) Bone marrow edema

SIJ Inflammation Changes in early stage AS/r-axSpA: Image courtesy of Dr. R. Inman

Late[2]



2) Area of sclerosis

AS=Ankylosing Spondylitis; MRI=Magnetic Resonance Imaging; r-axSpA=Radiographic Axial Spondyloarthritis; SIJ=Sacroiliac Joint.

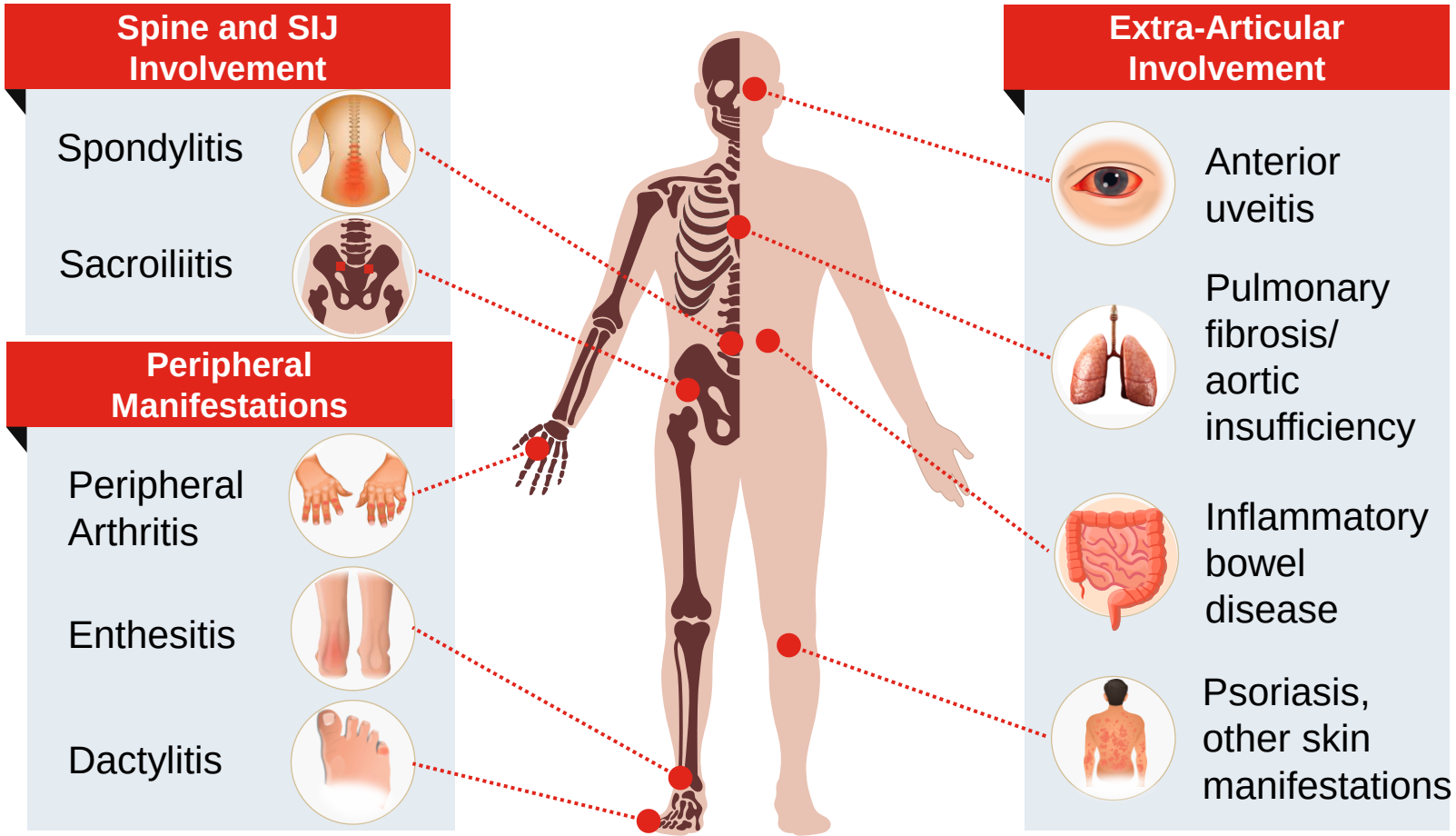
1. Lilly AS/r-axSpA nr-axSpA 3D Explorer: https://medical.lilly.com/us/diseases/disease-education-resources/rheumatology/axial-spondyloarthritis/education-resources/axial-spondyloarthritis-as-nr-axspa-3d-explorer-as-r-axspa (Accessed January 30, 2025). 2. Sieper J, et al. *Ann Rheum Dis.* 2009;68 Suppl 2:ii1–44 [page ii11, Box 17, A1 and A2].

Clinical Manifestations of axSpA

axSpA Clinical Manifestations

- axSpA refers to the inflammation of the axial skeleton[1-3]*
- Clinical features are similar for AS/r-axSpA and nr-axSpA, but the frequencies of some manifestations vary[4,5]
- Most common symptoms include inflammatory back pain, stiffness, and fatigue[1,2]

axSpA Clinical Manifestations[1-6]



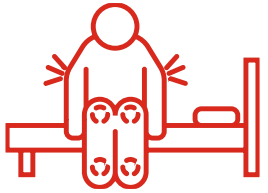
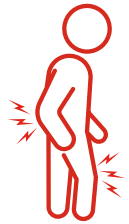
*Vertebral column, ribs, sternum, and skull.[1,7]

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SIJ=Sacroiliac Joint.

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574. 2. Ward MM, et al. *Arthritis Rheumtol.* 2016;68(2):282-298. 3. van der Linden S, et al. *Arthritis Rheum.*1984;27(4):361-368. 4. de Winter JJ et al. *Arthritis Res Ther.* 2016;18:196. 5. Proft F et al. *Ther Adv Musculoskel Dis*. 2018;10(5-6):129–139. 6. van der Heijde D. *Primer on the Rheumatic Diseases*. 13th ed. New York, NY: Springer; 2008:193,194,196. 7. Caetano AP, et al. *Front Med (Lausanne).* 2021;8:658538.

Common Symptoms of axSpA

axSpA strikes patients early in life (peak onset between 20 and 30 years of age), leading to longer disease burden over their lifetime.[1]

	Low back pain[3a]	Fatigue[3,4]	Morning stiffness[3,4a]	Mobility restriction[3,4,7b]	Sleep difficulty[3,4c]
Patients affected	 **72%[2]**	 **66%[4]**	 **81%[5]**	 **89%[6]**	 **35-90%[8]**
Symptoms					
Characteristics	Worsens with rest and improves with exercise.[3]	Influenced by multiple factors including chronic inflammation and pain.[4]	May last a few hours; reflects ongoing inflammation.[4]	Can permanently be affected due to progressive joint fusion.[4]	Caused by inflammatory back pain and spinal deformities in more advanced patients.[4]

[a]In ankylosing spondylitis patients.[3,4] [b]Patients with Grade II (moderate: Lumbar movement 3-6 cm, thoracic or cervical movement 20°-40°) and Grade III (severe: Lumbar movement <3 cm, thoracic or cervical movement <20°) spinal mobility.[7] [c]Reported as poor sleep quality/too little sleep.[8]

axSpA=Axial Spondyloarthritis.

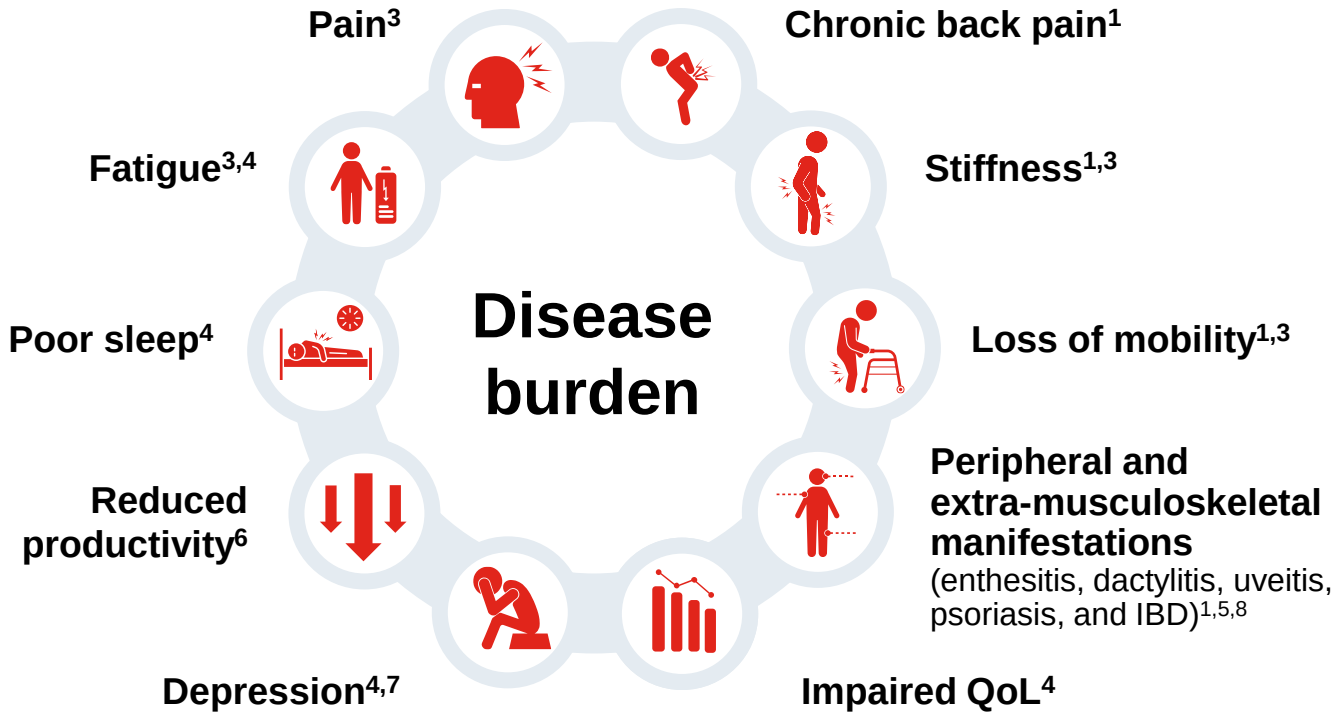
1. Poddubnyy D, et al. *Rheumatology (Oxford).* 2022 Aug 3;61(8):3299-3308. 2. Rojas-Vargas M, et al. *Rheumatology (Oxford).* 2009. 48(4):404-9. 3. Walsh JA, Magrey M. *J Clin Rheumatol.* 2021 Dec 1;27(8):e547-e560. 4. Strand V, Singh JA. *J Clin Rheumatol.* 2017 Oct;23(7):383-391. 5. Şaş S, et al. *J Rheum Dis*. 2023;30(3):176-184. 6. Morton L, et al. *Arthritis Care Res (Hoboken).* 2022;74(9):1541-1549.
7. Carette S, et al. *Arthritis Rheum*. 1983;26:186-190. 8. Fongen C, et al. *Scand J Rheumatol.* 2024;53(2):130-139.

axSpA Carries a High Disease Burden

Chronic inflammatory back pain and **sacroiliitis** are hallmarks of AS.[1]

~80% of patients develop their first symptom when they are <30 years of age.[2]

Patients with AS/r-axSpA and nr-axSpA share a similar disease burden.[3]



AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; IBD=Inflammatory Bowel Disease; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; QoL=Quality of Life.

1. Braun J, et al. *Lancet*. 2007;369:1379-1390. 2. Wenker KJ, et al. NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK470173/. 3. Mease PJ, et al. *Arthritis Care Res.* 2018;70:1661-1670. 4. Ates A, et al. *Ann Rheum Dis*. 2015;74:497-498. Poster FRI0202. 5. de Winter JJ, et al. *Arthritis Res Ther*. 2016;18:196. 6. Osterhaus JT. *Arthritis Res Ther*. 2014;16:R16. 7. Zhao S, et al. *Arthritis Res Ther*. 2018:140. 8. Navarro-Compán V, et al. *Ann Rheum Dis.* 2021;80(12):1511-1521.

AS/r-axSpA and nr-axSpA

Similarities

- Similar levels of disease activity (BASDAI, BASFI, QoL)
- Similar prevalence of most peripheral and extra-articular signs
- Where inflammation is present, responses to TNF blockade are similar
- A proportion of patients progress from nr-axSpA to AS, which explains in part the longer disease duration in AS

Differences

- Uveitis is more prevalent in AS/r-axSpA than nr-axSpA patients
- HLA-B27 is more frequent in AS /r-axSpA than in nr-axSpA
- Higher burden of objective inflammation at baseline as measured by MRI or CRP levels in AS /r-axSpA compared to nr-axSpA
- Female gender is more prevalent in nr-axSpA than AS/r-axSpA
- Male gender is more prevalent in AS/r-axSpA

nr-axSpA can be challenging to diagnose due to:

- Lack of radiographic confirmation of disease
- Lower grade of inflammation (on MRI) in women
- Attribution of inflammatory pain to other causes, such as fibromyalgia

AS=Ankylosing Spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C-Reactive Protein; HLA=Human Leukocyte Antigen; MRI=Magnetic Resonance Imaging; nr-axSpA=Nonradiographic Axial Spondyloarthritis; QoL=Quality of Life; r-axSpA=Radiographic Axial Spondyloarthritis; TNF=Tumor Necrosis Factor.

Ghosh N, Ruderman EM. *Arthritis Res Ther.* 2017;19:286.

Summary

- The IL-17 pathway is key in axSpA pathogenesis[1]
- HLA-B27 is the genetic factor known to play an important role in axSpA[2]
- axSpA refers to inflammation of the axial skeleton and encompasses two subtypes of the same disease such as AS/r-axSpA (presence of radiographic changes of the sacroiliac joints) and nr-axSpA (absence of radiographic changes of the sacroiliac joints) as defined by mNY criteria[3]
- Clinical features are similar for AS/r-axSpA and nr-axSpA, but the frequencies of some manifestations vary[4-6]
- Patients with axSpA (AS/r-axSpA and nr-axSpA) carry a similar and high disease burden[6]
- Chronic inflammatory back pain and sacroiliitis are hallmarks of axSpA[7]
- Delay in disease control is associated with worse physical function, increased structural damage, reduced response to treatment, and poor quality of life[8-10]

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; IL=Interleukin; mNY=modified New York; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. McGonagle DG, et al. *Ann Rheum Dis.* 2019;78(9):1167-1178. 2. López-Larrea C, et al. *Mol Med Today.* 1998;4(12):540-549. 3. Sieper J, et al. *Ann Rheum Dis*. 2009;68(Suppl 2):ii1-44. 4. Deodhar AA. *Am J Managed Care*. 2019;25(17, suppl):S319-S330. 5. Baraliakos X, et al. *RMD Open*. 2015;1:e000053. 6. Mease PJ, et al. *Arthritis Care Res.* 2018;70(11):1661-1670. 7. Braun J, et al. *Lancet*. 2007;369:1379-1390. 8. Lapane KL, et al. *BMC Fam Pract.* 2021;22(1):251. 9. Zhao SS, et al. *Rheumatology (Oxford).* 2021;60(4):1620-1628. 10. Yi E, et al. *Rheumatol Ther.* 2020;7(1):65-87.

US Medical Education

For additional resources on axSpA, scan the code

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axSpA=Axial Spondyloarthritis.