Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

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MetroHealth Medical Center
Cleveland, OH
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Firstly my biggest mistake:

I devoted too much time to my profession and not enough with my two sons as they were growing up.

What are my excuses?
In a new country in academic medicine, I did not want anyone to think that I am not as good as anyone else.

My work efficiency requires no noise, radio, music or other distractions. Moreover, I am a “night owl”, not an “early bird”.

My physical limitations did not allow me to participate in playing sports with my sons or in other recreational activities.
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Do spend time with your children as they are growing up; they deserve more of your time and interaction during their formative years.

Help them with their homework, read books with them, travel with them, etc, etc.

LEARN HOW TO BALANCE YOUR PROFESSIONAL TIME AND YOUR FAMILY OBLIGATIONS

MONEY IS NOT EVERYTHING
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Ours is a NOBLE profession and be honest with yourself, your family, your staff and colleagues, and with your patients.

We need to gain the trusts of our patients.

Our patients are not our “clients”.

They need our empathy and compassion, and reasonable time to interact with us.
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Do not look at your wrist watch (or the clock on the wall) when you are taking clinical history from your patients.

Patient privacy is mandatory.
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Patients need to be educated about their illness, and we need to obtain their compliance with our recommendations.

The word “DOCTOR” means an educator, not a “HEALER”.

Days of “Dr. Google”

Extreme poverty, lack of affordable health care, and presence of folk medicine, homeopathy, quackery, number 1 versus number 2 medications, websites selling ‘snake oil’, etc.
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Record keeping; computerized record keeping

Communication with the patient and the referring doctor

Learning from experience

Academic aspects of medicine, and educating others from one’s experience
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Take business management and leadership courses

Take care of your health

Have time for playing sports and pursuing some hobbies
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Passion for learning and staying up to date

Knowledge available everywhere on the Internet, and it is quite often free to obtain

www.ASAS-group.org
www.SPARTANgroup.org
www.GRAPPAnetwork.org
www.NLM.NIH.gov
www.Spondyloarthritis.com
Advice from a Senior Rheumatologist to the Upcoming Young Rheumatologists

Religion can be a guide for moral thinking and actions; give zakat and charity; sometimes provide free care to the needy; pay full taxes and set such good examples for your children

Learn some languages, even at a rudimentary level
Advances in Management of Axial Spondyloarthritis

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Case Western Reserve University
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Cleveland, OH
Conflicts of Interest
Disclosure Statement

Consultant/Clinical Studies/Speaker
• Abbvie
• Amgen
• Celgene
• Janssen
• Crescendo Bioscience
The Concept of Axial SpA

Non-radiographic stage of Axial SpA

- Back pain
- MRI: active sacroiliitis

Radiographic stage (AS)

- Back pain
- Radiographic sacroiliitis
- Back pain
- Syndesmophytes

Time (years)

Inflammatory Back Pain for 2 years

Normal or equivocal radiograph of the SI joints

Courtesy of Martin Rudwaleit

MRI SI joints, STIR technique
Proposed Sequence of Structural Damage in Ankylosing Spondylitis

Inflammation  Erosive damage  Repair  New bone formation

Management of AS

Patient Education

Physical therapy and rehabilitation
Training

Lifelong Exercises

Lifestyle and employment modification

Complete avoidance of smoking

Patient self-help groups and associations

Spondylitis.org  Nass.co.uk  ASAS-group.org
Spondyloarthritis.com  HLAB27.com
Smoking: An environmental risk factor for worse disease

Patients demonstrating at least 2 mSASSS units progression after 2 years

Non-smoker  Smoker

<table>
<thead>
<tr>
<th>Syndrome present</th>
<th>Elevated CRP</th>
<th>Normal CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% n = 6</td>
<td>55% n = 11</td>
<td></td>
</tr>
<tr>
<td>19% n = 16</td>
<td>33% n = 15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Syndrome not present</th>
<th>Elevated CRP</th>
<th>Normal CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>7% n = 31</td>
<td>20% n = 15</td>
<td></td>
</tr>
<tr>
<td>4% n = 71</td>
<td>13% n = 45</td>
<td></td>
</tr>
</tbody>
</table>

2010 ASAS*/EULAR Recommendations for the Management of AS

Patient Education
- Exercise
- Physical therapy
- Rehabilitation,
- Patient associations & self-help groups

NSAIDs
- Axial disease
- Peripheral disease
  - One DMARD, preferably SSZ
  - Local C/S injection

TNF antagonists

*ASAS = Assessment in Spondyloarthritis International Society
Superiority of Etoricoxib over Naproxen in AS

52 week RCT (with placebo group for the first 6 weeks)
Proportions remaining in the study

RCT: Continuous Celecoxib Therapy Retards Radiographic Progression of AS at 2 Years


n = 150

NSAIDs also reduce the risk of any clinical fracture

Vosse D et al. ARD. 2009; 68(12):1839-42
Active SpA

Sacroiliac  Spinal  Enthesitis  Peripheral

NSAIDS, Exercise

Injections?  ???  Injections  Injections

Sulfasalazine?

Anti-TNF

infliximab, etanercept, adalimumab, golimumab, certolizumab
(Remicade)  (Enbrel)  (Humira)  (Simponi)  (Cimzia)
ASAS 40 Response After 24 Weeks of Treatment with TNF Blockers

Assessment of disease activity in AS

**BASDAI**
5 items
- Fatigue
- Spinal pain
- Peripheral joint pain
- Localized tenderness
- Morning stiffness
  Severity / Duration

**ASDAS (AS Disease Activity Score)**
- Total back pain
- Patient global of disease activity
- Pain/swelling peripheral joints
- Duration of morning stiffness
- Either CRP or ESR

**ASDAS_{CRP}**:  
0.121 x total back pain  
+ 0.110 x patient global  
+ 0.073 x periph joint pain/swelling  
+ 0.058 x morning stiffness duration  
+ 0.579 x natural logarithm of CRPmg/L +1

www.asas-group.org  
Download on iPhone an app called ASDAS-Calculator


www.asas-group.org Download on iPhone an app called ASDAS-Calculator
Besides **HLA-B27** there are at least **40 additional genes** (mostly non-MHC genes) that show association with AS among populations of European descent; such as:

**ERAP1**

Its epistasis (gene-gene interaction) with **HLA-B27** provides the most powerful disease risk factor for AS, and implicates aberrant peptide handling in the ER as a contributory factor for this disease.

**IL23R** : A major role for the IL-23/1L-17 axis.

These advances point to several potential novel therapeutic approaches in AS and related SpA

Brown MA. Progress in the Genetics of AS. *Briefings in Functional Genomics.* 2011 Sep;10(5):249-57
HLA-B27 misfolding and activation of the UPR can lead to increased IL-23 production in an animal model, with implications for triggering of IL-23 receptor on Th17 cells.

Layh-Schmitt G and Colbert RA. Curr Opin Rheum 2008; 20:392-397 (with permission)
<table>
<thead>
<tr>
<th>Genetic Associations with AS</th>
<th>Target Molecules</th>
<th>Treatments &amp; Therapeutic Trials in AS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNFR1</strong></td>
<td>TNF</td>
<td>Etanercept, infliximab, adalimumab, golimumab, certolizumab</td>
</tr>
<tr>
<td><strong>IL12B, IL23R</strong></td>
<td>IL-17A</td>
<td><strong>Secukinumab</strong> <em>(Cosentyx)</em></td>
</tr>
<tr>
<td><strong>IL12B, IL23R</strong></td>
<td>P40 subunit of IL-12 &amp; IL-23</td>
<td><strong>Ustekinumab</strong> <em>(Stelara)</em></td>
</tr>
<tr>
<td><strong>PTGER4</strong></td>
<td>Prostaglandins</td>
<td>NSAIDs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Drug target</th>
<th>US status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen (New Jersey)</td>
<td>Ustekinumab (Stelara)</td>
<td>IL-12/23</td>
<td>Approved in 2009 for moderate to severe plaque psoriasis; and active PsA in 2014</td>
</tr>
<tr>
<td>Novartis (Basel)</td>
<td>Secukinumab (Cosentyx)</td>
<td>IL-17</td>
<td>Approved in 2005 for psoriasis; ongoing phase 3 in PsA &amp; AS</td>
</tr>
<tr>
<td>Amgen (San Francisco)</td>
<td>Brodalumab</td>
<td>IL-17</td>
<td>Phase 3 in psoriasis &amp; PsA</td>
</tr>
<tr>
<td>Eli Lilly (Indianapolis)</td>
<td>Ixekizumab</td>
<td>IL-17</td>
<td>Phase 3 in psoriasis &amp; PsA</td>
</tr>
<tr>
<td>Merck (New Jersey)</td>
<td>Tildrakizumab</td>
<td>IL-23</td>
<td>Phase 3 in psoriasis</td>
</tr>
<tr>
<td>Pfizer (New York)</td>
<td>Tofacitinib (Xeljanz)</td>
<td>JAK3</td>
<td>Phase 3 in ps &amp; PsA, Phase 2 in AS</td>
</tr>
<tr>
<td>Celgene (New Jersey)</td>
<td>Apremilast (Otezla)</td>
<td>PDE4</td>
<td>Approved for ps &amp; PsA, Ph 3 AS</td>
</tr>
</tbody>
</table>

Ratner M. Nature Biotechnology. 2014; 35:505-7
Enthesis (the junction between tendon and bone) has been suggested to be a key target in SpA. This zone is now shown to contain a unique population of resident T cells, which, when activated by the cytokine IL-23, can promote pathogenesis that is characteristic of SpA.

Structural damage in SpA has to be seen differently from that seen in RA

RANKL = RANK ligand; DKK1 = Dickkopf proteins; BMP = bone morphogenetic proteins; TGF = transforming growth factor beta; Wnt = Wingless proteins.

(This figure is from the cover of the ARD July 2007 issue.)
Axial Disease
Sacroiliitis
Enthesitis
Dactylitis
Peripheral Arthritis

Osteopenia
Osteoporosis
30-50% of AS patients have osteopenia or osteoporosis of spine and hip but not peripheral skeleton. DEXA overestimates bone mineral density when syndesmophytes present

Syndesmophytes
Spinal Ankylosis

Vertebral Compression Fracture (over a 30 year period)
14% in AS vs 3.4% controls

AS

Spinal Ankylosis

Vertebral compression fracture (over a 30 year period): 14% in AS vs 3.4% controls

High risk of post-traumatic spinal fracture (the trauma can sometimes be quite trivial)
SPINAL FRACTURES in AS

Incidence of spinal cord injuries 11 times higher in AS, compared to the general population

Caused by ground level falls in 53% of AS cases vs 7% of the cases in general population

The fracture usually occurs in the cervical spine (81%)

Neurologic compromise in 67%

18% mortality within 3 months

Neurologic compromise can occur during surgery to correct severe kyphosis, and sometimes over-correction of kyphotic spines can result in subsequent neurological deterioration in some patients.

Acute Anterior Uveitis 25 – 45 %

Skin
Psoriasis & Nail Changes 5 – 16 %

Gut
UC & Crohn 5 – 8 %,
(Microscopic lesion 22 – 69 %)

Lung
Restrictive Lung Disease
Apical Fibrocystic Disease 1 – 2%
Obstructive sleep apnea* (OSA in >12% in AS vs. 1-4% in general population)

Heart
Aortic Insufficiency / Heart Block 2 – 3 %
Increased risk CAD as a result of chronic inflammation and inactivity
Hypertension
NSAID induced risks

Kidneys
IgA nephropathy 1 to 2%
Does not respond to TNF-i
Renal amyloidosis 0.3– 1.2 %
4-7% in some countries; associated with disease severity and duration, and poor compliance. Proteinuria improves with TNF-i
NSAID induced nephropathy

Cauda Equina Syndrome 0.5 %
ASAS Classification Criteria for Predominantly Axial SpA

In patients with chronic (>3 months) back pain, age at onset <45 years

<table>
<thead>
<tr>
<th>Sacroiliitis**</th>
<th>or</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus</td>
<td></td>
<td>plus</td>
</tr>
<tr>
<td>≥ 1 clinical parameter*</td>
<td></td>
<td>≥ 2 other clinical parameters*</td>
</tr>
</tbody>
</table>

Sacroiliitis (x-rays or MRI):
- Definite **radiographic** sacroiliitis (grade 2 bilat or grade 3-4 unilat; according to modified NYcriteria 1984)
  - or
- Active (acute) inflammation of sacroiliac joints on MRI, highly suggestive of sacroiliitis associated with SpA

*Clinical parameters:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn’s disease / ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- Elevated CRP
- HLA-B27

Not included are miscellaneous entities, such as Behcet's disease, FMF (Familial Mediterranean Fever) & SAPHO syndrome. SpA = spondyloarthritis, nr-axSpA = non-radiographic axial SpA, PsA = psoriatic arthritis, AAU = acute anterior uveitis, AI+HB = aortic incompetence plus heart block.

Ankylosing Spondylitis (AS):
What the Clinicians Need to Know

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Case Western Reserve University
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Conflicts of Interest Disclosure Statement

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- Celgene
- Janssen
- Crescendo Bioscience
Ankylosing Spondylitis

Chronic Back Pain

- Insidious onset
- Pain at night (with improvement upon getting up)
- Age at onset <40 years
- Improvement with exercise
- No improvement with rest

Best trade-off if ≥ 4 of the above 5 parameters are fulfilled
(Sensitivity 80%, Specificity 72%)


X-ray Evidence of Sacroiliitis

Khan MA: In: Hochberg et al. RHEUMATOLOGY (3rd Ed.) 2003
Structural damage in SpA has to be seen differently from that seen in RA

![Diagram showing osteoclasts and osteoblasts with annotations for RANKL, DKK1, BMP, TGF, and Wnt]

RANKL = RANK ligand; DKK1 = Dickkopf proteins; BMP = bone morphogenetic proteins; TGF = transforming growth factor beta; Wnt = Wingless proteins.

(This figure is from the cover of the ARD July 2007 issue.)
Proposed Sequence of Structural Damage in Ankylosing Spondylitis

Inflammation  Erosive damage Repair  New bone formation

Syndesmophytes

Clinical Characteristics

METROLOGY
- Chest expansion
- Modified Schober
- Intermalleolar distance
- Lateral lumbar flexion
- Occiput-to-wall & tragus-to-wall
- Cervical rotation
- Tender & swollen joint counts
- Dactylitis evaluation
- Enthesitis evaluation/locations

Chronic Back Pain

- Insidious onset
- Pain at night (with improvement upon getting up)
- Age at onset <40 years
- Improvement with exercise
- No improvement with rest

Best trade-off if ≥ 4 of the above 5 parameters are fulfilled
(Sensitivity 80%, Specificity 72%)

Mnemonic “IPAIN” or “iPAIN”


### Diagnostic value of some clinical feature

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory back pain</td>
<td>80%</td>
<td>72%</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**Positive Likelihood Ratio** = \( \frac{80}{(100-72)} = \frac{80}{28} = 2.9 \)

### Diagnostic value of some clinical feature

<table>
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<tr>
<th>Feature</th>
<th>Sensitivity</th>
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<th>+LR</th>
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<tbody>
<tr>
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<td>72%</td>
<td>2.9</td>
</tr>
<tr>
<td>Enthesitis (heel pain)</td>
<td>37</td>
<td>89</td>
<td>3.4</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>40</td>
<td>90</td>
<td>4.0</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>18</td>
<td>96</td>
<td>4.5</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>22</td>
<td>97</td>
<td>7.3</td>
</tr>
<tr>
<td>Positive family history for AS, AAU, IBD, ReA</td>
<td>32</td>
<td>95</td>
<td>6.4</td>
</tr>
</tbody>
</table>

**Positive Likelihood Ratios (+LR)**

They are not additive (2.9+7.3+6.4) but multiplicative

Therefore +LR = 2.9 x 7.3 x 6.4 = 135

---

## Diagnostic value of some clinical feature

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory back pain <em>(updated information)</em></td>
<td>80%</td>
<td>72%</td>
<td>2.9</td>
</tr>
<tr>
<td>Enthesitis (heel pain)</td>
<td>37%</td>
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<td>32%</td>
<td>95%</td>
<td>6.4</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>10%</td>
<td>96%</td>
<td>2.5</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>4%</td>
<td>99%</td>
<td>4.0</td>
</tr>
<tr>
<td>Good response to NSAIDs</td>
<td>77%</td>
<td>85%</td>
<td>5.1</td>
</tr>
<tr>
<td>↑acute phase reactants</td>
<td>50%</td>
<td>80%</td>
<td>2.5</td>
</tr>
<tr>
<td>HLA-B27 <em>(updated information)</em></td>
<td>Variable</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>MRI (STIR) sacroiliitis <em>(updated information)</em></td>
<td>Variable</td>
<td>Variable</td>
<td></td>
</tr>
</tbody>
</table>

Spondylitic Disease Without Radiologic Evidence of Sacroiliitis

“.. The spectrum of the clinical manifestations of AS may include individuals with symptomatic disease, but without radiographic evidence of abnormalities of the sacroiliac joints or the spine.

“The relatively large number of females we found in this group suggests that women are more likely to manifest this variety of disease than are men”.

But reliable early diagnosis can be made even when the conventional X-ray changes are absent.

Inflammatory Back Pain for 2 years

Normal or equivocal radiograph of the SI joints

Courtesy of Martin Rudwaleit
The Concept of Axial SpA

Chronic Inflammatory Back Pain

Non-Radiographic Axial SpA

Ankylosing Spondylitis

Ch Inflamm Back Pain

Ch Inflamm Back Pain

MRI+: active sacroiliitis

Radiographic sacroiliitis

Syndesmophytes

Time (years)

Modified by Khan MA. 2013
# HLA-B27 Associations in SpA (among “whites” in US)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>~ 80 (%)</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>30–70</td>
</tr>
<tr>
<td>IBD spondyloarthropathy</td>
<td>30–70</td>
</tr>
<tr>
<td>Psoriatic SpA</td>
<td>40–50</td>
</tr>
<tr>
<td>Juvenile enthesitis-related arthritis</td>
<td>~ 70</td>
</tr>
<tr>
<td>Undifferentiated SpA</td>
<td>~ 70</td>
</tr>
</tbody>
</table>

**General Population**

~ 7

Weaker associations among African Americans*

---

Prevalence of HLA-B27

Management of AS

- Patient Education
  - Physical therapy and rehabilitation
    - Training
  - Lifelong Exercises
  - Lifestyle and employment modification
  - Complete avoidance of smoking

- Patient self-help groups and associations

Spondylitis.org    Nass.co.uk    ASAS-group.org
Spondyloarthritis.com    HLAB27.com
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Superiority of Etoricoxib over Naproxen in AS

52 week RCT (with placebo group for the first 6 weeks)
Proportions remaining in the study

Placebo

RCT: Continuous Celecoxib Therapy Retards Radiographic Progression of AS at 2 Years


n = 150

NSAIDs also reduce the risk of any clinical fracture

Active SpA

- Sacroiliac
- Spinal
- Enthesitis
- Peripheral

**NSAIDS, Exercise**

- Injections?
- ???
- Injections
- Injections

**Anti-TNF**

- infliximab, etanercept, adalimumab, golimumab, certolizumab
  - (Remicade) (Enbrel) (Humira) (Simponi) (Cimzia)
ASAS 40 Response After 24 Weeks of Treatment with TNF Blockers

- Infliximab vs. Placebo: 47% improvement
- Etanercept vs. Placebo: 45% improvement
- Adalimumab vs. Placebo: 39% improvement
- Golimumab vs. Placebo: 44% improvement
- Certolizumab vs. Placebo: 53% improvement

Incidence of TB By Country (in 2009)

Incidence is highest in Africa, Southeast Asia and Western Pacific Regions

World Health Organization. Global Tuberculosis Control 2010 [monograph].
## Projected Incremental TB Risks in Asian Countries with Anti-TNF Therapy

<table>
<thead>
<tr>
<th>Country</th>
<th>TB Incidence (%)</th>
<th>Projected Incidence of TB on TNF-i’s (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADA</td>
<td>ETN</td>
</tr>
<tr>
<td>Cambodia</td>
<td>0.44</td>
<td>13</td>
</tr>
<tr>
<td>Philippines</td>
<td>0.28</td>
<td>8.2</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.23</td>
<td>6.8</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.23</td>
<td>6.6</td>
</tr>
<tr>
<td>Vietnam</td>
<td>0.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Indonesia</td>
<td>0.19</td>
<td>5.5</td>
</tr>
<tr>
<td>India</td>
<td>0.17</td>
<td>4.9</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.14</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>0.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Korea</td>
<td>0.09</td>
<td>2.6</td>
</tr>
<tr>
<td>Taiwan</td>
<td>0.09</td>
<td>2.6</td>
</tr>
<tr>
<td>Malaysia</td>
<td>0.08</td>
<td>2.4</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>0.08</td>
<td>2.4</td>
</tr>
<tr>
<td>Singapore</td>
<td>0.04</td>
<td>1.1</td>
</tr>
<tr>
<td>Japan</td>
<td>0.02</td>
<td>0.6</td>
</tr>
</tbody>
</table>

TB, tuberculosis; ADA, adalimumab; ETN, etanercept; IFX, infliximab.

Tang B, et al. Presented at American College of Rheumatology; November 5-9, 2011; Chicago, IL; Abstract 413.
Besides *HLA-B27* there are at least 40 additional genes (mostly non-MHC genes) that show association with AS among populations of European descent; such as:

*ERAP1*

Its epistasis (gene-gene interaction) with *HLA-B27* provides the most powerful disease risk factor for AS, and implicates aberrant peptide handling in the ER as a contributory factor for this disease.

*IL23R : A major role for the IL-23/1L-17 axis.*

These advances point to several potential novel therapeutic approaches in AS and related SpA


Brown MA. Progress in the Genetics of AS. *Briefings in Functional Genomics.* 2011 Sep;10(5):249-57


Enthesis (the junction between tendon and bone) has been suggested to be a key target in SpA. This zone is now shown to contain a unique population of resident T cells, which, when activated by the cytokine IL-23, can promote pathogenesis that is characteristic of SpA.


Axial Disease
Sacroiliitis
Enthesitis
Dactylitis
Peripheral Arthritis

Osteopenia
Osteoporosis
30-50% of AS patients have osteopenia or osteoporosis of spine and hip but not peripheral skeleton. DEXA overestimates bone mineral density when syndesmophytes present

Syndesmophytes
Spinal Ankylosis

Spinal Ankylosis

Vertebral compression fracture (over a 30 year period): 14% in AS vs 3.4% controls

High risk of post-traumatic spinal fracture (the trauma can sometimes be quite trivial)
AS and Associated Manifestations/Comorbidities

Acute Anterior Uveitis
25 – 45%

Skin
Psoriasis & Nail Changes
5 – 16%

Gut
UC & Crohn 5 – 8 %,
(Microscopic lesion 22 – 69 %)

Lung
Restrictive Lung Disease
Apical Fibrocystic Disease 1 – 2%
Obstructive sleep apnea*
(OSA >12% in AS vs 1-4% in general population).

Heart
Aortic Insufficiency / Heart Block
2 – 3%
Increased risk CAD as a result of chronic inflammation and inactivity
Hypertension
NSAID induced risks

Kidneys
IgA nephropathy 1 to 2%
Renal amyloidosis 0.3– 1.2 %
4-7% in some countries
NSAID induced nephropathy

Cauda Equina Syndrome 0.5 %

Mortality in AS: 1.5 to 4 fold increase

Possibly due to:
- Cardiovascular disease
- Pulmonary diseases, smoking
- Spinal fractures
- Violence; alcohol related injury
- Gastrointestinal bleeding
- Miscellaneous: e.g., associated diseases, radiation related, amyloidosis, etc.

By 20 yrs after diagnosis 68% had survived versus 89% expected (P=0.001).

The graph line smoothed

Khan MA et al. *J Rheumatol* 1981; 8:86