Ankylosing Spondylitis

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Disclosures

• No financial relationships to disclose
Objectives

- Understand the definition of ankylosing spondylitis as one of the seronegative spondyloarthropathies.
- Learn how the diagnosis of ankylosing spondylitis is made.
- Learn treatment options.
- Understand the long-term outcome of treated and untreated disease.
Spondyloarthopathies (SpAs)

- Definition: group of inflammatory arthropathies that share distinctive clinical, radiographic, and genetic features and include:
  - Ankylosing spondylitis (AS)
  - Reactive arthritis (ReA, Reiter’s syndrome)
  - Psoriatic arthritis
  - Enteropathic arthritis (Crohn’s, ulcerative colitis)

Spondyloarthopathies (SpAs)

- Patients not fulfilling individual criteria but possessing overlapping features may be classified as having undifferentiated SpA (uSpA).
- Prevalence of all SpAs ~1% to 2%, similar to rheumatoid arthritis (RA).
- Associated with presence of HLA-B27.

HLA - B27

- Human Leukocyte Antigen.
- MHC class I - participates in antigen presentation.
- Genetic marker with disease association.
- >90 % of patient with ankylosing spondylitis.
- 50-75% of patients with other spondyloarthropathies.
- Present in 5-15% of general population.
- <5% of patients with HLA-B27 will develop a spondyloarthropathy.
# Spondyloarthropathies: Seronegative inflammatory back arthritis

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SERONEGATIVE</th>
<th>SEROPOSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Arthritis</td>
<td>Usually asymmetric Large joints Lower extremity</td>
<td>Usually symmetric Small and medium sized joints Upper and lower extremities</td>
</tr>
<tr>
<td>Axial Involvement</td>
<td>SI joints Apophyseal joints of the spine</td>
<td>Almost never Rarely</td>
</tr>
<tr>
<td>Enthesitis (tendon insertion)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Periostitis</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>Achilles, plantar fascia</td>
<td>Finger tendons</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>Never</td>
<td>Often</td>
</tr>
<tr>
<td>Iritis</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Aortic root dilatation</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Scaly skin rash</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Bowel inflammation</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Uretheritis</td>
<td>Common</td>
<td>Unusual</td>
</tr>
</tbody>
</table>
## Spondyloarthropathies: Differentiating Inflammatory vs. Mechanical Back Pain

<table>
<thead>
<tr>
<th>Features</th>
<th>Inflammatory Back Pain</th>
<th>Mechanical Back Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM Stiffness</td>
<td>Usually prolonged &gt;60 min.</td>
<td>Minor &lt;45 min.</td>
</tr>
<tr>
<td>Max. Pain/Stiffness</td>
<td>Early AM</td>
<td>Late in day</td>
</tr>
<tr>
<td>Exercise/Activity</td>
<td>Improves symptoms</td>
<td>Worsens symptoms</td>
</tr>
<tr>
<td>Duration</td>
<td>Chronic</td>
<td>Acute or Chronic</td>
</tr>
<tr>
<td>Age at onset</td>
<td>12-40 yrs (peak 25 yrs)</td>
<td>20-65 yrs</td>
</tr>
<tr>
<td>Radiographs</td>
<td>Sacroiliitis, Syndesmophytes, Spinal ankylosis.</td>
<td>Osteophytes, Disc space narrowing, Malalignment.</td>
</tr>
</tbody>
</table>
SpAs: Axial Features

- Spine – inflammation, stiffening, and ankylosis
  - Cervical
  - Thoracic
  - Lumbar
- SI joints – sacroiliitis and fusion
- Hips – synovitis and cartilage degeneration
SpAs: Extra-axial Features

- Cutaneous—keratoderma blennorrhagicum and psoriasis or nail lesions (onycholysis, dystrophy, pitting)
- Periarticular—dactylitis, enthesitis, tendonitis
- Ocular—uveitis, conjunctivitis
- Gastrointestinal
  - Painless oral ulcerations
  - Asymptomatic gut inflammation
  - Symptomatic colitis
- Genitourinary—urethritis, vaginitis, balanitis
- Cardiac—aortitis, valvular insufficiency, heart block
<table>
<thead>
<tr>
<th>Feature</th>
<th>Ankylosing Spondylitis</th>
<th>Psoriatic</th>
<th>Reactive Arthritis</th>
<th>IBD associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>9:1</td>
<td>1:1</td>
<td>8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age of onset</td>
<td>20s</td>
<td>35-45 yrs</td>
<td>20s</td>
<td>Any age</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>25%</td>
<td>96%</td>
<td>90%</td>
<td>Common</td>
</tr>
<tr>
<td>Distribution</td>
<td>Axial, lower limbs</td>
<td>Any joint</td>
<td>Lower limbs</td>
<td>Lower limbs</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Uncommon</td>
<td>35%</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>100%</td>
<td>40%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Skin Lesions</td>
<td>Rare</td>
<td>100%</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Type of skin lesions</td>
<td>Nil specific</td>
<td>Psoriasis vulgaris</td>
<td>Keratoderma Blenorrhagica, Circinate balanitis</td>
<td>Pyoderma grangrenosum, E. Nodosum</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Rare</td>
<td>Occasional</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Rare</td>
<td>Occasional</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Aortic</td>
<td>Occasional</td>
<td>Rare</td>
<td>Occasional</td>
<td>Occasional regurgitation</td>
</tr>
<tr>
<td>Familial Aggregation</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>90%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Etiology Factors

- Interplay between genetic, environmental, and immunological factors.

- Increase in HLA B27:
  - Concordance rate of 67% for monozygotic twins, 23% for dizygotic twins.
  - Molecular mimicry theory based on similarity between bacterial epitopes and HLA B27.
  - Arthritogenic peptides preferentially presented.
    - Oxidation of cysteine 67 in recognition pocket.
    - Free B27 heavy chains bind as homodimer to activate CD4+.

- Chromosome 4 and chromosome 14 may also be important.
Prevalence of SpAs Varies With Geographic Region

<table>
<thead>
<tr>
<th></th>
<th>SpA</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan (total population)</td>
<td>0.0095%</td>
<td>&lt;1.0%</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.12%</td>
<td>Not availab</td>
</tr>
<tr>
<td>Germany (adults)</td>
<td>1.9%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Russia and Alaska</td>
<td>2.0% to 3.4%</td>
<td></td>
</tr>
<tr>
<td>Eskimo (adults)</td>
<td>2.5%</td>
<td>&gt;20.0%</td>
</tr>
</tbody>
</table>

Ankylosing Spondylitis

- Men: women affected 9:1
- Usually axial disease, including shoulder, hips.
- Inflammatory back pain at night (awaken 2AM to 5AM).
- Peripheral arthritis usually occurs late in the illness:
  - Early is a predictor of progression
  - Usually asymmetric in LE
- Enthesitis, arthritis is aggravated by rest and improved with activity.
- Extra-articular:
  - Iritis, particularly acute anterior uveitis (20-30 % of patients)
  - Cardiac manifestations, including dilatation of aortic root and conduction deficits
  - Apical fibrosis of the lungs
  - Amyloidosis
  - Aspergilloma
  - Cauda equina syndrome
Ankylosing Spondylitis in US

- Diagnosed and treated: 146,000
- Undiagnosed/untreated: 179,000

Mild disease: 55,000
Moderate disease: 44,000
Severe disease: 25,000
Fused: 23,000

Age at Onset and Diagnosis of AS

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptom Onset</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Germany (N=1486)</td>
<td>28.5 years</td>
<td>33.7 years*</td>
</tr>
<tr>
<td>Europe (tri-nation) (N=210)</td>
<td>22.7 years</td>
<td>31.9 years</td>
</tr>
</tbody>
</table>

*Age when first seen by rheumatologist.

HLA-B27 and Disease Expression

- HLA-B27+ individuals more likely to have earlier onset, sacroiliitis, spondylitis, acute anterior uveitis, and more severe clinical course.
- HLA-B27- patients more likely to develop peripheral arthritis, skin and nail disease, or inflammatory bowel disease.
- Thus, HLA-B27+ increases risk of spondylitis and uveitis.

|                                    | NY Criteria 1968 | Modified NY Criteria 1984 | ASAS 2009  
( Assessment of Spondyloarthritis International Society) |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical:</strong></td>
<td></td>
<td></td>
<td>Back pain &gt; 3 months and Age of onset &lt; 45 years</td>
</tr>
<tr>
<td>1. Limitation of LS motion in all planes</td>
<td></td>
<td>1. Low back pain of at least 3 months duration improved by exercise and not relieved by rest</td>
<td>Plus Sacroiliitis on imaging study or HLA-B27 positivity</td>
</tr>
<tr>
<td>2. Pain in the thoracolumbar junction or the lumbar spine</td>
<td></td>
<td>2. Limitation of LS in sagittal and frontal planes</td>
<td>And 2 or more of the following:</td>
</tr>
<tr>
<td>3. Limitation of chest expansion to 2.5 cm</td>
<td></td>
<td>3. Chest expansion decreased relative to normal for age and sex</td>
<td>- inflammatory back pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Enthesitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Uveitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Dactylitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Psoriasis</td>
</tr>
<tr>
<td><strong>Radiological grading</strong></td>
<td></td>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>0=normal</td>
<td></td>
<td></td>
<td>Response to NSAIDs</td>
</tr>
<tr>
<td>1=suspicious</td>
<td></td>
<td></td>
<td>Family history of spondyloarthropathy</td>
</tr>
<tr>
<td>2=minimal sacroiliitis</td>
<td></td>
<td></td>
<td>Elevated CRP</td>
</tr>
<tr>
<td>3=moderate sacroiliitis</td>
<td></td>
<td>Bilateral sacroiliitis grades 2-4</td>
<td>Normal Radiographs</td>
</tr>
<tr>
<td>4=ankylosis</td>
<td></td>
<td>Unilateral sacroiliitis grades 3-4</td>
<td></td>
</tr>
</tbody>
</table>
AS & ASAS Classification Criteria

- **AS Criteria**
  - Modified New York Criteria\(^1\)
    - Relies mainly on detection of radiologic sacroiliitis.

- **ASAS Criteria**
  - Assessment of SpondyloArthritis International Society
    - Allows classification BEFORE radiographic changes occur.

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Radiologic Changes in AS

- SI joints commonly initial sites of inflammation
  - NY criteria:
    - Grade 1: suspicious
    - Grade 2: erosions and sclerosis
    - Grade 3: erosions, sclerosis, ankylosis
    - Grade 4: total ankylosis

- Thoracolumbar junction with subsequent caudal and distal progression.

- Squaring of vertebra is followed by development of syndesmophytes.

- Total ankylosis occurs with ossification of the longitudinal ligaments.

- Enthesitis can be detected as spurs at the insertion of plantar fascia.
Ankylosing Spondylitis
Disease Progression
Prognosis

- First symptoms generally occur in the early 30’s (average age 26).
- Rare to present after age 40.
- Deformities and disability occur within the first 10 years.
- Work disability is associated with older age, longer disease, co-morbidity, severe functional disability.
- Survival is reduced by RR 1.93 vs non-affected population.
Treatment in AS

- Physical therapy
- Regular exercise program
- Patient education
- Pharmacological treatment
Non-pharmacologic Treatment

- Hospital vs home program.
- Spa therapy.
- Group physical therapy.
  - Advantage cost savings.
- Individualized exercise program-important.
- Sleeping in a straight position with thin pillow preferred.
- Avoid:
  - Prolonged immobility
  - Poor posture
  - Smoking
  - Excessive spinal manipulation
Nonsteroidal Antiinflammatory Drugs (NSAIDs) in AS

- NSAIDs are first-line treatment for AS
  - Diclofenac, enteric coated aspirin, indomethacin, naproxen, phenylbutazone, sulindac, and celecoxib.
- Relieve back pain and stiffness.
- Rapid response (48 hours) has been included in classification criteria.
- As the disease progresses, these drugs may be less effective.
- Some evidence that NSAIDs (Cox-2) inhibit disease progression.
Glucocorticoids in AS

- Oral glucocorticoids limited efficacy.
  - Axial and peripheral joint pain may respond in short term, however long-term use with significant side effects.
- Local glucocorticoid injections of joints and entheses may be helpful temporarily.
  - Particularly into SI joints.
- Topical glucocorticoids for acute anterior uveitis is effective.
Traditional DMARDs in the Treatment of SpA

- Disease-modifying antirheumatic drugs (DMARDs) are sometimes used in SpAs when NSAIDs are inadequate.
- Recommendations to fail 2 NSAIDs.
- None of the DMARDs are FDA approved for the SpAs.
- Few controlled clinical trials address the use of traditional DMARDs in SpAs.
Sulfasalazine in AS

- Ankylosing Spondylitis
  - 264 pts/placebo/36 weeks/SSZ 2000mg/d
  - No clinical improvement/decreased ESR
  - Trend for SSZ in peripheral arthritis
  - Minimal toxicity
Sulfasalazine in SpAs

- 619 patients (AS, psoriatic arthritis, and ReA)
  - Axial disease (n=187)
  - Peripheral articular (n=432)
  - Placebo or 2 g/day sulfasalazine
  - 36 weeks

- Axial—no sulfasalazine response
- Peripheral—sulfasalazine response ($P=0.0007$)
- Conclude sulfasalazine effective for peripheral arthritis of SpAs

Methotrexate (MTX) in AS

- AS¹
  - 51 patients, 7.5 mg/week for 12 months, placebo controlled
  - Negative results/improved peripheral joints (?)
- AS²
  - 31 patients, 7.5 mg/week for 6 months, placebo controlled
  - Significantly more patients had good response with MTX than placebo (53% vs 13%, $P=0.019$)

Oral Gold in AS

- Auranofin
- 238 patients
  - 6 mg/day
  - 6 months, placebo controlled
- Improvements in physician global and daily function scores.
- No effect on axial skeleton.
- 10% withdrawal due to adverse effects or toxicity.

Pamidronate in AS

- Bisphosphonate bone-resorption inhibitor.
- 84 AS patients with active disease refractory to NSAIDs.
  - Randomized, double-blinded assignment.
  - Infusions of 60 mg vs 10 mg pamidronate/month for 6 months.
- Significant improvement in axial symptoms in the 60-mg group vs 10-mg group.
- No significant difference in joint pain or C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR)
- Well tolerated, low withdrawal rate

Leflunomide in AS

- Open-label, 24-week study of 20 NSAID-refractory patients
  - Primary outcome $\geq 25\%$ BASDAI reduction
  - 50% discontinued for lack of efficacy, side effects, or noncompliance
  - No significant change in BASDAI or a number of other component measures
  - Peripheral symptoms showed significant improvement with leflunomide

Thalidomide in AS

- Despite well-known teratogenic effects, useful in several different diseases.
- 26 AS patients
  - 12-month, open-label trial
  - 200 mg/day
- 80% had improvement >20% in 4 of 7 indices.
- 9 patients became pain free.
- Appears to act by decreasing expression of tumor necrosis factor (TNF) and other proinflammatory cytokines.

Summary: Traditional DMARDs in AS

- Few well-designed studies exist.
- No evidence of true “disease modification”.
- Response generally favors peripheral disease over axial disease.
  - Pamidronate is an exception
- Preliminary data suggest oral agents that potentially affect TNF expression (leflunomide and thalidomide) may be beneficial.
Rationale for TNF Inhibition in AS

- Overexpression of TNF in mouse model produces an AS-like disease\(^1\)
- Serum and joint fluid/tissue of AS patients have elevated levels of TNF\(^2,3\)
- Success with TNF inhibitors in psoriatic arthritis, which is an SpA\(^4,5\)

TNF inhibitors in AS

- FDA approved TNF inhibitors for AS
  - Etanercept (Enbrel)
  - Infliximab (Remicade)
  - Adalimumab (Humira)
  - Golimumab (Simponi)
MRI of Sacroiliac and Spinal Inflammation of an AS Patient Before and After Therapy With Infliximab


35-year-old AS patient, 6-y disease duration
TNF Inhibitor Safety

• Safer than traditional DMARDs:
  – Less osteoporosis; less bone marrow, hepatic and renal toxicity; less infection and neoplasm.

• TNF inhibition is associated with some safety issues.
  – Common: upper respiratory infection.
  – Rare: tuberculosis and other opportunistic infections.
Summary: TNF Inhibitors in AS

- Biologic rationale based on human and animal studies.
- TNF inhibitors are effective in AS disease activity and show significant impact on spinal symptoms.
- Differences among individual agents, but TNF inhibitors are generally safe in AS.
- TNF inhibitors offer great symptomatic and functional benefits as measured by mobility.
- True disease modification is under study with long-term imaging studies.
AS Treatment Summary

- Regular exercise program.
- NSAIDs (fail at least 2).
- Sulfasalazine or MTX for peripheral arthritis.
- Anti-TNF for purely axial disease or concomitant inflammatory bowel disease.
- Corticosteroid injections for SI joint pain.
- No treatment modality treats all aspects of disease.
- Conventional therapies do not halt disease progression.
- Combinations of modalities are required.
Conclusions

• New therapies are available to reduce symptoms and have the potential to modify disease progression.
• Earlier diagnosis and referral will enable eligible patients to receive the appropriate therapy.
• New studies are underway to determine effect of new therapies on structural progression of AS.
# New Approaches to AS Treatment

<table>
<thead>
<tr>
<th>Old Approach</th>
<th>New Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphasis on symptoms</td>
<td>Emphasis on limiting progression</td>
</tr>
<tr>
<td>Less aggressive</td>
<td>Earlier aggressive therapy</td>
</tr>
<tr>
<td>Single agents</td>
<td>Use of biologic agents or combination therapy</td>
</tr>
<tr>
<td>Toxicity frequent</td>
<td>Limit toxicity</td>
</tr>
</tbody>
</table>
How to Refer a Patient

• Consider rheumatologic disease
  – Classic presentations
• Appropriate X-rays and lab studies helpful prior to referral
• Call or Fax referral
  – Phone (907) 562-2277
  – Fax (907) 563-3460
• All referrals are reviewed
• We will contact patient to schedule if appropriate
QUESTIONS?