Ankylosing Spondylitis: Overarching Concerns
New Concepts and New Treatment for Spondyloarthritis

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What is Ankylosing Spondylitis

The word is from Greek *ankylos* meaning stiffening, *spondylos* meaning vertebra, and *-itis* meaning inflammation.

The cause of ankylosing spondylitis is unknown however, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism is believed to be autoimmune or autoinflammatory. Diagnosis is typically based on the symptoms with support from medical imaging and blood tests. AS is a type of seronegative spondyloarthropathy, meaning that tests show no presence of rheumatoid factor (RF) antibodies.
What is Spondyloarthritis?

is an umbrella term for inflammatory diseases that involve both the joints and entheses--the sites where the ligaments and tendons attach to the bones.

The most common of these diseases is Ankylosing Spondylitis.
And includes many others.
AS is one of the Spondyloarthritides (SpA)

Khan MA, Ankylosing Spondylitis. 2009;1-47
Van der Linde S et al. Kelley’s Textbook of Rheumatology. 8th ed. 2008; 1169-1189
Famous people with Ankylosing Spondylitis

• Dan Reynolds lead singer with Imagine Dragons.
  • His story “started in my hips. I couldn’t move and felt drilling in my nerves”
  • Scariest moments when he “could not get out bed”
  • When he was first diagnosed he was newly married and then had a baby.
  • Misdiagnosed by “lots of Doctors”
  • Finally saw rheumatologist and “got on medicine and now I am in remission”
  • He is now 29 and came forward with his disease
  • “The disease has taught me a lot about life and ‘gave me compassion’, taught me discipline”.
  • It has given me “more passion for life”
  • Now is a spokesperson for AS and thisaslife.com
Learning objectives

1. Discuss new concepts of the natural history of the AxSpA
2. Differentiate between old and new criteria for diagnosis of axial SpA
3. Explain the role of conventional radiography and MR imaging, lab testing and genetic markers
4. Adopt management strategies using older and newer pharmaceutical agents
Spondyloarthritis—More common than RA?

“Oh axial spondyloarthritis may be as prevalent as rheumatoid arthritis”

- 2009-2010 NHANES
  - 6,684 screened ages 20-69
  - 5,106 interviewed
  - 20% of Americans have low back pain
  - 6% have inflammatory low back pain
  - axSpA 0.9-1.4% prevalence

Rheumatoid prevalence 0.6%-1%
axSpA 0.9-1.4%
Could it be that we are underdiagnosing?
Come in to my office. You’ll see a lot more of this than this. Why?
Prevalence of Ankylosing Spondylitis (AS) and Spondyloarthritis (SpA) vs. Rheumatoid Arthritis (RA)


Courtesy of Assessment of Spondyloarthritis International Society
There Are More Than 100 Forms of Arthritis
Epidemiology of Rheumatic Diseases

- 1 in 8 persons has osteoporosis
- 1 in 10 persons has osteoarthritis
- 1 in 33 persons has fibromyalgia
- 1 in 100 persons has RA
- 1 in 350 persons has PsA
- 1 in 1000 persons has ankylosing spondylitis
- + IBD arthritis
- + Undiff. Sacroiliitis
- + ReA Reactive arthritis
  = 1.3-1.4 million in USA

- 1 in 2000 persons has systemic lupus erythematosus
- 1 in 10,000 persons has scleroderma
New concept of AS and Related Spondyloarthritis (SpA)

<table>
<thead>
<tr>
<th>Predominately Axial Disease</th>
<th>Predominately Peripheral Disease</th>
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<tr>
<td>Ankylosing spondylitis (radiograph SpA)</td>
<td>Reactive arthritis ReA</td>
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<tr>
<td>Nonradiographic Axial SpA (nr-AxSpA)</td>
<td>Psoriatic arthritis PsA</td>
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<td>Inflammatory bowel disease-associated arthritis</td>
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<td>Undifferentiated SpA</td>
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- Predominately Axial Disease: Ankylosing spondylitis (radiograph SpA), Nonradiographic Axial SpA (nr-AxSpA)
- Predominately Peripheral Disease: Reactive arthritis ReA, Psoriatic arthritis PsA, Inflammatory bowel disease-associated arthritis, Undifferentiated SpA
Index of Background terms

- SpA
- ax-SpA
- nr-SpA (undifferentiated SpA)

- ASAS

- PsA
- ReA-(Reiter’s)

- AS

- Spondyloarthritis
- Axial spondyloarthritis
- Non-radiographic axial spondyloarthritis

- Assessment of Spondyloarthritis International Society

- Psoriatic Arthritis
- Reactive Arthritis

- Ankylosing Spondylitis
Case study

• 39 year old Caucasian male referred for LBP

• CC: Acute onset of Low back and bilateral buttock pain after skiing 5 weeks previously.

• HPI: In addition to low back and buttock pain he complains of neck soreness and then the discomfort went to his mid back between his shoulder blades and then his hips. It became difficult to breathe and had anterior chest pain.

• PMHx: History of Crohn’s disease, anemia, hypertension, CKD stage III with negative renal biopsy, except scarring likely due to hypertension.
Case Study

• Labs:
  • ESR-85 mm/hr
  • CRP-46.0 mg/L ULN 10
  • BMP-CREAT 1.89 mg/Dl
  • BUN-31 mg/Dl
  • HLA B-27 negative
  • RF-negative
  • ANA-negative
  • CBC- Hgb 11.7 Hct 31.2
Case History
Radiology

• Radiology-x-ray bilateral hip and SIJ:
  
  • Significant sclerosis and irregularity of the SIJ consistent with osteoarthritis but no evidence of hip disease.

  • Impression: sclerosis and irregularity of bilateral SIJs consistent with sacroiliitis

• X-ray thoracic spine: Impression

  • There is mild curvature of the thoracic spine with convexity to the left in the lower thoracic spine. This curvature was not present in 10/27/2008.
SIJ X-Ray

What is the X-ray finding?
Epidemiology of AS

• AS is 2 to 3 times more common in males than in females

• Symptoms usually start between 20 and 30 years of age

• Most patients with AS are either diagnosed late or already compromised upon diagnosis

• The mean delay in the diagnosis of AS ranges between 5 to 11 years
Etiology of AS

- Precise etiology unclear

- Strong genetic predisposition highlighted by familial occurrence and HLA-B27
  - ~ 50% of the risk of developing AS is from HLA-B27
  - However HLA B-27 is not necessary or sufficient to cause the disease

- Twin studies show susceptibility of 90%

- Recurrence risk ratios of developing AS in a 1° relative is ~8%
Modified New York Criteria for AS 1984

Clinical criteria:

1. Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes
3. Limitation of chest expansion relative to normal values correlated for age and sex

Radiological criteria:

Sacroiliitis grade $\geq 2$ bilaterally or grade 3-4 unilaterally

Definite AS:

*If the radiological criterion is associated with at least 1 clinical criterion*

ASAS classification for Axial spondyloarthritis (SpA)

In patients with ≥ 3 months of back pain and age at onset <45 years old:

- Sacroiliitis on imaging plus ≥ 1 SpA feature
- HLA-B27 + plus ≥ 2 other SpA features

SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn’s disease/colicis
- FHx of SpA
- Elevated CRP

Sacroiliitis on imaging:
- Active inflammation on MRI
- Definite x-ray sacroiliitis according to modified NY criteria

Sensitivity 82.9%
Specificity 84.4%

Rundelwait 2009
Diagnosis of AS

• Establishing the diagnosis is often difficult
• The presenting manifestations can be wide ranging
• Thus, a variety of health care professionals may see these patients
  • Primary care providers
  • Ophthalmologists
  • Podiatrists
  • Other medical and surgical specialists (pain practices, orthopods)
  • Rheumatologists
Inflammatory Back Pain
Definition

• It is important to distinguish between mechanical low back pain and Inflammatory back pain.

• Duration > 30 minutes
• No improvement with rest
• Awakening from pain in the second half of the night
• Alternating buttock pain

sensitivity of 70.3% and a specificity of 81.2%

Approach to diagnosis of axial spondyloarthropathy

Chronic low back pain (5% probability of axial SpA)

Inflammatory back pain

Yes (14% probability)

HLA-B27

Yes (59%)

Rheumatologist:
Evaluation of clinical SpA
(enthesis, uveitis, buttock pain,
Peripheral arthritis, dactylitis,
Psoriasis, Crohn’s, + NSAID reponse
-Acute phase reactants
-HLA-B27
-Imaging (x-ray MRI)

No (2% probability)

No (2% probability)

Judgement on probability of axial SpA

No further testing
Unless SpA strongly suspected
Clinical Conceptualization of the Natural History of axSpA: An Emerging Model

Subclinical process in genetically predisposed patients

Inflammatory back pain

Spontaneous remission

Quiescent disease activity

Non-radiographic axSpA

Non-progressing AS

AS late complications

axSPA

Other features outside the spine

- Asymmetric oligoarthritis
- Psoriasis
- Uveitis
- Enthesitis

No radiographic evidence at early stages
Asymmetric oligoarthritis
Acute uveitis

Direct and consensual photophobia to light in left eye
25-40% develop this sign
Enthesitis
Hallmark of AS

• Enthesis=attachment of tendon, ligament or joint capsule. Enthesis is a complex structure that appears to be a principal site of inflammation of SpA

• Enthesitis can be an early and prominent feature of SpA

• Inflammation in AxSpA primarily affects the sacroiliac joints and axial skeleton

• Bony tenderness occurs from enthesitis at many other sites-costosternal, spinous process, greater trochanter, iliac crests, and ischial tuberosity, tibial tubercles or heels.¹²

Inflammatory Enthesitis
Sacroiliitis on Pelvis film
Stage III

Irregular borders
Fluffy boney appearance
Narrowing
Case study of pt. with 2 years of symptoms

Sacroiliitis by MRI

Normal SI joint x-ray
Pt had sx of Inflammatory back pain for 2 yr

Thick Arrows: Subchondral marrow inflammation shown by increased MRI signal

Thin Arrow: Joint cavity
What is the role of MRI in AS?

• Chronic low back for > 3 months
• Started before the age of 45
  • 5% chance of having SpA

So in this age of cost control and concern regarding ordering expensive tests what do you do?
Then
H and P should include

• Does the patient have a family history or past history of AS/SpA?
• Does the patient have inflammatory back/buttock pain? - increases odds to 14%
• Does the patient have difficulty touching his/her toes?
• Are they tender over one or both SIJs?
• Do they have a + Schober test?

In this situation
if either
HLA-B27 is +
or abnormal x-ray or MRI then
Odds are increased or the Dx can be made
Pathology of AS

AS is characterized by 2 key pathological findings: inflammation at the enthesis and new bone formation in the sacroiliac joint and in the spine.
Schematic sequence of events in AS vs RA

**AS**
- Inflammation fluctuating
- Erosive Bone Destruction
- Inflammation replacement by repair tissue
- Osteoproliferation syndesmophytes

**RA**
- Inflammation persisting
- Erosive Bone Destruction

**AS** Structural damage score

**RA** Structural damage score

Time
1. Rheumatoid is catabolic
   • Cartilage loss
   • Erosions

2. Spondyloarthritis catabolic plus anabolic
   • Anabolic causes syndesmophyte formation
   • And ankylosis of joints

Genetic Marker

HLA-B27

• AS Caucasians 90% + for HLA-B27

**Mechanism of action**

Four major hypothesis¹

1. MHC class I antigen presentation in HLA-B27+ pts
   • Molecule misfolds
   • Result-more easily recognized by natural killer cells

2. HLA-B27 can modulate the human microbiome
   • cross reacts with certain gram negative bacteria
   • as seen with reactive arthritis
   • high prevalence of subclinical intestinal inflammation in AS patients

¹ The Rheumatologists vol. 10 July 2016 pages 16-17
Treatment options

• Physical therapy
  • Extension exercises, weight maintenance/reduction

• Smoking cessation-restrictive disease due to chest wall involvement

• NSAIDs important role
  • Majority 50% or > response

• DMARDs limited role
  • Sulfasalazine-may be useful in peripheral arthritis
  • Methotrexate-no efficacy
  • Leflunomide-no efficacy
Treatment options

• TNF inhibitors:
  • Etanercept
  • Infliximab
  • Adalimumab
  • Golimumab
  • Certolizumab

• improve quality of life
  • anemia
  • sleep quality
  • fatigue
  • bone density
  • forced vital capacity¹−⁵

Similar in efficacy

Treatment options

• Other Biologic Response Modifiers
  • Abatacept
  • Rituximab
  • Tocilizumab
  • Tofacitinib

All approved for RA but no significant results in AS\textsuperscript{1-3}

Newer treatment options for AS

• Secukinumab - IL-17A inhibitor
• Indications: AS, PSO, PSA
• Dosage-150 mgs Q 1 week for 4 as induction
• Then 150 mgs monthly
• Side effect profile- same as TNF inhibitors
• TB screening
• Avoid live vaccines
• Pregnancy category B
Newer treatment options for PSO

• Ixekizumab- IL-17A inhibitor
• Indications: PSO
• Dosage-80 mgs 2 SQ week 0, then 80 mgs 2,4,6,8,10,12 then Q 4
• 80 mgs monthly
• Side effect profile- slight uptick in IBD associated symptoms in pts with IBD.
• TB screening
• Avoid live vaccines
• Pregnancy no data
Pathogenesis of PSA/PSO/AS

- **B-cell inhibitor**: Rituximab
- **T-cell inhibitor**: abatacept

**Antibodies**
- Antibodies
  - **Immune complexes**
  - IFN-γ and other cytokines

**Macrophage**
- **Macrophage**
  - TNF INHIBITORS
  - TNF-α INHIBITORS
- **Chondrocytes**
  - IL-6 Tocilizumab
  - Secukinumab IL-17a
  - Ixekizumab IL-17a

**JAK inhibitors Small molecules**
- Tofacitinib

**Production of collagenase and other neutral proteases**

2010 ASAS/EULAR Recommendation for Management of AS

- Non-pharmacologic therapy
  - Patient education
  - Regular exercise
  - Physical therapy land or water based
  - Patient association and self help groups may be useful

- Extra-articular manifestations psoriasis, uveitis, IBD should be managed with collaboration of appropriate specialists

- Rheumatologists and PC should be aware of increased CV risk and Osteoporosis risk
2010 ASAS/EULAR Recommendation for Management of AS

1. Pt education
2. Exercise
3. Physical therapy
4. Rehabilitation
5. Pt associations and self help groups

- NSAIDS
  - Axial involvement
  - Peripheral joint involvement
    - Sulfasalazine
    - Local steroid injections
  - TNF Antagonists IL-17A

- Analgesics
- Surgery
Immunizations in SpA
Primary Care ➔ Rheumatology

• SpA patients have reduced responses to immunizations; medications may blunt these responses further

• No evidence that vaccinations exacerbate or precipitate rheumatic disease

• Influenza and pneumococcal vaccinations are recommended
  • Postimmunization titers may be lower

• Hepatitis B immunization if appropriate


Herpes zoster (shingles) vaccine guidelines for immunocompromised patients. American College of Rheumatology web site.
**Immunizations in SpA Primary Care → Rheumatology**

- **Live virus vaccines** should be avoided in patients on immunomodulators:
  - Intranasal influenza, mumps/measles/rubella (MMR), yellow fever, typhoid, oral polio
  - Wait at least 2 weeks after giving these vaccines before initiating immunomodulators

- Zoster vaccine should be avoided in patients on **biologic** agents
  - May be given to patients on MTX and prednisone <20 mg/d

- Other immunizations are safe:
  - Influenza (injection), tetanus, pneumococcus, meningococcus, hepatitis A, hepatitis B, *H. influenzae* B (HiB), human papillomavirus (HPV)

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Herpes zoster (shingles) vaccine guidelines for immunocompromised patients. American College of Rheumatology web site.
How do you make the diagnosis of SpA?

• Several important key factors:
  • You must think of it in any pt. male or female who has chronic low back pain. Have the pt point to the pain and decide clinically where it is.
  
• The history is key, labs and imaging are also helpful
  • Ask the questions-IBD, iritis, psoriasis, FMHx, inflammatory back pain
  • Get labs including HLA-B27
  • Order an SIJ film and if negative with a high suspicion then order MRI
  • Try NSAIDs and if no response then refer
  • Consider referral to rheum for dactylitis, migratory joint pain and psoriasis, inflammatory back pain, enthesitis, FmHx of SpA, iritis, or unexplained erosions seen on x-ray evaluation.
Tasks ahead
unanswered questions

• With earlier detection can we alter the disease and damage it does?
• MRI scanning of SI joints can be vital in earlier diagnosis
• Are NSAIDs and TNF inhibition the best way to achieve remission
  as defined by preventing osteoproliferation and fat infiltration?

Personalize treatment is possible with improved understanding of the
  genetics and baseline characteristics that can predict response.
Thank You!

Questions?

Address questions to:
rick.pope@wchn.org
Dept of Rheumatology
Western CT Health Network
References

- www.the-rheumatologist.org/details/article/6139751
  *Rheumatologist* make progress defining the spectrum of axial spondyloarthritis
  Atul Deodhar MD

- Google images
- American College of Rheumatology-rheumatology.org
- Advanced Rheumatology Course on Spondyloarthritis-ACR