ANKYLOSING SPONDYLITIS: REVIEW AND UPDATE

MANISH RELAN, MD FACP RhMSUS
ARTHRITIS & RHEUMATOLOGY CARE CENTER, PA.
JACKSONVILLE, FLORIDA.
(904) 503-6999.
Final Stage of AS with Severe Kyphosis of Thoracic and Cervical Spine

Unable to look ahead while walking ("patient cannot see the sun")
Prevalence of SpA in US adults 20-69 years of age: the NHANES 2009-2010 survey

Axial SpA Usually Starts in the Third Decade of Life

- An onset after 45 years of age is exceptional.

Disease duration ≤ 5 years; data from 1993 to 1998, national database of the German Collaborative Arthritis Centres

Adapted from: Zink A et al. Ann Rheum Dis 2001;60:199-206 (with permission)
Age at First Symptoms and at First Diagnosis in Ankylosing Spondylitis Patients

Average delay in diagnosis: 9 years

The Role of Genes in Ankylosing Spondylitis

- Twin studies show the heritability of AS is >90%.¹
  - Nearly all of the risk of developing AS is determined by genes.
  - The environmental trigger for most AS is likely to be something very common.

- The severity of AS, including the rate of ankylosis, is mainly determined by genes.²
  - Heritability of radiographic severity is 62%.

² Brophy S et al. J Rheumatol 2004;31:1775-8
Concept of Spondyloarthritides (SpA)

- Non-radiographic axial SpA
  - Ankylosing Spondylitis
- Reactive arthritis
  - Psoriatic Arthritis
  - Arthritis with inflammatory bowel disease
- Undifferentiated SpA

- Predominantly Axial SpA
- Predominantly Peripheral SpA
Spondyloarthritis: Characteristic Parameters Used for Diagnosis

**Symptoms**
- Inflammatory back pain

**Imaging**

**Lab**
- ESR/CRP

**Patient’s history**
- Good response to NSAIDs
The Relationship Between Spondyloarthritis, Reactive Arthritis (ReA), and Septic Arthritis

- **Spondyloarthritis**
  - Bacterial role unproven
  - Adaptive immunity implicated
  - Sacroiliitis
  - Antibiotics ineffective

- **Septic arthritis**
  - Culturable pathogen in joint
  - Microbial virulence
    - > immune response
  - Monoarthritis
  - Antibiotics curative

- **Reactive arthritis**
  - Pathogen in joint in Chlamydia-induced ReA
  - Innate immunity implicated
  - Asymmetric oligoarthritis
  - Antibiotics may be effective

- **HLA-B27相关**

- **HLA-B27 unrelated**

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Gracey E et al. Nat Rev Rheumatol 2012;8:55-9 (with permission)
Spondyloarthritides (SpA)

- Undifferentiated SpA
- "Juvenile SpA"
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Arthritis associated with Ulcerative Colitis / Crohn’s Disease
- Reactive Arthritis
- Acute anterior Uveitis
## Ankylosing Spondylitis / Axial Spondyloarthritis

### Typical Manifestations

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>inflammatory back pain</td>
<td>71-75 %</td>
<td>75-80 %</td>
<td>3.1</td>
<td>0.33</td>
</tr>
<tr>
<td>enthesitis (heel pain)</td>
<td>16-37 %</td>
<td>89-94 %</td>
<td>3.4</td>
<td>0.71†</td>
</tr>
<tr>
<td>peripheral arthritis</td>
<td>40-62 %</td>
<td>90-98 %</td>
<td>4.0</td>
<td>0.67†</td>
</tr>
<tr>
<td>dactylitis</td>
<td>12-24 %</td>
<td>96-98 %</td>
<td>4.5</td>
<td>0.85†</td>
</tr>
<tr>
<td>anterior uveitis</td>
<td>10-22 %</td>
<td>97-99 %</td>
<td>7.3</td>
<td>0.80†</td>
</tr>
<tr>
<td>psoriasis</td>
<td>10-20 %</td>
<td>95-97 %</td>
<td>2.5</td>
<td>0.94†</td>
</tr>
<tr>
<td>inflammatory bowel disease</td>
<td>5-8 %</td>
<td>97-99 %</td>
<td>4.0</td>
<td>0.97†</td>
</tr>
<tr>
<td>positive family history for SpA</td>
<td>7-36 %</td>
<td>93-99 %</td>
<td>6.4</td>
<td>0.72</td>
</tr>
<tr>
<td>good response to NSAIDs</td>
<td>61-77 %</td>
<td>80-85 %</td>
<td>5.1</td>
<td>0.27</td>
</tr>
<tr>
<td>elevated acute phase reactants</td>
<td>38-69 %</td>
<td>67-80 %</td>
<td>2.5</td>
<td>0.63</td>
</tr>
<tr>
<td>HLA-B27 (axial involvement)</td>
<td>83-96 %</td>
<td>90-96 %</td>
<td>9.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Sacroiliitis on MRI</td>
<td>60-85 %</td>
<td>90-97 %</td>
<td>20.0*</td>
<td>0.41</td>
</tr>
<tr>
<td>Sacroiliitis (≥ grade 3) on x-rays</td>
<td>40%</td>
<td>98 %</td>
<td>20.0*</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Positive likelihood ratio (LR+) = sensitivity / (100 – specificity)
Negative likelihood ratio (LR-) = (100 – sensitivity) / specificity

* best estimate

† It is recommended to ignore a negative test result of these tests in an early state of possible axial SpA

Axial Spondyloarthritis

Non-radiographic stage
- Back pain
- Sacroiliitis on MRI

Radiographic stage
- Back pain
- Radiographic sacroiliitis
- Back pain
- Syndesmophytes

Modified New York Criteria 1984

Time (years)

ESSG-Classification Criteria
(European Spondyloarthropathy Study Group)

Inflammatory Back Pain or Synovitis
- asymmetric or
- predominantly in the lower limbs

plus one of the following:
- enthesitis (heel)
- positive family history
- psoriasis
- Crohn's disease, Colitis ulcerosa
- urethritis / cervicitis or acute diarrhea within one month before arthritis
- buttock pain (alternating between right and left gluteal areas)
- sacroiliitis

ASAS Classification Criteria for Spondyloarthritis (SpA)

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

Sacroilitis on imaging plus ≥1 SpA feature OR HLA-B27 plus ≥2 other SpA features

SpA features
- inflammatory back pain (IBP)
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn’s/colicis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

Sensitivity: 79.5%, Specificity: 83.3%; n=975

In patients with peripheral symptoms ONLY

Arthritis or enthesitis or dactylitis plus

≥1 SpA feature
- uveitis
- psoriasis
- Crohn’s/colicis
- preceding infection
- HLA-B27
- sacroilitis on imaging

OR

≥2 other SpA features
- arthritis
- enthesitis
- dactylitis
- IBP ever
- family history for SpA

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31 (with permission)
Sacroiliitis by MRI and X-ray in Patients with Axial Spondyloarthritis

Active inflammatory sacroiliitis without bony changes

Sacroiliitis with bony changes (grade II)
**Inflammatory Back Pain (IBP) According to Various Criteria**

<table>
<thead>
<tr>
<th>Calin et al.¹</th>
<th>Rudwaleit et al.²</th>
<th>IBP experts (ASAS)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>• age at onset &lt; 40 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• duration of back pain &gt; 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• insidious onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• morning stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• improvement with exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• morn. stiffness &gt; 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• improvement with exercise, not with rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• awakening at 2. half of the night because of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• alternating buttock pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• age at onset &lt; 40 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• insidious onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• improvement with exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• no improvement with rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• pain at night (with improvement upon getting up)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IBP if 4 / 5 are present.  
IBP if 2 / 4 are present.  
IBP if 4 / 5 are present.

Diagnostic Pyramide for Axial Spondyloarthritis

- Chronic low back pain
- Inflammatory back pain + LR 3.1
- Heel pain (enthesitis) + LR 3.4
- Peripheral arthritis LR 4.0
- Dactylitis LR 4.5
- Acute anterior uveitis LR 7.3
- Pos. family history LR 6.4
- Good response to NSAIDs LR 5.1
- Elevated acute phase reactants LR 2.5
- HLA-B27 + LR 9.0
- Sacroiliitis on MRI LR 20.0
- Sacroiliitis (≥ grade 3) on x-rays LR 20.0

LR = likelihood ratio

3.1 x 3.4 x 9.0 = 94.9
(LR product)

83 %

Diagnostic Pyramide for Axial Spondyloarthritis

- Chronic low back pain
  - Inflammatory back pain + LR 3.1
  - Heel pain (enthesitis) + LR 3.4
- Peripheral arthritis LR 4.0
- Dactylitis LR 4.5
- Acute anterior uveitis LR 7.3
- Pos. family history LR 6.4
- Good response to NSAIDs LR 5.1
- Elevated acute phase reactants LR 2.5
- HLA-B27 + LR 9.0
- Sacroiliitis on MRI + LR 20.0
- Sacroiliitis (≥ grade 3) on x-rays LR 20.0

LR = likelihood ratio

3.1 x 3.4 x 9.0 x 20.0 = 1897 (LR product)

99%

Structural Damage in AS: More Ankylosis of the Spine in Males Compared to Females

Male patients

Female patients

Percentage of patients

Duration since occurrence of first spondyloarthritic symptoms

grade I

grade II

grade III

grade IV

N = 24
71 101 137 148 131 131 77 31 18

N = 15
34 67 79 82 57 32 23 9 7

grade I – no radiographic changes
grade II – radiographic sacroiliitis only
grade III – partial ankylosis of the spine
grade IV – total ankylosis of the spine

Feldtkeller E. Aktuelle Rheumatologie 1998;23:176–81
Developing Syndesmophytes over 2 Years in Ankylosing Spondylitis

Progression from syndesmophytes to bridging syndesmophytes

Progression of bridging syndesmophytes

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)
Frequency of Severe Pain Decreases in Male Patients with AS after a Long Disease Duration but not in Female Patients

Feldtkeller E. Aktuelle Rheumatologie 1998;23:176–81
Vertebral Fracture (arrow) in Advanced Ankylosis of the Spine with Fusion of the Facet Joints

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)
ASAS/EULAR Recommendations for the Management of AS: Overarching Principles

1. AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.

2. The primary goal of treating the patient with AS is to maximise long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation.

3. Treatment of AS should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

4. The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.
1. The treatment of AS should be tailored according to
   
   - the current manifestations of the disease (axial, peripheral, entheséal, extra-articular symptoms and signs),
   - the level of current symptoms, clinical findings, and prognostic indicators,
   - the general clinical status (age, gender, co-morbidity, concomitant medications, psychosocial factors).
ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis

Education, exercise, physical therapy, rehabilitation, patient associations, self help groups

NSAIDs

Axial disease

Peripheral disease

Sulfasalazine

Local corticosteroids

TNF Blockers

Dosage of NSAIDs Used to Treat Ankylosing Spondylitis

<table>
<thead>
<tr>
<th>drug</th>
<th>half-life (hours)</th>
<th>approved maximal daily dosage -normally for arthritis- (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>about 4</td>
<td>200</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>8-12</td>
<td>400</td>
</tr>
<tr>
<td>Diclofenac*</td>
<td>about 2</td>
<td>125-150</td>
</tr>
<tr>
<td>Etoricoxib#</td>
<td>about 22</td>
<td>90</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.8-3.5</td>
<td>2400-3200</td>
</tr>
<tr>
<td>Indomethacin*</td>
<td>about 2</td>
<td>150-200</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1.5-2.5</td>
<td>200-300</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>about 20</td>
<td>15</td>
</tr>
<tr>
<td>Naproxen</td>
<td>10-18</td>
<td>1000</td>
</tr>
<tr>
<td>Phenylbutazone#</td>
<td>50-100</td>
<td>600</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>30-60</td>
<td>20</td>
</tr>
</tbody>
</table>

*retard formula available
# not approved in the US

Adapted from Song IH et al. Arthritis Rheum 2008;58:929-38
Possible Screening Approach for Axial SpA Among Patients with Chronic Low Back Pain

- Chronic Back Pain (> 3 months)
- First symptoms < 45 years of age

**Inflammatory back pain**
- sensitivity: 75% specificity 76%
- about 1 out of 5 patients has axial SpA, if positive
- simple to apply: yes
- costs: low

**HLA-B27+**
- sensitivity: 80-90%, specificity 90%
- about 1 out of 3 patients has axial SpA, if positive
- simple to apply: yes
- costs: moderate (only once)

**Sacroilitis on any imaging**
- only if available
- not recommended for screening

Refer to Rheumatologist