New Concepts in Spondyloarthritis: Epidemiology and Clinical Practice

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Oregon Health & Science University
Portland, OR

Northwest Rheumatism Society, Seattle, April 28th, 2017
New Concepts in SpA: Epidemiology & Clinical Practice: Outline

- Epidemiology:
  - US Paradox: Population prevalence: axSpA > RA (NHANES Study), but rheumatology practices: RA >> axSpA
  - Recent studies to understand the reasons behind this Paradox:
    - Administrative Claims Database Study
    - ProSpA Study
    - Northern California Kaiser study
  - The flip side: Over-diagnosis of axSpA

- Clinical Practice:
  - The ACR-SAA-SPARTAN Treatment Guidelines & the EULAR-ASAS Treatment guidelines
  - T2T & Minimal Disease Activity in axSpA
NHANES: “To monitor the health & nutritional status of the civilian, non-institutionalized population of the US”
# NHANES Study (2009-2010)

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Overall sample</td>
<td>5103</td>
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<tr>
<td>Age Group</td>
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<tr>
<td>20-35 years</td>
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<td>36-49 years</td>
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<td>40-69 years</td>
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<td>Racial/Ethnic Groups</td>
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<tr>
<td>Other Hispanic</td>
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<tr>
<td>Caucasians, not Hispanic</td>
<td>2244</td>
<td>44.0</td>
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<tr>
<td>African-Americans</td>
<td>963</td>
<td>18.9</td>
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<tr>
<td>Other</td>
<td>296</td>
<td>5.6</td>
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NHANES (2009-10):
Prevalence of HLA-B27 in U.S. Adults Ages 20-69 Years

<table>
<thead>
<tr>
<th>Selected Characteristic</th>
<th>n</th>
<th>N</th>
<th>%</th>
<th>SE</th>
<th>95% CI</th>
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<tr>
<td>Overall US Prevalence</td>
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<td>2320</td>
<td>6.1</td>
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<tr>
<td>Sex</td>
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<td>Males</td>
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<td>1123</td>
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<td>1.0</td>
<td>(3.9-8.4)</td>
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<td>Females</td>
<td>71</td>
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<td>6.5</td>
<td>1</td>
<td>(4.7-8.9)</td>
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<td>Non-Hispanic Whites</td>
<td>79</td>
<td>1021</td>
<td>7.5</td>
<td>1.2</td>
<td>(5.3-10.4)</td>
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<td>Mexican-Americans</td>
<td>27</td>
<td>622</td>
<td>4.6</td>
<td>0.6</td>
<td>(3.4-6.1)</td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>20-29 Years</td>
<td>39</td>
<td>498</td>
<td>8.0</td>
<td>2.0</td>
<td>(4.6-13.4)</td>
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<tr>
<td>30-39 Years</td>
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<td>471</td>
<td>5.6</td>
<td>1.3</td>
<td>(3.4-9.2)</td>
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<tr>
<td>40-49 Years</td>
<td>34</td>
<td>508</td>
<td>8.1</td>
<td>1.2</td>
<td>(5.8-11.2)</td>
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<td>50-59 Years</td>
<td>11</td>
<td>404</td>
<td>2.9</td>
<td>0.9</td>
<td>(1.4-5.8)*</td>
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<td>60-69 Years</td>
<td>14</td>
<td>439</td>
<td>4.6</td>
<td>1.9</td>
<td>(1.9-10.7)*</td>
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NHANES (2009-10): *Prevalence of axSpA by ESSG Criteria in U.S. Adults (20-69 yrs)*

<table>
<thead>
<tr>
<th>Case Type</th>
<th>n</th>
<th>N</th>
<th>%</th>
<th>SE</th>
<th>L 95% CI</th>
<th>U 95% CI</th>
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<tbody>
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<td>Overall AS</td>
<td>28</td>
<td>5103</td>
<td>0.55 (reporting as having a dx of AS)</td>
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<td>Overall axSpA</td>
<td>70</td>
<td>5103</td>
<td>1.4</td>
<td>0.2</td>
<td>1.0</td>
<td>1.9</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49 Years</td>
<td>49</td>
<td>3188</td>
<td>1.5</td>
<td>0.2</td>
<td>1.1</td>
<td>2.0</td>
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<tr>
<td>50-69 Years</td>
<td>21</td>
<td>1915</td>
<td>1.3</td>
<td>0.4</td>
<td>0.7</td>
<td>2.5</td>
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<tr>
<td><strong>Sex</strong></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Males</td>
<td>24</td>
<td>2472</td>
<td>1.1</td>
<td>0.3</td>
<td>0.6</td>
<td>2.0</td>
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<tr>
<td>Females</td>
<td>46</td>
<td>2631</td>
<td>1.7</td>
<td>0.3</td>
<td>1.2</td>
<td>2.5</td>
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<tr>
<td><strong>Race/Ethnicity</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Mexican-Americans</td>
<td>15</td>
<td>1024</td>
<td>1.5*</td>
<td>0.5</td>
<td>0.7</td>
<td>3.0</td>
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<tr>
<td>Non-Hispanic Whites</td>
<td>38</td>
<td>2244</td>
<td>1.5</td>
<td>0.3</td>
<td>1.0</td>
<td>2.3</td>
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<tr>
<td>Non-Hispanic Blacks</td>
<td>9</td>
<td>963</td>
<td>0.9*</td>
<td>0.3</td>
<td>0.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Axial SpA may be **More Common** than RA in US


If axSpA is More Common Than RA in the US, Where are These Patients?

- axSpA patients are seen by others before rheumatologists
  - Family practice, Internal medicine
  - Chiropractors, Osteopaths, Orthopedic surgeons, Spine surgeons, Neurosurgeons
  - Dermatologists, Ophthalmologists, Gastroenterologists

- Commonest MRI scan ordered is L Spine: SI joints missed

- Are US rheumatologists missing axSpA amongst patients with back pain they see?

- Transient nature of arthritis/enthesitis in true SpA patients

- Lack of reliable biomarkers outside of HLA-B27

- 95% of backache is ‘mechanical’: rheumatologists have little to offer
Diagnostic prevalence of AS in KPNC

- Kaiser Permanante Northern California clinical databases analysis to estimate the prevalence of clinically recognized axSpA
- Patients included with at least 12 months of enrollment in KPNC between 1996-2009
- Patients identified on basis of having at least 1 ICD-9 code of 720.X, and 3% of cases identified randomly selected for validation by detailed review of the medical records
- Overall, 5,568 KPNC members with at least 1 code of 720.X identified; (point prevalence for axSpA of 0.23%)
- 53% (2,965) had a single code assigned by a PCP
  - Upon examination of a random sample of these, only 1 of 44 patients actually had a confirmed diagnosis; therefore these patients were excluded
- For the 2,603 patients remaining the final point prevalence was 0.1%

Diagnostic prevalence of AS in KPNC: Summary

• Estimated point prevalence of axSpA in KPNC registry using a validation of randomly selected cases was 1.07 per 1,000 (95% CI, 1.03-1.11)
• These prevalence numbers are substantially lower than those observed in NHANES study
• Many of these patients were not referred to a rheumatologist

Ankylosing spondylitis diagnosis in US patients with back pain: identifying providers involved and factors associated with rheumatology referral delay

Atul Deodhar¹,³ • Manish Mittal² • Patrick Reilly² • Yanjun Bao² • Shivaji Manthena² • Jaclyn Anderson² • Avani Joshi²
AS diagnosis in patients with back pain in the US

- Retrospective, longitudinal cohort study using the Truven Health MarketScan® US Commercial Claims Database
- Patients aged 18-64 identified based on an initial diagnosis of back pain in a non-rheumatology setting

Who is Making the AS Diagnosis in the US?

These data suggest that 63% of patients were diagnosed with AS outside of a rheumatology practice; the breakdown of actual diagnosing provider is shown below.

An additional 347 patients were initially diagnosed by a non-rheumatologist but had a rheumatologist visit after diagnosis. Of these, 145 (41.8%) had their AS diagnosis confirmed by the rheumatologist.

AS diagnosis in patients with back pain in the US: Summary

- Large proportion (63%) of patients with AS received their diagnosis from a non-rheumatologist
- Only 42% of patients with an initial diagnosis of AS by a non-rheumatologist had that diagnosis confirmed by a rheumatologist
- These results suggest non-recognition of AS features by non-rheumatologists
- Conclusion: “Additional efforts to educate the non-rheumatologists regarding appropriate referrals for patients with suspected AS is warranted”

Frequency of Axial Spondyloarthritis Diagnosis Among Patients Seen by US Rheumatologists for Evaluation of Chronic Back Pain

Atul Deodhar,¹ Philip J. Mease,² John D. Reveille,³ Jeffrey R. Curtis,⁴ Su Chen,⁵ Kailash Malhotra,⁵ and Aileen L. Pangan⁵
Frequency of axSpA in chronic back pain patients seen by US rheumatologists

- To determine the proportion axSpA in a population of patients with: chronic back pain for ≥3 months starting before age of 45 years with one or more of the following: HLA-B27 +, current IBP or Imaging evidence of sacroiliitis
- 751 enrolled patients 46% were diagnosed as having axial SpA by the investigator, and 47% fulfilled the ASAS criteria
- Using investigator's clinical diagnosis as the gold standard, the specificity and sensitivity of the ASAS criteria were 79% and 81%
- Mean symptom duration in these patients was 14 years
- These findings indicate that among patients with CBP for ≥3 months beginning at ages younger than 45 years, the presence of ≥1 of 3 SpA features is an effective way to identify those with possible axial SpA.

Problem of “Over-diagnosis” of axSpA Based on SIJ MRI Scans

Bottom line: In young adults with chronic LBP onset <45 years, MRI “sacroiliitis” was present in 21%, but expected prevalence of axSpA in this population was 5%
SPECIAL ARTICLE

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Michael M. Ward,1 Atul Deodhar,2 Elie A. Akl,3 Andrew Lui,4 Joerg Ermann,5 Lianne S. Gensler,4 Judith A. Smith,6 David Borenstein,7 Jayme Hiratzka,2 Pamela F. Weiss,8 Robert D. Inman,9 Vikas Majithia,10 Nigil Haroon,9 Walter P. Maksymowych,11 Janet Joyce,12 Bruce M. Clark,13 Robert A. Colbert,1 Mark P. Figgie,14 David S. Hallegua,15 Pamela E. Prete,16 James T. Rosenbaum,17 Judith A. Stebulis,18 Filip van den Bosch,19 David T. Y. Yu,20 Amy S. Miller,12 John D. Reveille,21 and Liron Caplan22
2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis

Désirée van der Heijde, ¹ Sofia Ramiro, ¹ Robert Landewé, ²,³ Xenofon Baraliakos, ⁴ Filip Van den Bosch, ⁵ Alexandre Sepriano, ¹,⁶ Andrea Regel, ⁴ Adrian Ciurea, ⁷ Hanne Dagfinrud, ⁸ Maxime Dougados, ⁹,¹⁰ Floris van Gaalen, ¹ Pál Géher, ¹¹ Irene van der Horst-Bruinsma, ¹² Robert D Inman, ¹³ Merryn Jongkees, ¹⁴ Uta Kiltz, ⁴ Tore K Kvien, ¹⁵ Pedro M Machado, ¹⁶ Helena Marzo-Ortega, ¹⁷,¹⁸ Anna Molto, ⁹,¹⁰ Victoria Navarro-Compàn, ¹⁹ Salih Ozgocmen, ²⁰ Fernando M Pimentel-Santos, ²¹ John Reveille, ²² Martin Rudwaleit, ²³,²⁴,²⁵ Jochen Sieper, ²⁶ Percival Sampaio-Barros, ²⁷ Dieter Wiek, ²⁸ Jürgen Braun ⁴

Recommendations for the treatment of active AS

**NSAIDs**
- Use continuously
- No preferred drug

**Physical Therapy**
- Active over passive
- Land-based over aquatic

**Systemic glucocorticoid**
- Consider if peripheral flare, pregnancy, IBD flare

**LEGEND**
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against
- Qualifier

**Slow-Acting Drugs** (SSZ, pamidronate)
- Consider if peripheral arthritis or TNFi contraindications

**TNFi**
- No preferred drug
- Recurrent iritis
- IBD
- Use infliximab or adalimumab
- Use TNFi monoclonals

**Alternative TNFi**
- Isolated sacroiliitis
- Local GC
- Peripheral arthritis
- Local GC Consider if ≤ joints; use infrequently
- Enthesitis
- Local GC Avoid achilles, patellar, quadriceps

Monitor validated AS disease activity measure, and CRP or ESR regularly

Unsupervised back exercises, formal group or individual self-management education, fall evaluation/counseling

Recommendations for the treatment of stable AS

- Monitor validated AS disease activity measure, and CRP or ESR regularly
- Unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling

**NSAIDS**
- Use on demand

**NSAIDs & TNFi**
- TNFi alone (monotherapy)

**Slow-acting drugs and TNFi**
- TNFi alone (monotherapy)

**Physical therapy**

**LEGEND**
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against
- Qualifier

2016 Treatment Recommendations for axSpA (ASAS/EULAR)

- Most recommendations & overarching principals similar to 2010 recommendations, with following changes:

  - **1st line biologic treatment**: In patients with persistently high disease activity despite conventional treatments: use biologic DMARDs TNFi & IL-17i. Start with TNFi (level of evidence 1a: meta-analysis of RCTs, and 1b for IL-17i one RCT)

  - **2nd line biologic treatment**: TNFi failure patients: Switch to another TNFi (level of evidence 2) or IL-17i (level of evidence 1b from at least one RCT)

ASAS-EULAR recommendations for use of biologic in axSpA

- Rheumatologist’s diagnosis of axial SpA
  - and
- Elevated CRP and/or positive MRI and/or Radiographic sacroiliitis*
  - and
- Failure of standard treatment: all patients
  - at least 2 NSAIDs over 4 weeks (in total)
  - patients with predominant peripheral manifestations
    - one local steroid injection if appropriate
    - normally a therapeutic trial of sulfasalazine
  - and
- High disease activity: ASDAS ≥ 2.1 or BASDAI ≥ 4
  - and
- Positive rheumatologist’s opinion
  *

* Radiographic sacroiliitis is mandatory for infliximab and IL17i

Treat to target in Spondyloarthritis

- **Active SpA***
  - Main target
  - Adapt therapy to disease activity

- **Low disease activity**
  - Use measures of clinical disease activity and acute phase reactants as needed

- **Remission**
  - Use measure of clinical disease activity and acute phase reactants as needed

- **Sustained remission**
  - Adapt therapy if state is lost

- **Sustained low disease activity**
  - Adapt therapy if state is lost

- **Alternative target**
  - Adapt therapy according to disease activity

Is this patient’s axSpA in Remission?

• 63 year old man with known AS for 40+ years
• Advanced AS, fused spine, hip replacements
• On Etanercept for the last 6 years: very stable, BASDAI 1.8, CRP 0.2 mg/dl, ASDAS 1.2
• Presents to the clinic with acute attack of AAU
• On enquiry: has had no back pain, enthesitis, peripheral arthritis for >3 years, but has had 3 attacks of AAU in the last year
• According to BASDAI & ASDAS, he is in remission

..........but does he have ‘minimal disease activity’?

Mr. KM on Mount Hood, OR, at 11,000 feet, May 2003
Minimal Disease Activity (MDA) for axSpA

• We need a MDA for axSpA because the current disease activity measures concentrate only on spinal/peripheral arthritis, enthesitis, fatigue & stiffness

• axSpA is a multifaceted disease: involving extra-articular tissues such as skin and nails, and can cause uveitis, IBD, dactylitis

• While separate disease activity measures are available for other aspects of disease (e.g. skin, nail, IBD, uveitis), no ‘composite’ disease activity measure assesses all manifestations

• MDA could be such a ‘composite’ measurement, and would be useful in daily clinical practice & clinical trials of T2T

• SPARTAN is undertaking the development of MDA in axSpA
What have we learnt today?

• While according to NHANES, the prevalence of axSpA is higher than that of RA, in practice most patients are being missed

• Only 37% of AS patients in the US are diagnosed by rheumatologists

• Patients with CBP starting before the age of 45 years, with either IBP, HLA B27 or sacroiliitis on imaging should be referred to rheumatologist – nearly half of these patients have axSpA

• The 2016 ASAS-EULAR treatment guidelines are similar to ACR-SAA-SPARTAN guidelines with some differences re mandatory disease activity measurements before changing therapy

• T2T in axSpA patients needs careful measurement of disease activity in all aspects of the disease