Patient-centered Management of Spondyloarthropathies: Current Evidence

Current Evidence and Best Practices for Identification, Differentiation, and Treatment

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Disclosures

• Consulting Fee: Amgen, GlaxoSmithKline, Horizon, Janssen, Pfizer, Regeneron, Sanofi, UCB
• Speakers Bureau: AbbVie, Bristol-Myers Squibb, Crescendo, Genentech, Janssen, UCB

Disclosures

• Leonard Calabrese, DO
  - Amgen Consulting, Teaching and Speaking
  - Biogen Consulting
  - Crescendo Consulting, Teaching and Speaking
  - Genentech/Roche Consulting, Teaching and Speaking
  - Janssen Consulting, Data Safety Monitoring Board
  - Idec Consulting
  - Pfizer Consulting, Data Safety Monitoring Board
  - Roche Pharmaceuticals Consulting
  - Savient Consulting
  - UCB Consulting

• The following faculty have indicated they have no relationship which, in the context of their presentation(s), could be perceived as a potential conflict of interest:
  - M. Elaine Husni, MD, MPH
Case

- A 37-year-old woman with mild SLE began to experience back pain over 12 months. It began as a nagging, localized pain in the central lumbar area and then radiated to both buttocks.
- Her examination was normal, except for limited flexion. Pelvis and LS plain films were normal and, ultimately, a LS MRI was normal as well.
- She was treated with NSAIDS and PT, which helped a bit. Ultimately, her pain was so severe in the mornings that she was unable to wipe herself after using the toilet.

LS = lumbosacral; MRI = magnetic resonance imaging; PT = physical therapy; SLE = systemic lupus erythematosus.

Case (continued)

- After 12 months, the physiatrist suggested a rheumatology consult for possible “ankylosing spondylitis” (!)
- On evaluation, her back pain was worse in the morning, was chronic, and was partially better with exercise and NSAIDS.

Learning Objectives

- Discuss the spectrum of SpA diseases based on clinical presentation and assessment
- Outline the role of imaging modalities (radiographic and MRI) in the diagnosis of early SpA
- Apply guidelines and evidence to the diagnosis and classification of axSpAs earlier in the progression of disease
- Outline the safety, efficacy, and role of available and emerging treatment modalities for SpAs
- Develop collaborative care efforts that improve the management of patients with SpAs

axSpA = axial spondyloarthritis; SpA = spondyloarthropy.
History of Spondyloarthritis

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Progression of Ankylosing Spondylitis


Skeleton described by Bernard Connor (1685)
**Nosology**

- Vladimir Bekhterev, 1892
- Adolph Strümpell, 1884; 1897
- Pierre Marie, 1898

**William Osler and Ankylosing Spondylitis (7th Edition)**

- Recognized
  - Von Bechterew form, “limited to the spine”
  - Strümpell-Marie form, affecting spine and fusion of large joints
  - Noted to be limited to the neck, rib fusion, and male predominance but also “nerve–roots causing great pain”
- “Both appear to be forms of arthritis deformans and should neither be regarded nor described as separate diseases.” (1920 edition)

**The Importance of Sacroiliac Changes in the Early Diagnosis of Ankylosing Spondylitis**

- “From the examination of 153 cases of ankylosing spondyloarthritis, it appears that sacro-iliac joints are roentgenographically involved in over 98 percent of the cases.”

Lumpers

- Rheumatoid arthritis
- Rheumatoid variants, including AS, PsA, and ReA
- US view largely believed AS to be an RA-like disease, with similar synovial changes in peripheral joints
- "Rheumatoid spondylitis"

Short, Bauer, and Reynolds 1957; "AS was spinal localization of RA"

Splitters

- From the 1950s on
- Rose-Waaler, 1948
- Male predominance, uveitis, absence of nodules, different joints, lack of response to gold
- 1963 American Rheumatism Association
- "Ankylosing spondylitis"

Terminology and Classification 1950-1963

AS = ankylosing spondylitis; PsA = psoriatic arthritis; ReA = reactive arthritis.


Heredity and Genetics

- 1973 LANDMARK DISCOVERY
  - Brewerton et al, London
  - Schlossstein et al, Los Angeles
  - Clearly established that AS and RA were distinct
  - Paved way for appropriate classification
  - New concepts in pathogenesis


Outline

- The problem of LBP in nonrheumatologic practice
- Classification versus diagnostic criteria in AS or SpA
- The concept of SpA – the new paradigm
- Delay in diagnosis
- Inflammatory back pain as an epidemiologic tool
- X-ray and imaging findings
- Critical pathways

LBP = low back pain.
Low Back Pain

- LBP is common, with 20% of the population experiencing in 1 month and two-thirds in a lifetime
- Majority is self-limiting and of unknown origin in 85%
- 10% to 28% of individuals experience pain of >12 weeks (chronic LBP)
- One important cause of CLBP is spondyloarthritis (0.9% to 1.4% prevalence) – a diagnosis easily missed in primary care practices

CLBP = chronic low back pain.

SpA Spondyloarthritis

- The diagnosis of SpA is challenging, given the general lack of specific symptoms or referral tools by which it can be readily discriminated from other causes of LBP.
- In a study of 634 patients with CLBP (aged 20 to 45 years) in Dutch primary care, 24% fulfilled ASAS criteria for SpA.

ASAS = Assessment of SpondyloArthritis International Society.

LBP in Osteopathic Ambulatory Care

- In the National Ambulatory Medical Care Survey (2003-2004), 61.7 million visits for LBP were reported.
- Osteopathic physicians were more likely to provide care for LBP and CLBP (OR: 4.39; 95% CI: 2.5, 7.8), including patients aged 20 to 45 years
- Osteopathic physicians were less likely to utilize NSAIDS

Cl = confidence interval; OR = odds ratio.
The Problem and the Solution

- If osteopathic primary care providers see CLBP at rates higher than other physicians, it is assumable that they see an enriched population of patients with SpA.
- SpA is highly treatable with PT, NSAIDS, and biologic therapeutics.
- What tools may be available to aid in the recognition, assessment, treatment, and referral selection for diagnostic confirmation and advanced care?

SpA is not just Ankylosing Spondylitis

Spondyloarthritis

IBD = inflammatory bowel disease
Case

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• Her examination was normal except for limited flexion. Pelvis and LS plain films were normal and, ultimately, an LS MRI was normal as well.
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Case (continued)

• After 12 months, the physiatrist suggested a rheumatology consult for possible “ankylosing spondylitis” (!)
• On evaluation, her back pain was worse in the morning, was chronic, and was partially better with exercise and NSAIDS.
• An MRI of her pelvis was obtained.

Return to our Case

• Next logical step(s)
X-ray of Pelvis

STIR IMAGES OF SI JOINT WITH BONE MARROW EDEMA

SI = sacroiliac; STIR = short inversion time inversion recovery

Challenges to the Recognition and Diagnosis of SpA in Ambulatory Care
Progression of Ankylosing Spondylitis


Delay in the Diagnosis of AS 5 to 9 Years

$\text{STEP 1: Classification of SpA According to the Symptoms}$

- Predominant peripheral manifestations
  - Peripheral arthritis
  - Enthesitis
  - Dactylitis

- Predominant axial involvement
  - Inflammation of the sacroiliac joints
  - Inflammation of the spine
What Are We Going to Discuss Today?

- What is SpA today?
- How many people in the United States have SpA?
- How do we diagnose SpA?
  - Imaging
  - Inflammatory back pain
  - Genetics
- Treating SpA – does it make a difference?
- Patients today with SpA – different from what I learned in medical school

Concept of Spondyloarthritis

Spondyloarthritis

Axial  Peripheral
Non-radiographic Axial Spondyloarthritis  Undifferentiated Spondyloarthritis
Ankylosing Spondylitis  Reactive Arthritis
Psoriatic Arthritis
IBD Arthritis
Features that were “Atypical” but Typical Today

- Woman
- Older-age onset
- B27 negative
- Peripheral arthritis at onset
- Back pain not necessarily present at onset
- Adverse reaction to anti-TNF drugs
- Less responsive to anti-TNF drugs

TNF = tumor necrosis factor

Inflammatory Back Pain as an Entry to AS/SpA Detection

20% of people have chronic back pain
5% will have AS
5% to 6% have inflammatory back pain
14% will have SpA

Of those with nrSpA, 12% develop SpA in 1 year
70% lifetime

nrSpA = non-radiographic axial spondyloarthritis
Test Operating Characteristics

- B27, which alone is 95% sensitive but only 20% specific

Test Operating Characteristics

- Age at onset <40 years
- Duration of pain >3 months
- Insidious onset
- Improvement in pain with exercise
- Presence of morning stiffness

A simple, cheap, reproducible screening technique compared with B27, which alone is 95% sensitive but only 20% specific.

Who has SpA Today, Using Clinical Criteria?

- 1% of the general population
- 3% of HLA-B27 positive
- 5% of chronic low back pain
- 15% of inflammatory back pain (IBP)
- >25% of age <45 IBP with other features
Examination

- Tenderness
- Mobility
- Movement
- Neurologic/MST

Classification of SpA According to the Symptoms

- Predominant axial involvement
  - Inflammation of the sacroiliac joints
  - Inflammation of the spine

- Predominant peripheral manifestations
  - Peripheral arthritis
  - Enthesitis
  - Dactylitis
  - Chest pain

CASE: Peripheral SpA

- A 43-year-old male basketball coach was referred for anterior chest pain of 3 years’ duration. The pain was located over the 2nd costochondral areas (right and left) and was very tender. X-ray was negative. The area was injected, with temporary relief. All laboratory results (ESR, CBC, CMP, etc.) were normal.
- He also had a history of plantar fasciitis and nonspecific LBP (normal LS spine films and MRI) for which he was receiving chiropractic treatment.
- He had a 20-year history of mild psoriasis.
- He was found to be HLA-B27 positive.

CBC = complete blood count; CMP = comprehensive metabolic panel; ESR = erythrocyte sedimentation rate.
X-ray and Imaging in the Diagnosis of SpA

SpA is More than Back Pain: Past History

- Response to NSAIDs
- Family history
- Genetic testing
  - HLA-B27

Predisposing Concomitant Diseases

- Infection*
- Psoriasis
- Crohn’s Disease

*Positive staining for chlamydia.

40% to 60% with anterior uveitis have SpA

STEP 2: Role of Imaging in the Diagnosis of SpA
SpA Evolution

Non-radiographic stage
- Back pain
- Sacroiliitis on MRI

Radiographic stage
- Modified New York Criteria 1984
- Back pain
- Radiographic sacroiliitis
- Back pain
- Syndesmophytes

Time (years)

Ankylosing Spondylitis
Radiographic Features

Sacroiliitis Grade 0 (Normal)

References:
The Role of MRI

- MRI is the imaging option of choice for patients with suspected axSpA and normal plain x-rays
  - T2 fat-suppressed sequences (STIR) bone marrow edema (BME)
  - T1 reveals structural damage such as erosions, sclerosis, fat deposition, and ankylosis
    - Gadolinium is not indicated

Spectrum of axSpA

Patients with chronic back pain ≥3 months and age of onset <45 years

- axSpA (ASAS criteria)
- AS (mNY criteria)
- Preradiographic axSpA
  - Generally presenting with inflammatory back pain
  - Does not meet mNY criteria
  - Observational studies suggest that 12% of individuals develop AS over 1 year and 70% develop it over a lifetime
  - QOL–SF-36 and BASDAI are comparable to AS
  - Although not approved, TNF inhibitors are effective in treating nonradiographic SpA

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; mNY = modified New York Criteria; QOL = quality of life.
Step 3: Laboratory Testing

**Symptoms**
- IBP
- Enthesitis
- Urethritis

**Imaging**
- Sacroilitis - X-ray
- Sacroilitis - MRI

**Lab**
- ESR / CRP

CRP = C-reactive protein.

SpA Tools for Diagnosis: Laboratory

**GENETICS**
- B27

- Present in 65% to 89% of SpA
- Present in 8% of the general population
- Elevated in 50% to 80% of SpA (when active)
- Very low specificity

Clinical Conceptualization of the Natural History of axSpA
Treatment of SpA

• GOALS
  – Reduce signs and symptoms, maintain/improve function, improve QOL
  – Manage comorbidities
    • IBD, psoriasis, uveitis, etc
    • Cardiovascular disease risk reduction, metabolic complications
  • PT for all
    – Active exercise, posture training, flexibility
  • Osteopathic manipulative treatment with caution (occult fusion)

Treatment of SpA

• STEP 1
  – Full-dose, continuous NSAIDS
  – >3 months
  – Improve signs/symptoms, QOL, possible retarding of progression

Treatment of SpA

• STEP 2
  – Biologics for all who are incompletely controlled or who have adverse events from NSAIDS
  – All improve signs and symptoms, QOL, function, and possible retardation of radiographic progression
    • TNF inhibitor (etanercept, adalimumab, infliximab, certolizumab, golimumab)
    • IL12/23 i – ustekinumab
    • IL17i – secukinumab
    • More on the way
Efficacy of TNFα Inhibitors

ASAS 40 Responses in 5 separate trials

<table>
<thead>
<tr>
<th>TNFα inhibitor</th>
<th>Etanercept</th>
<th>adalimumab</th>
<th>infliximab</th>
<th>golimumab</th>
<th>certolizumab</th>
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<td>39</td>
<td>47</td>
<td>68</td>
<td>48</td>
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</tbody>
</table>


Anti-TNFα-Therapy Over 2 Years Does not Inhibit Radiographic Progression

The Impact of Tumor Necrosis Factor α Inhibitors on Radiographic Progression in Ankylosing Spondylitis

Nhit Haroon,1 Robert D. Innis,3 Thomas J. Leach,1 Michael H. Weinblatt,1 Mislija Loz0,1 Mohamed H. Kahhale,1 Michael M. Ward,1 John D. Reveille,1 and Lianna S. Golden1

TNFα-inhibitors and Radiographic Progression

Not only the use of TNF-inhibitors but also the total duration and delay in starting therapy are important in determining the rate of radiographic progression.

Probability of No Progression

Real-life Approach to the Recognition of SpA in Ambulatory Care
SpA Diagnosis in Ambulatory Care

- Complex
- No single laboratory test or clinical finding
- X-rays often are normal or equivocal early
- MRI helpful but can be misinterpreted
- Ultimately guided by clinical findings, imaging, AND laboratory tests
- Referral in cases of indeterminate specificity essential

Algorithm for the Diagnosis or Exclusion of Axial Spondyloarthritis

- Appropriate clinical context
- “Must rule outs” ie, infection, cancer, etc.
- Comorbidities: fibromyalgia, mood disorders, structural disease

Ambulatory Care Strategies for CLBP

- Red flags? Must rule outs –
  CANCER INFECTION
    1. History of cancer
    2. Urinary dysfunction
    3. Low back pain associated with fever, chills
    4. Unexplained weight loss
    5. Nocurnal pain
    6. Saddle anesthesia
    7. Progressive or severe neurological deficits
    8. Refractory pain despite proper medication
    9. Trauma history in elderly patients

- Mechanical versus inflammatory
- Context
### The Complete Course

#### In patients with ≥3 months back pain and age at onset <45 years
- **SpA features**
  - IBP
  - Arthritis
  - Enthesitis (heel)
  - Uveitis
  - Dactylitis
  - Psoriasis
  - Crohn’s/colitis
  - Good response to NSAIDs
  - Family history of SpA
  - HLA-B27
  - Elevated CRP

#### EXPERT APPROACH: ASAS Classification Criteria for SpA

<table>
<thead>
<tr>
<th>In patients with ≥3 months back pain and age at onset ≤45 years</th>
<th>In patients with peripheral symptoms ONLY</th>
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<tbody>
<tr>
<td><strong>HLA-B27 PLUS ≥2 SpA feature or ≥1 SpA feature</strong></td>
<td><strong>≥1 SpA feature</strong></td>
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<tr>
<td>SpA features</td>
<td>Activity or enthesitis or dactylitis PLUS</td>
</tr>
<tr>
<td>- IBP</td>
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<td>- IBP ever</td>
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<tr>
<td>- Family history of SpA</td>
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</tbody>
</table>

Sensitivity: 76.5%, Specificity: 83.2%, N=975.

#### Recommendations for Screening and Referral for SpA in Ambulatory Care

- **Inflammatory BP**
  - Sensitivity: 70%, specificity: 76%
  - Approximately 1 out of 5 patients has axSpA, if positive
  - Simple to apply: yes
  - Costs: low

- **Sacroiliitis on any imaging**
  - Sensitivity: 90% to 97%, specificity: 90%
  - Approximately 1 out of 2 patients has axSpA, if positive
  - Simple to apply: yes
  - Costs: moderate (only once)

- **HLA-B27+**
  - Sensitivity: 90% to 97%, specificity: 90%
  - Approximately 1 out of 2 patients has axSpA, if positive
  - Simple to apply: yes
  - Costs: moderate (only once)

Refer to Rheumatologist

Conclusions

- Identification of early disease
  - Recognize inflammatory back pain
  - Use of MRI
  - Simple referral pattern
- Early treatment for AS
  - Reduce time to diagnosis
  - Treatment can be enhanced if given in earlier stages
- Biologic therapies are efficacious and can slow the rate of radiographic progression
### ASAS Classification Criteria for Axial Spondyloarthritis

<table>
<thead>
<tr>
<th>Sacroiliitis on Imaging* PLUS ≥1 SpA feature†</th>
<th>HLA-B27 PLUS ≥2 other SpA features†</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA</td>
<td>• Definite radiographic sacroiliitis according to mNY</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Sacroiliitis on Imaging*</td>
<td>Definite radiographic sacroiliitis according to mNY</td>
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*Sensitivity: 92.6%, specificity: 64.2%.

- To diagnose axial spondyloarthritis, patients with chronic back pain and age at onset <45 years. Imaging for sacroiliitis alone has a sensitivity of 82.9% and a specificity of 97.3%.
- Elevated CRP is considered an SpA feature in the context of chronic back pain.