Module 5

Assessment Tools Used in Clinical Trials and Clinical Practice

Learning Objectives

- Outline common assessment tools used in clinical trials and in practice
- Describe scores that are relevant in the interpretation of clinical assessment tools
- Describe the imaging modalities used in clinical trials and clinical practice

Content Flow

- Disease activity assessments: No simple and unique standard to measure disease activity
- Assessment tools used for treatment response, disease monitoring, health-related quality of life, and objective assessment of inflammation
- Imaging modalities in AS/r-axSpA and nr-axSpA
- Summary

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

Commentaries

Each outcome measure is defined and includes two commentaries

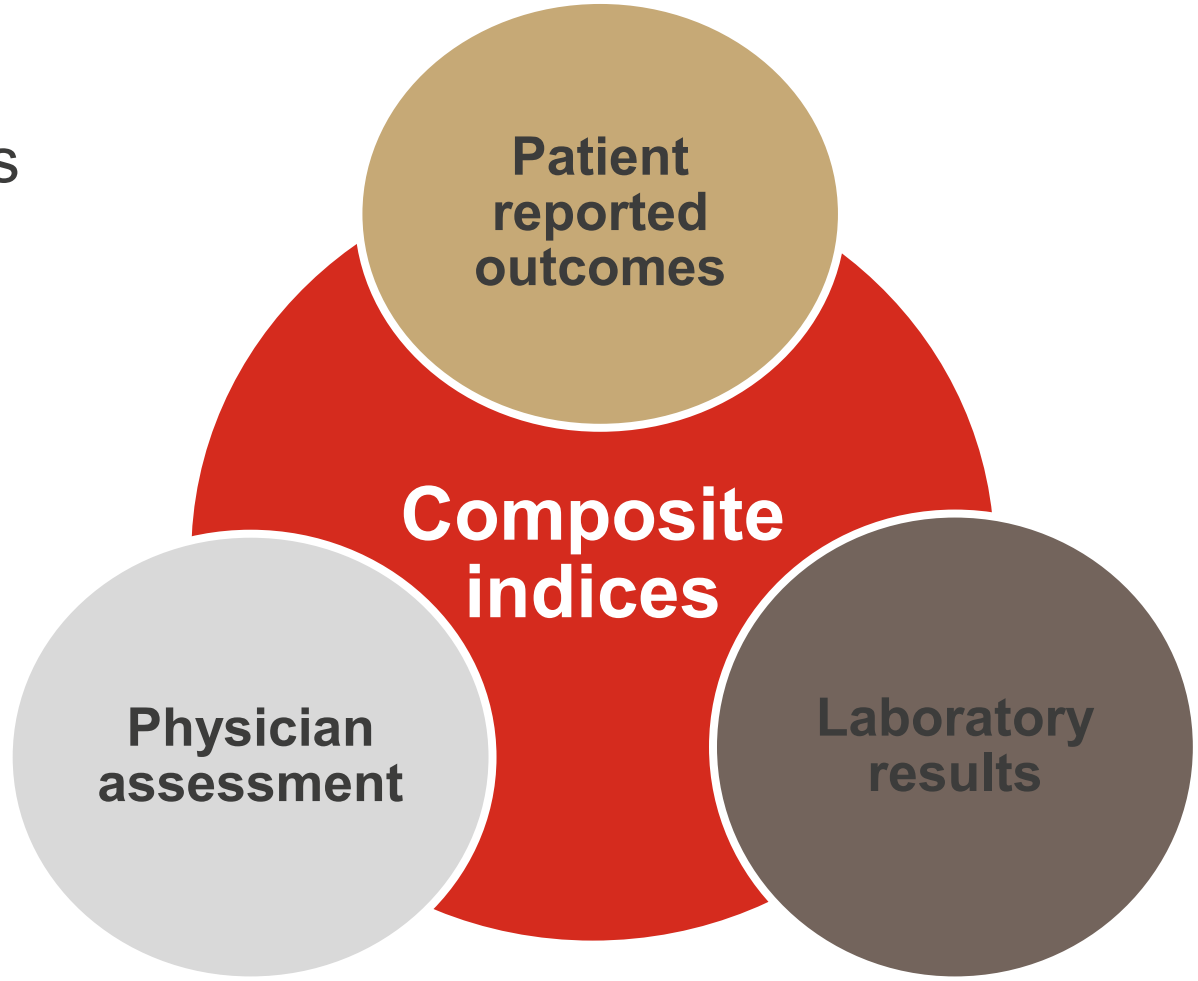
Purpose:
What does the outcome mean for physicians

For the Patient:
What does this measure mean for patients

Disease Activity Assessments: No Simple and Unique Standard to Measure Disease Activity

Clinical Disease Activity Assessments Tools

- There is no assessment tool that is considered the “gold standard” for measuring disease activity[1]
- To quantify disease activity in axSpA, it is necessary to consider many aspects—one variable or individual tool is not enough to assess the entire disease[1]



axSpA=Axial Spondyloarthritis.

1. Braun J, et al. *Clin Exp Rheumatol.* 2014;32(5 Suppl 85):S96-104.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a Frequently Used Instrument in Clinical Trials

- Patient-reported measure published 20 years ago[1]
- Easy to complete[2]
- Well known by most rheumatologists[2]
- Measures only part of the disease activity domain[3]
- Does not weigh individual clinical manifestations, as the variables are simply summed without relative importance[2,3]
- Lacks specificity for inflammatory processes[2,3]

Purpose: Validated test to measure disease activity and response to therapy

For the Patient: Simple measure of 6 major symptoms of axSpA

BASDAI50 Response

- Proportion of patients achieving ≥50% improvement in the BASDAI score or an absolute change of 2 units (on a 0 to 10 scale)
- Used to measure response to biologic therapy after 3 months of treatment

axSpA=Axial Spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis; Disease Activity Index.

1. Garrett S, et al. *J Rheumatol.* 1994;21:2286-2291. 2. Landewé R, van Tubergen A. *Curr Rheumatol Rep*. 2015;17(7):47. 3. Machado P, van der Heijde D. *Curr Opin Rheumatol.* 2011;23:339-345.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Relating to the past week, score out of 10 for each question (0 = None, 10 = Very Severe)	**Score / 10**
1. How would you describe the overall level of fatigue/tiredness you have experienced?	
2. How would you describe the overall level of as neck, back or hip pain you have had?	
3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?	
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?	
Total of Q1 to Q4 (out of 40) [A]	
5. How would you describe the overall level of morning stiffness you have had from the time you wake up?	
6. How long does your morning stiffness last from the time you wake up? (0 = 0 hours, 10 = 2+ hours)	
Total of Q5 to Q6 divided by 2 (out of 10) [B]	
BASDAI = Total Score out of 50 [A+B]/5	

Interpretation

- The score ranges from 0 (no disease activity) to 10 (very active disease)
- A cut-off of 4 is frequently used to define active disease

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index.

1. Landewé R, van Tubergen A. *Curr Rheumatol Rep*. 2015;17(7):47. 2. Garrett S, et al. *J Rheumatol* 1994;21:2286-91. 3. http://www.basdai.com/BASDAI.php (Accessed April 2019)

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a Frequently Used Instrument in Clinical Trials

Data-driven index that combines PROs and other measures in a weighted manner:[1]

1. Back pain
2. Peripheral pain/swelling
3. Duration of morning stiffness
4. Patient global assessment of disease activity
5. ESR (ASDAS-ESR) OR CRP (ASDAS-CRP)

ASDAS-CRP is recommended by the ASAS organization for clinical practice[1]

Purpose: Composite index to assess disease activity and response to treatment

For the Patient: Allows for evaluation of disease activity and definition of improvement

ASAS=Assessment in Spondyloarthritis International Society; ASDAS= Ankylosing Spondylitis Disease Activity Score; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score-C-reactive Protein; ASDAS-ESR= Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate; CRP=C-reactive Protein; ESR=Erythrocyte Sedimentary Rate; PRO=Patient-reported Outcome.

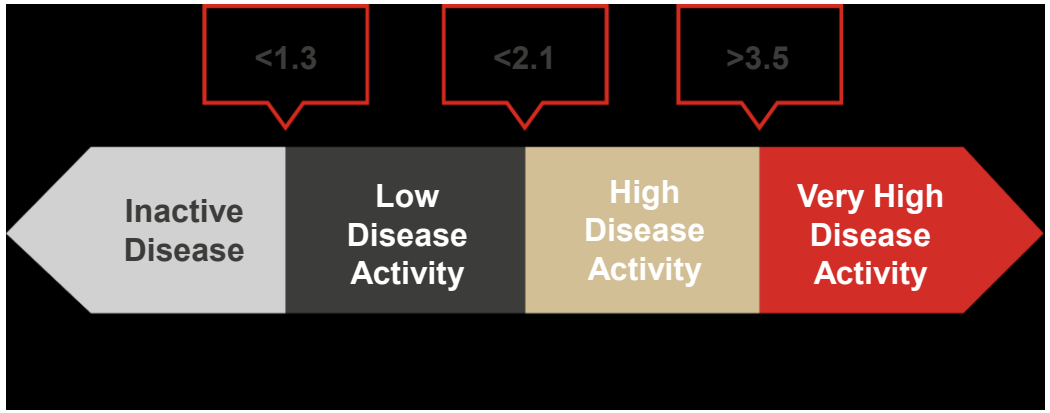
1. Landewé R, van Tubergen A. *Curr Rheumatol Rep.* 2015;17(7):47. 2. Machado P, van der Heijde D. *Curr Opin Rheumatol.* 2011;23:339-45.

Ankylosing Spondylitis Disease Activity Score (ASDAS)

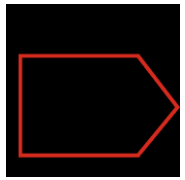
ASDAS-CRP: 0.121 x total back pain
+ 0.110 x patient global + 0.073
x peripheral pain/swelling + 0.058
x duration of morning stiffness + 0.579
x Ln(CRP) + 1

ASDAS-ESR: 0.113 x patient global
+ 0.293 x $\sqrt{ESR}$ + 0.086
x peripheral pain/swelling + 0.069
x duration of morning stiffness + 0.079
x total back pain

ASDAS disease activity states



ASDAS improvement criteria



Clinically Important Improvement

Major Improvement

ASDAS=Ankylosing Spondylitis Disease Activity; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score-C-reactive Protein; ASDAS-ESR= Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate; CRP=C-reactive Protein; ESR= Erythrocyte Sedimentation Rate.

1. Landewé R, van Tubergen A. *Curr Rheumatol Rep*. 2015;17(7):47. 2. ASAS. https://www.asas-group.org/clinical-instruments/asdas-calculator/. (Accessed on March 17, 2019).

ASAS/OMERACT Core Domains to be Measured for Patients with AS

SM-ARD/Physical Therapy
Physical function
Spinal stiffness
Patient global assessment
Spinal mobility
Pain
Fatigue

Clinical Record Keeping
+ Acute phase reactants
+ Peripheral joints/entheses

DC-ART
+ Spine radiograph

Purpose: The ASAS organization recommended domains of disease for assessment and instruments to measure these domains

For the Patient: Standardized assessment of disease activity

- Minimum of variables that should be collected for 3 different settings
- Each setting has different domains that should be measured with specific instruments

AS=Ankylosing Spondylitis; ASAS=Assessment of Spondyloarthritis International Society; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs; SM-ARD=symptom modifying antirheumatic drugs (NSAIDs); DC-ART=disease-controlling antirheumatic drugs ((include TNFi and sulfasalazine); OMERACT=Outcome Measures In Rheumatology Clinical Trials; TNFi=Tumor Necrosis Factor Inhibitor.

1. Sieper J, et al. *Ann Rheum Dis*. 2009;68 Suppl 2:ii1–44. 2. Landewé R, van Tubergen A. *Curr Rheumatol Rep.* 2015;17(7):47.

ASAS Response Criteria for Measuring Response and Remission

ASAS40 Improvement Criteria (4 domains)[1]

- An improvement of ≥40% and an absolute improvement of ≥2 units (on a VAS scale of 0-10) in ≥3 domains without any worsening in the remaining domain
- Domains:
  1. Patient global
  2. Pain
  3. Function (assessed by BASFI),
  4. Inflammation (mean of BASDAI question 5 and 6)

ASAS20 Improvement Criteria (4 domains)[1]

- An improvement of ≥20% and an absolute improvement of ≥1 unit (on a VAS scale of 0-10) in ≥3 domains, with no worsening of ≥20% and ≥1 unit in the remaining domain
- Domains are the same as for ASAS40

ASAS Partial Remission (4 domains)[2]

- Very low disease activity
- Value of ≤2 (on a 0 to 10 scale) for each domain:
  1. Patient global
  2. Pain
  3. Function (assessed by BASFI),
  4. Inflammation (mean of BASDAI question 5 and 6)

ASAS5/6 Improvement Criteria (6 domains)[2]

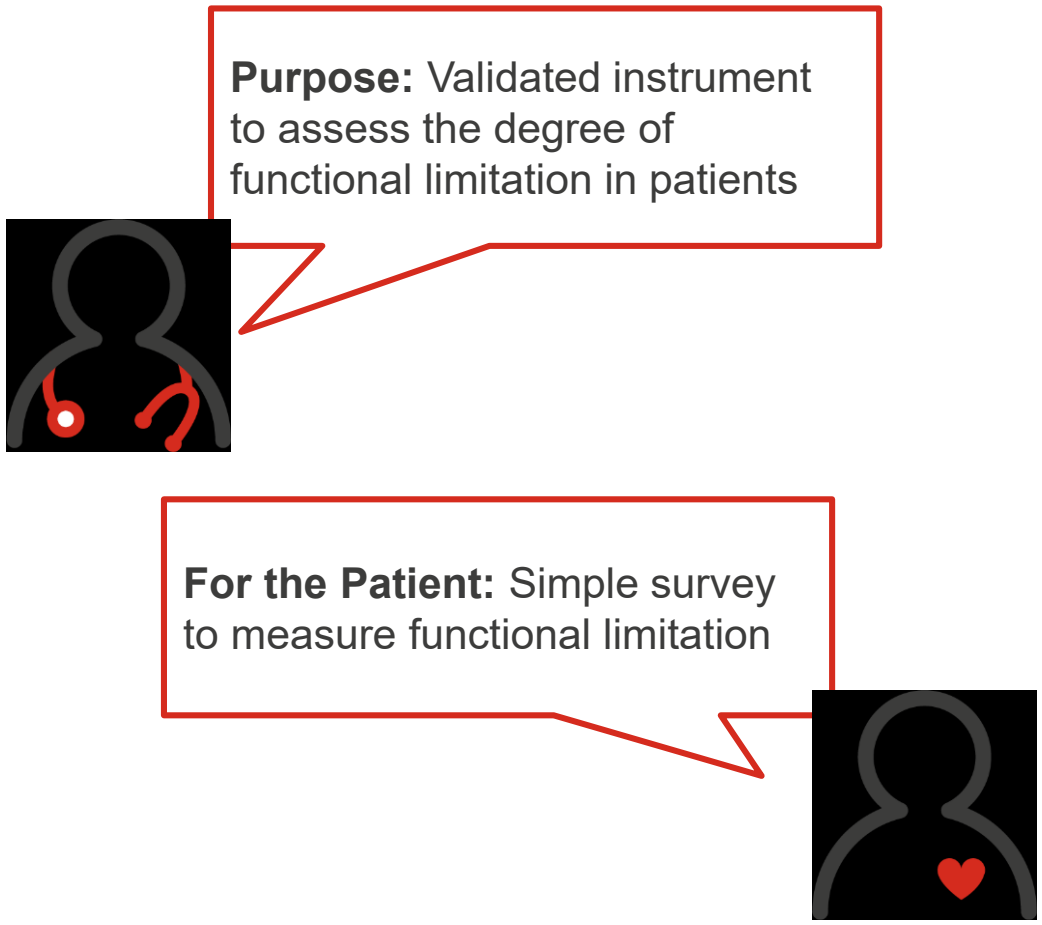
- ≥20% improvement in ≥5 of 6 domains
  1. Patient global
  2. Pain
  3. Function (assessed by BASFI),
  4. Inflammation (mean of BASDAI question 5 and 6)
  5. CRP
  6. Spinal mobility (assessed by lateral spinal flexion)

ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; VAS=Visual Analog Scale.

1. Sieper J, et al. *Ann Rheum Dis*. 2009;68 Suppl 2:ii1–44. 2. Landewé R, van Tubergen A. *Curr Rheumatol Rep.* 2015;17(7):47.

Bath Ankylosing Spondylitis Functional Index (BASFI)

- The BASFI scores ranges between 0 (easy) and 10 points (impossible)
- A higher score indicates a higher degree of functional limitations



BASFI=Bath Ankylosing Spondylitis Functional Index.

1. Calin A, et al. *Br J Rheumatol* 1995;34(8):793–4. 2.Sieper J, et al. *Ann Rheum Dis*. 2009;68 Suppl 2:ii1–44.

Bath Ankylosing Spondylitis Functional Index (BASFI)

Items to be scored by the patient:

- Putting on your socks or tights without help or aids (e.g., sock aid)
- Bending forward from the waist to pick up a pen from the floor without an aid
- Reaching up to a high shelf without help or aids (e.g., helping hand)
- Getting up out of an armless dining room chair without using your hands or any other help
- Getting up off the floor without help from lying on your back
- Standing unsupported for 10 min without discomfort
- Climbing 12 to 15 steps without using a handrail or walking aid. One foot at each step
- Looking over your shoulder without turning your body
- Doing physically demanding activities (e.g., physiotherapy, exercises, gardening or sports)
- Doing a full day's activities, whether it be at home or at work.

The BASFI is the mean of 10 item scores completed on a numerical rating scale.

Numerical rating scale

Alternatively, a VAS between 0 and 100 can be used. ASAS prefers to use an NRS.

ASAS=Assessment of Spondyloarthritis International Society; BASFI=Bath Ankylosing Spondylitis Functional Index; NRS=numerical rating scale; VAS=visual analogue scale.

1. Calin A, et al. *Br J Rheumatol* 1995;34(8):793–4. 2.Sieper J, et al. *Ann Rheum Dis*. 2009b;68 Suppl 2:ii1–44.

Assessment in Spondyloarthritis International Society Health Index (ASAS HI)

- Instruments discussed so far focus predominantly on specific aspects of health such as pain, disease activity, and physical function[1]
- ASAS HI provides an overall picture of impairments, limitations, and restrictions in activities or social participation[1]
- The ASAS HI is a linear composite index with 17 items, which cover most aspects of the International Classification of Functioning, Disability and Health (ICF) core set[1,2]
- Validated in 23 countries worldwide (including the USA)[3]

Purpose: Assessment of physical functioning, performance of daily activities, and social participation

For the Patient: How well they are functioning in life

ASAS=Assessment in Spondyloarthritis International Society; HI=Health Index; ICF=International Classification of Functioning, Disability and Health; USA=United States of America.

1. Landewé R, van Tubergen A. *Curr Rheumatol Rep.* 2015;17(7):47. 2. Assessment of SpondyloArthritis International Society. https://www.asas-group.org/clinical-instruments/asas-health-index/ (Accessed April 23, 2019).
3. Kiltz U, et al. *RMD Open.* 2016;2:e000311. doi:10.1136/rmdopen-2016- 000311.

ASAS HI Questionnaire – Sample Questions

	I agree	I do not agree
1. Pain sometimes disrupts my normal activities	☐	☐
2. I find it hard to stand for long	☐	☐
3. I have problems running	☐	☐
4. I have problems using toilet facilities	☐	☐
5. I am often exhausted	☐	☐
6. I am less motivated to do anything that requires physical effort	☐	☐
7. I have lost interest in sex	☐	☐
Etc. (17 total question)	☐	☐

ASAS=Assessment in Spondyloarthritis International Society; HI=Health Index.
Assessment of SpondyloArthritis International Society. https://www.asas-group.org/clinical-instruments/asas-health-index (Accessed April 23, 2019)

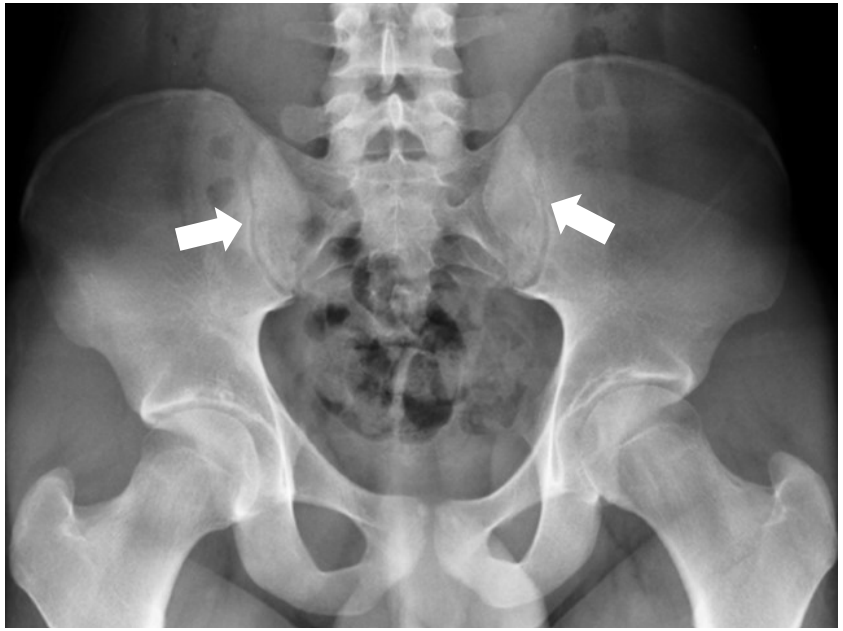
Imaging Modalities in AS/r-axSpA and nr-axSpA

Currently Available Imaging Techniques

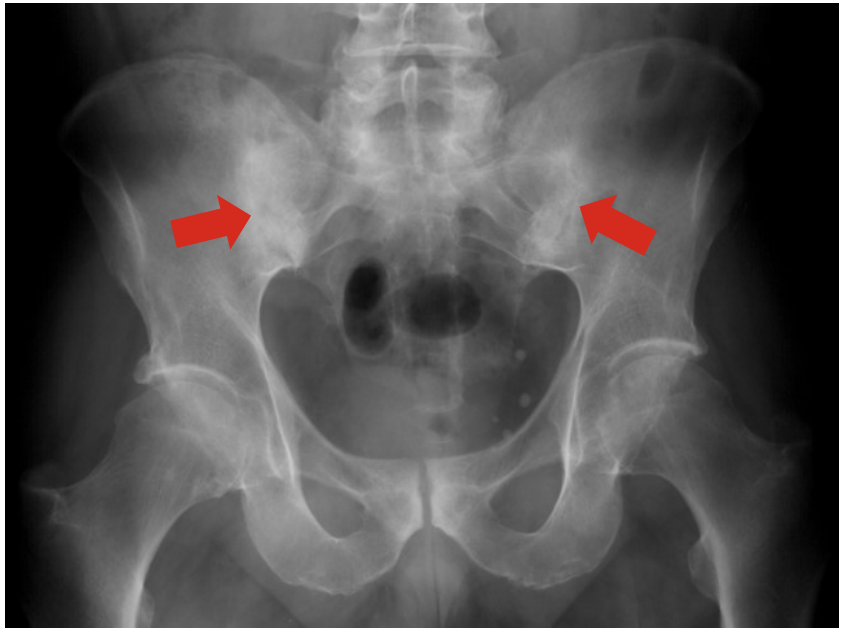
Imaging Technique	Pros	Cons
X-rays of the SI joints and spine	• Used frequently in practice	• Not sensitive for early changes
CT-scan of the SI joints and spine	• Better sensitivity	• Radiation exposure • Not for inflammatory changes
Scintigraphy	• Better when combined with CT or MRI	• Radiation exposure
MRI	• Much better in detecting early inflammatory changes • Can assess for response to therapy	• Expensive • Takes time to do • Some patients find it difficult to tolerate (supine and still for at least 30 mins) • Practicing HCPs and radiologists not familiar with the reading and interpretation of findings shown in images

CT=Computerized Tomography; HCP=Health Care Practitioner; MRI=Magnetic Resonance Imaging; SI=Sacroiliac.
Provided by Professor Mikkel Ostergaard, September 2018.

Radiographs of Sacroiliac Joint and Spine to Confirm Sacroiliitis



No definite radiographic sacroiliitis (grade 0)[1]



Definite radiographic sacroiliitis (grade 3 bilaterally)[1]

X-ray is the main diagnostic method used to confirm presence of sacroiliitis[1] and to follow characteristic spinal changes in AS[2]

AS=Ankylosing Spondylitis.
Image reproduced with permission from ASAS International Society (http://slides.asas-group.org/app/slides/search?q=)
1. Sieper J, et al. *Ann Rheum Dis*. 2009;68:ii1-44. 2. Sieper J, Poddubnyy D. *Lancet.* 2017;390(10089):73-84. 3. Louie GH, Ward MM. *Curr Opin Rheumatol.* 2014;26(2):145-150.

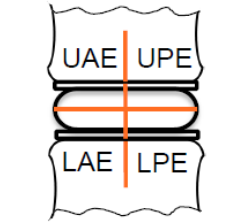
MRI Assessments

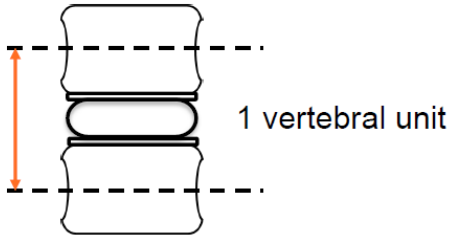
MRI-SPARCC[1]

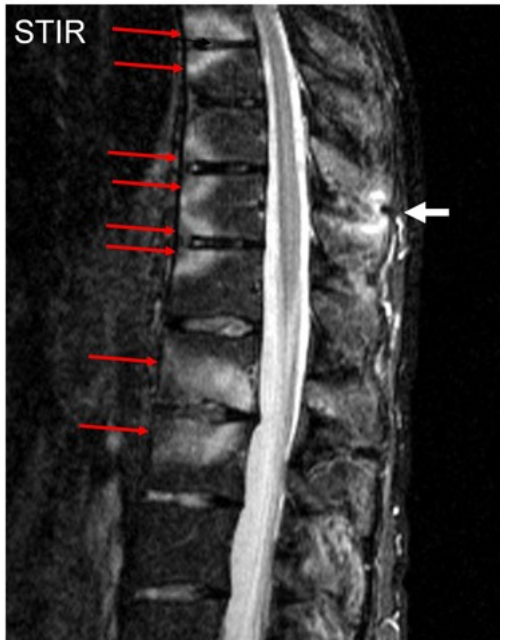
- Uses T2-weighted STIR MRI spine sequences
- 6 discovertebral levels selected for scoring after entire spine scanned
- Abnormal increased signal represents increased concentration of “free water” (BME)[2]

ASspiMRI-Berlin[3]

- Use of STIR technique and/or T1-weighted imaging after injection of gadolinium contrast agent
- Score is based on grading of both disease activity and chronicity on a scale of 0-6 for every vertebral unit







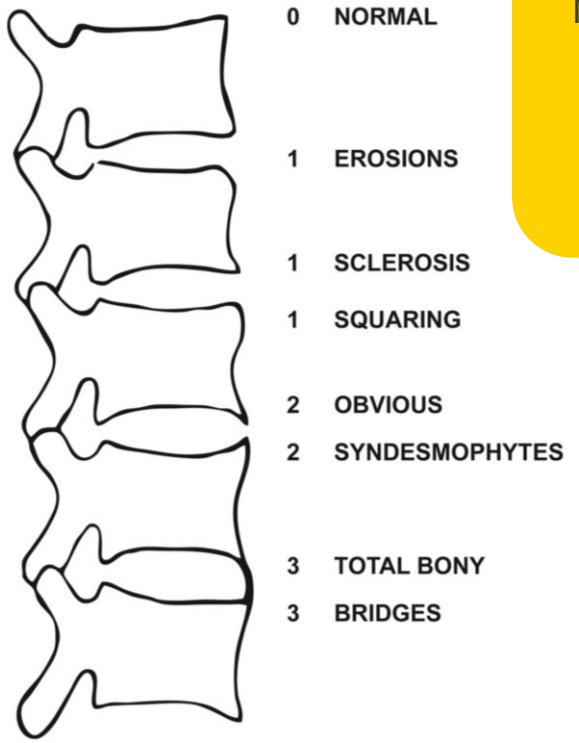
ASspiMRI=Ankylosing Spine MRI; BME=Bone Marrow Edema; LAE=lower anterior endplate; LPE=lower posterior endplate; MRI=Magnetic Resonance Imaging; SPARCC=Spondyloarthritis Research Consortium of Canada; STIR=Short τ Inversion Recovery; UAE=upper anterior endplate; UPE=upper posterior endplate.

Image reproduced with permission from ASAS International Society (http://slides.asas-group.org/app/slides/search?q=)

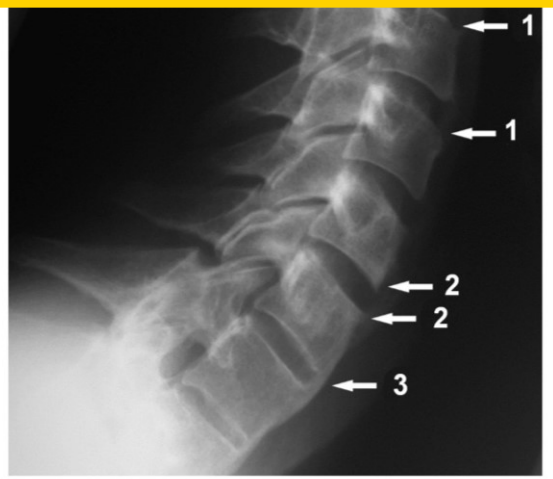
1. Maksymowych WP, et al. *Arthritis Rheum.*2005;53(4):502-509. 2. http://www.arthritisdoctor.ca/MRI%20of%20the%20sacroiliac%20joints-SPARCC%20Scoring%20methodology.pdf (Accessed March 2018). 3. Braun J, et al. *Arthritis Rheum.*2003;48(4):1126-1136.

Spine Radiograph: modified Stoke AS Spine Score (mSASSS)

- The anterior parts of the cervical and lumbar spine at a lateral view are scored for the presence of:
  - Squaring and/or erosion and/or sclerosis (1 point/site)
  - Non-bridging syndesmophytes (2 points/ site)
  - Bridging syndesmophytes (3 points/ site or 6 points/vertebral unit)
- The total score ranges from 0 to 72



Need to obtain permission from BMJ for Figure 45 (pg ii27)
Sieper J, et al. *Ann Rheum Dis*. 2009:68;ii1-ii44.



1. Creemers MCW, et al. *Ann Rheum Dis* 2005; 64(4):127-9. 2. Sieper J, et al. *Ann Rheum Dis*. 2009:68;ii1-ii44. 3. http://slides.asas-group.org/app/slides/search?q=stoke&submit= (Accessed April 23, 2019).

Summary

- In axSpA, as in other medical conditions, it is important to periodically assess and monitor the disease and treatment
- There is not one "gold standard" assessment tool for axSpA
- Many assessments are performed as part of the protocol in clinical trials
- Assessment tools include disease activity, response to therapeutic interventions, functionality, mobility, and HRQoL
- Imaging modalities are used to assess for objective inflammatory changes as well as for evaluation of structural progression

AS=Ankylosing Spondylitis; ASAS=Assessment in Spondyloarthritis International Society; MRI=Magnetic Resonance Imaging; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

