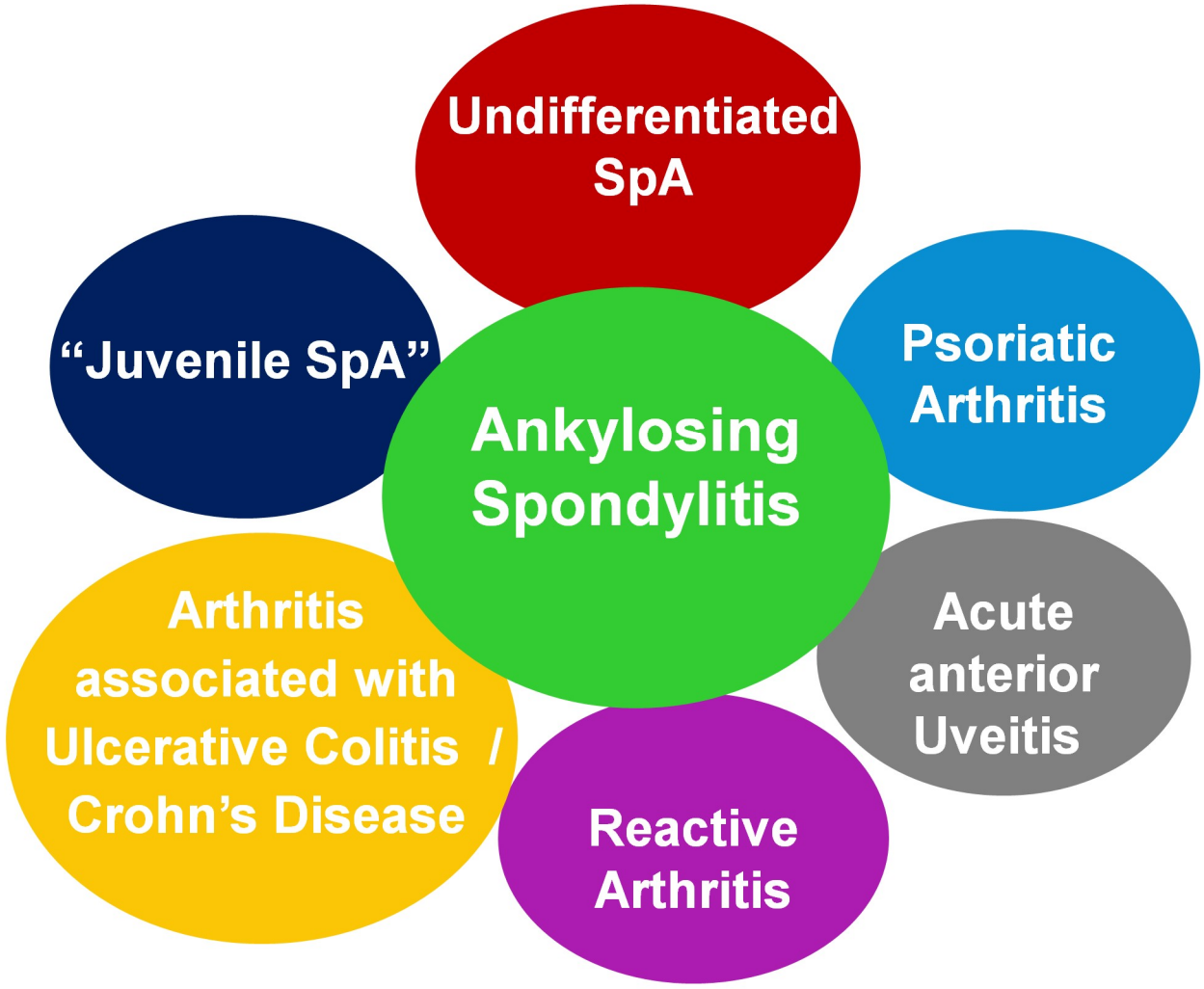
Spondyloarthropathies

Spondyloarthritides (SpA)



Seronegative spondyloarthropathies

A family of rheumatologic disorders that include:

1-Ankylosing spondylitis (AS)
2-Non-radiographic axial SpA (nr-axSpA)
3-Peripheral SpA (undifferentiated spondyloarthopathies)
4-SpA associated with psoriasis or psoriatic arthritis
5-SpA associated with Crohn disease and ulcerative colitis
6-Reactive arthritis
7-Juvenile-onset SpA

Common features among all SpA

- Strong genetic history and HLA-B27 association
- Enthesitis (both juxtaarticular and extraarticular)
- Axial skeleton arthritis
  - Spondylitis (inflammation of vertebral bodies)
  - Sacroiliitis (inflammation of sacroiliac joint)
- Peripheral arthritis :Asymmetric
- Extraarticular manifestations (skin and genital lesions, eye and bowel inflammation)
- Seronegativity for Rheumatoid factor and ANA

Concept of Spondyloarthritides (SpA)

Non-radiographic axial SpA

Ankylosing Spondylitis

Predominantly Axial SpA

Reactive arthritis

Psoriatic Arthritis

Arthritis with inflammatory bowel disease

Undifferentiated SpA

Predominantly Peripheral SpA

ASAS

Spondyloarthritis

- SPA are highly heritable disease.
- Polygenetic.
- The most important gene is HLA B27, mostly in AS
- <5% of B27 positive individuals develop AS
- HLA B27 is almost essential but other genes determine who will develop disease

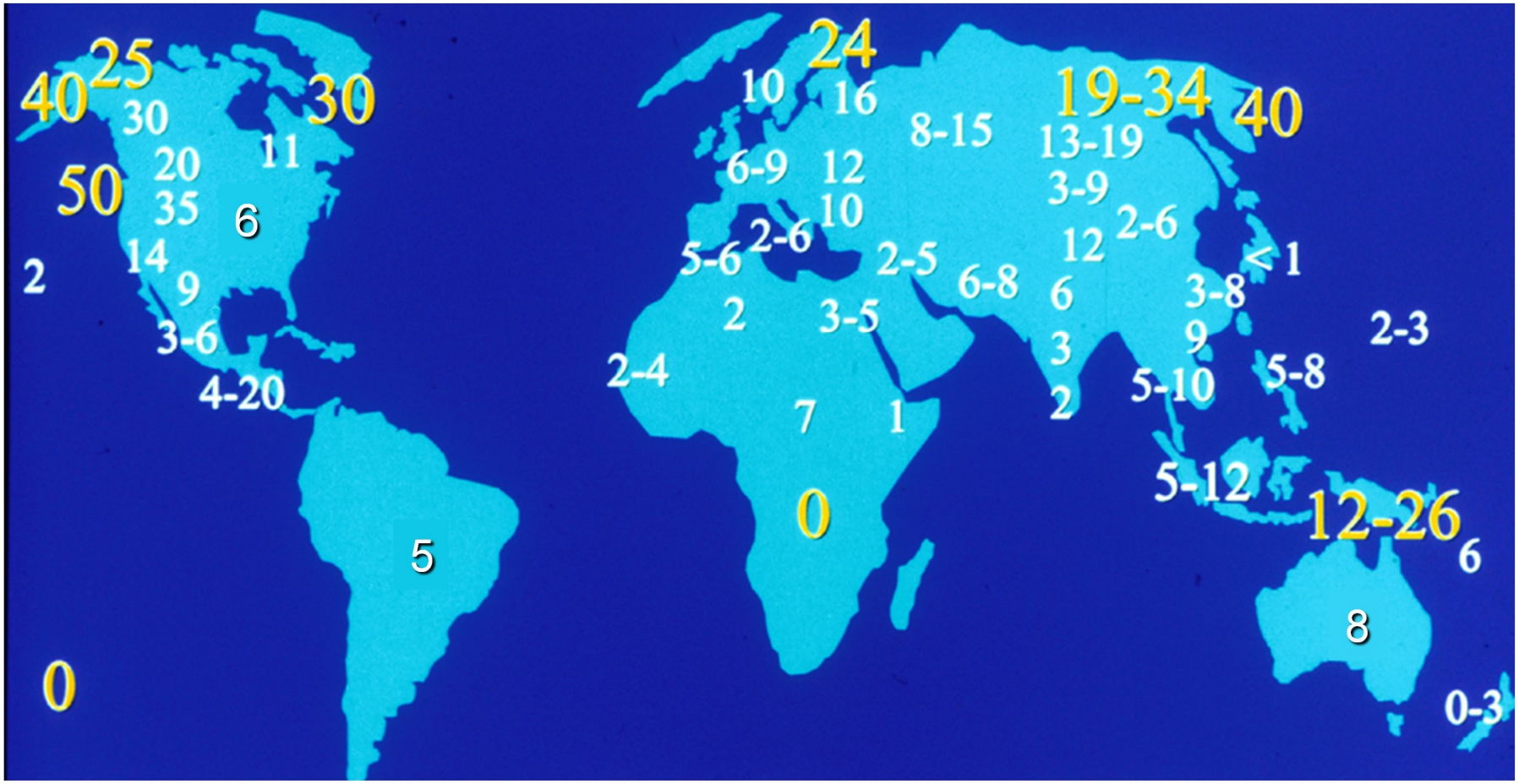
Epidemiology of SpA

- Considerable variation of the worldwide prevalence of spondyloarthritis (SpA) depending upon the genetic background in the country and HLA B27 prevalence.

- For Ankylosing spondylitis: in Europe 0.12 - 1.0 %, in Asia 0.17 %, and 0.07 % in Africa.

- Prevalence of axial SpA as a whole in the United States 1.0 to 1.4 %

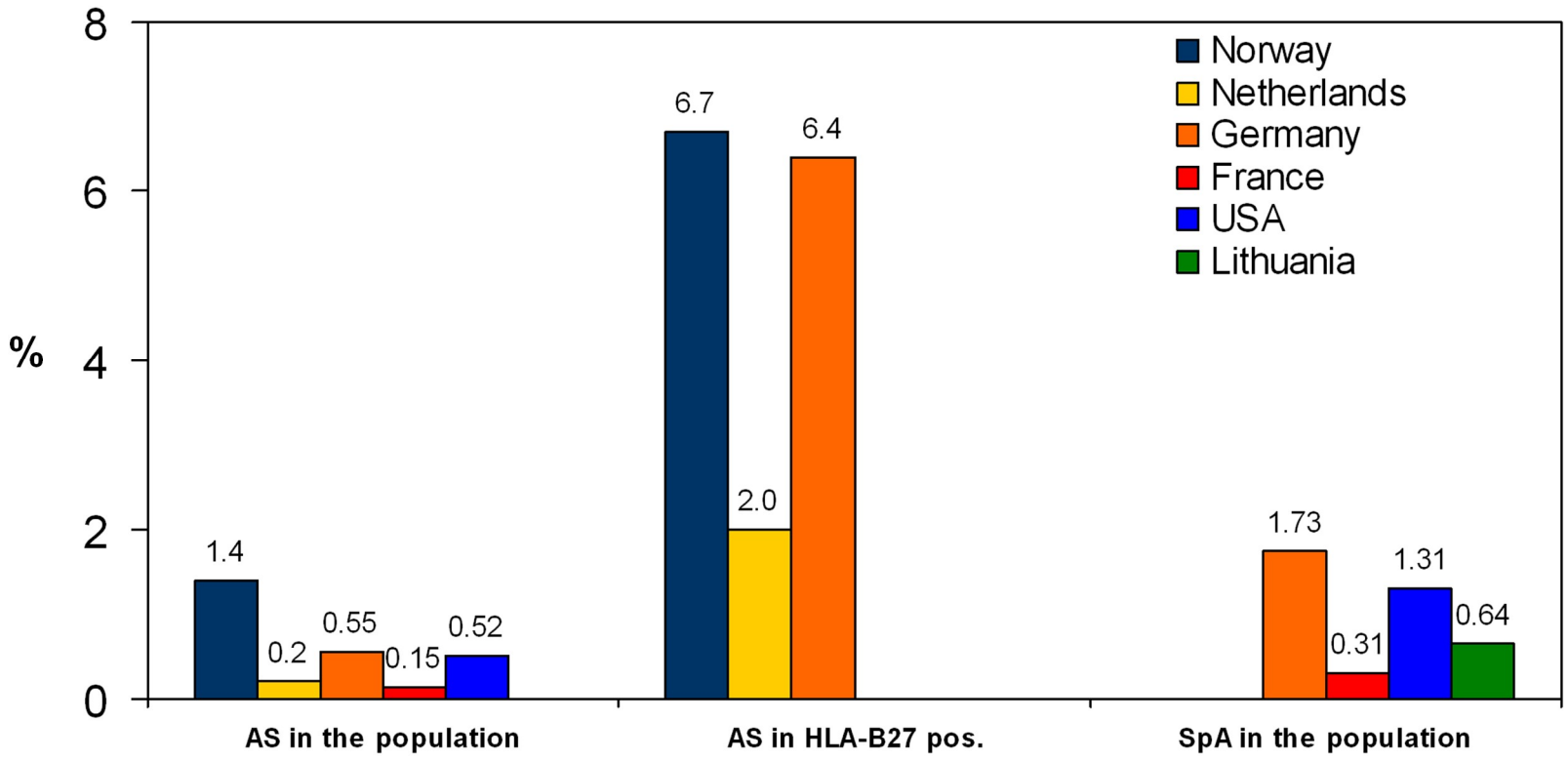
Percentage Prevalence of HLA-B27 in Various Populations of the World



Khan MA Curr Opin Rheumatol 1995;7:263-9
Khan MA J Clin Rheumatol 2008;14:50-2
Khan MA. In Mehra N (Ed). The HLA Complex in Biology and Medicine. New Dehli, India 2010; 422-46.
Reveille J et al. Arthritis Rheum 2012;64:1407-11

ASAS

Prevalence of Ankylosing Spondylitis (AS) and all Spondyloarthritis (SpA)



Norway: Gran JT et al. Ann Rheum Dis 1985;44:359-67 Germany: Braun J et al. Arthritis Rheum 2005;52:4049-50
Netherlands: van der Linden SM et al. Arthritis Rheum 1984;27:241-9 France: Saraux A et al. Ann Rheum Dis 2005;64:1431-5
Lithuania: Adomaviciute D et al. Scand J Rheumatol 2008;37:113-9 USA: Helmick CG et al. Arthritis Rheum 2008;58:15-25

Etiology

- AS has been closely associated with the expression of the HLA-B27 gene

- The response to the therapeutic blockade of TNF alpha indicates that this cytokine plays a central role in AS

- Examination of inflamed SI joints in AS patients has demonstrated high levels of CD4+ and CD8+ T cells and macrophages.

- The overlapping features with reactive arthritis and IBD suggests a possible role for intestinal bacteria in the pathogenesis of AS.

HLA B 27 in Spondyloarthritis

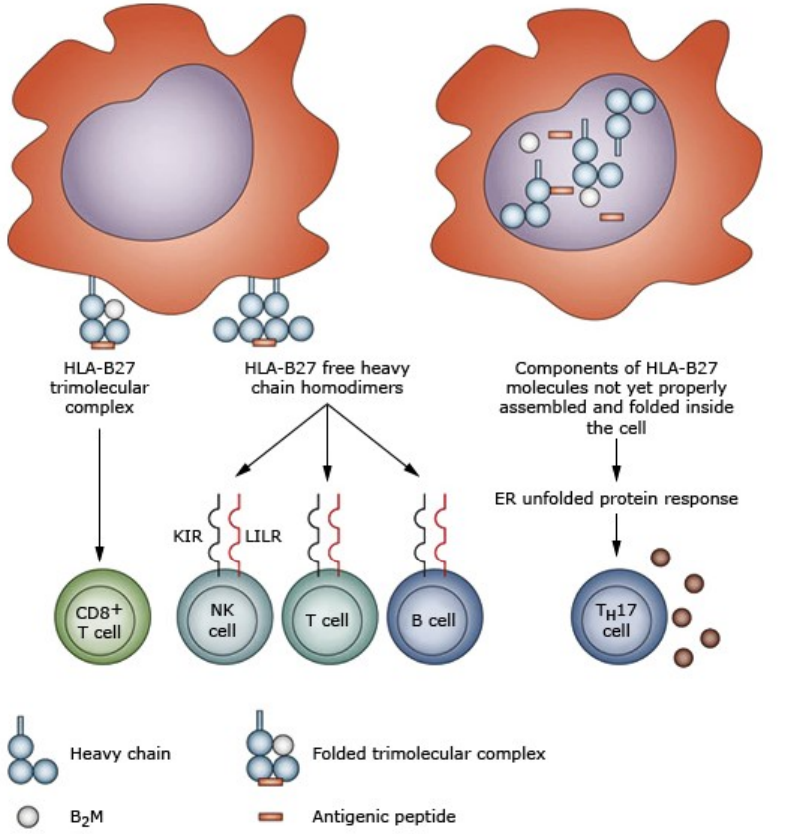
- HLA-B27 in the major histocompatibility complex (MHC) locus contributes to ~20.1% of AS heritability

- Prevalence of + HLA B27:
  - ✓ Ankylosing spondylitis: 95%
  - ✓ Ethnically matched controls: 8%
  - ✓ Reactive arthritis: 70%
  - ✓ Enteropathic arthritis: 50%
  - ✓ Psoriatic arthritis: 35%

HLA B27 is an MHC class II molecule and participates in antigen presentation.

The onset of AS may result from aberrant peptide presentation , misfolded HLA-B27 molecules , HLA-B27 dimers or β2m accumulation and deposition

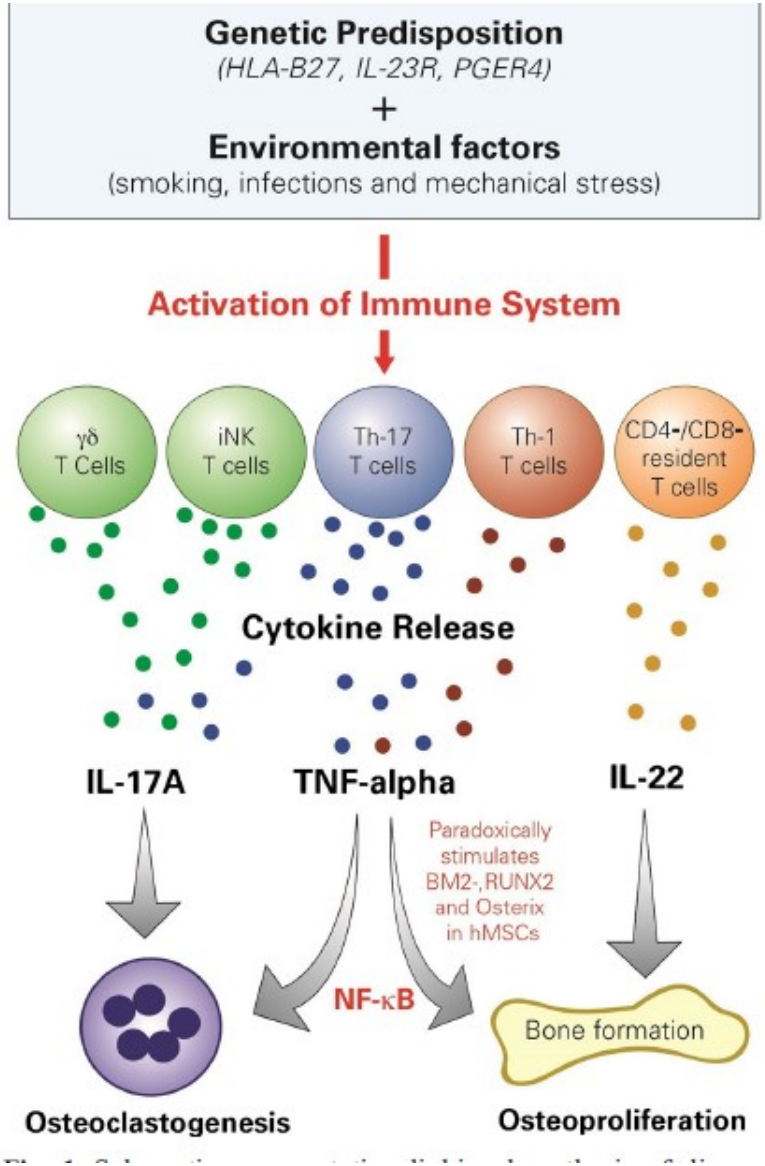
Three different HLA-B27 structures and hypotheses as to how they might induce disease processes in ankylosing spondylitis



HLA-B27 are first generated as free heavy chains, which inside the cells become associated and folded with the beta-2-microglobulin and antigenic peptide, and then become expressed on the cell surface as a trimolecular complex. It can also be expressed on the cell surface as homodimers of heavy chains without the beta-2-microglobulin.

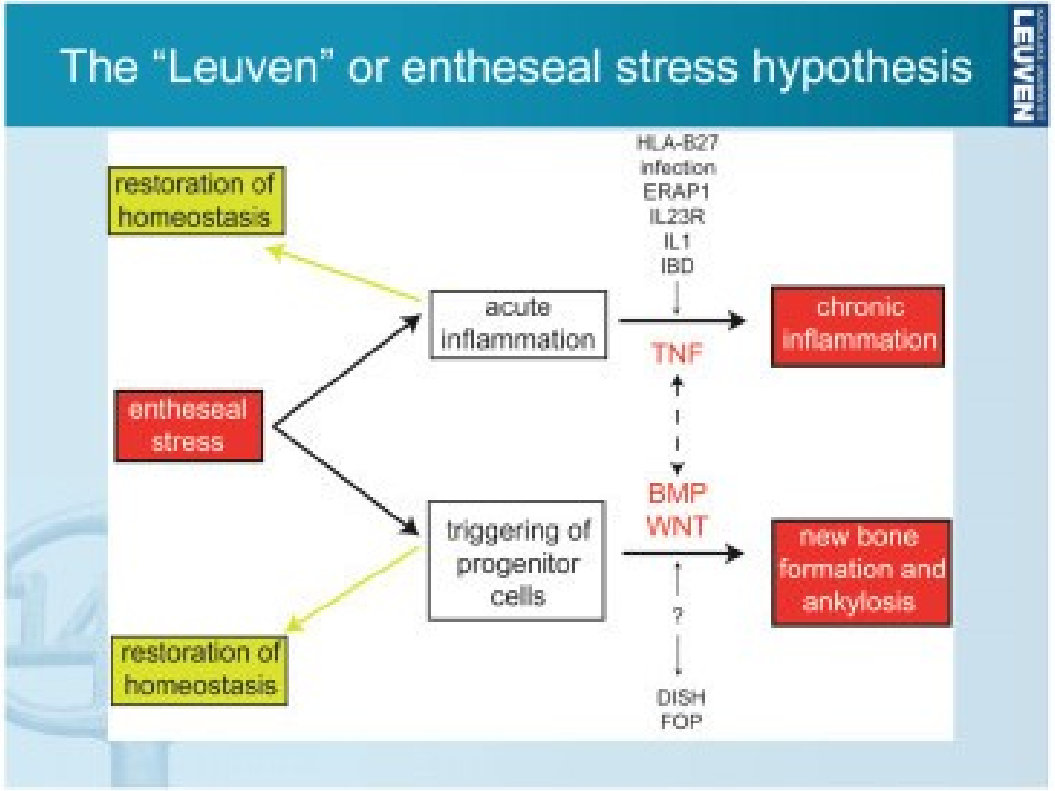
HLA: human leukocyte antigen.

http://www.nature.com


Genetic Predisposition
(HLA-B27, IL-23R, PGER4)
+
Environmental factors
(smoking, infections and mechanical stress)
Activation of Immune System
γδ T Cells
iNK T cells
Th-17 T cells
Th-1 T cells
CD4-/CD8- resident T cells
Cytokine Release
IL-17A
TNF-alpha
IL-22
Paradoxically stimulates BM2-,RUNX2 and Osterix in hMSCs
NF-κB
Bone formation
Osteoclastogenesis
Osteoproliferation

Entheseal stress hypothesis

Defines microdamage or cell stress in the enthesis as a trigger for inflammation



Enthesitis

The most common is swelling at the heels, at the insertion of the Achilles tendon or at the insertion of the plantar fascia ligament into the calcaneus

Other sites of enthesitis : iliac crests, greater trochanters, epicondyles at the elbows, tibial plateaus, costochondral junctions at the sternum, humeral tuberosities, manubrial-sternal joints, occiput, and spinous processes

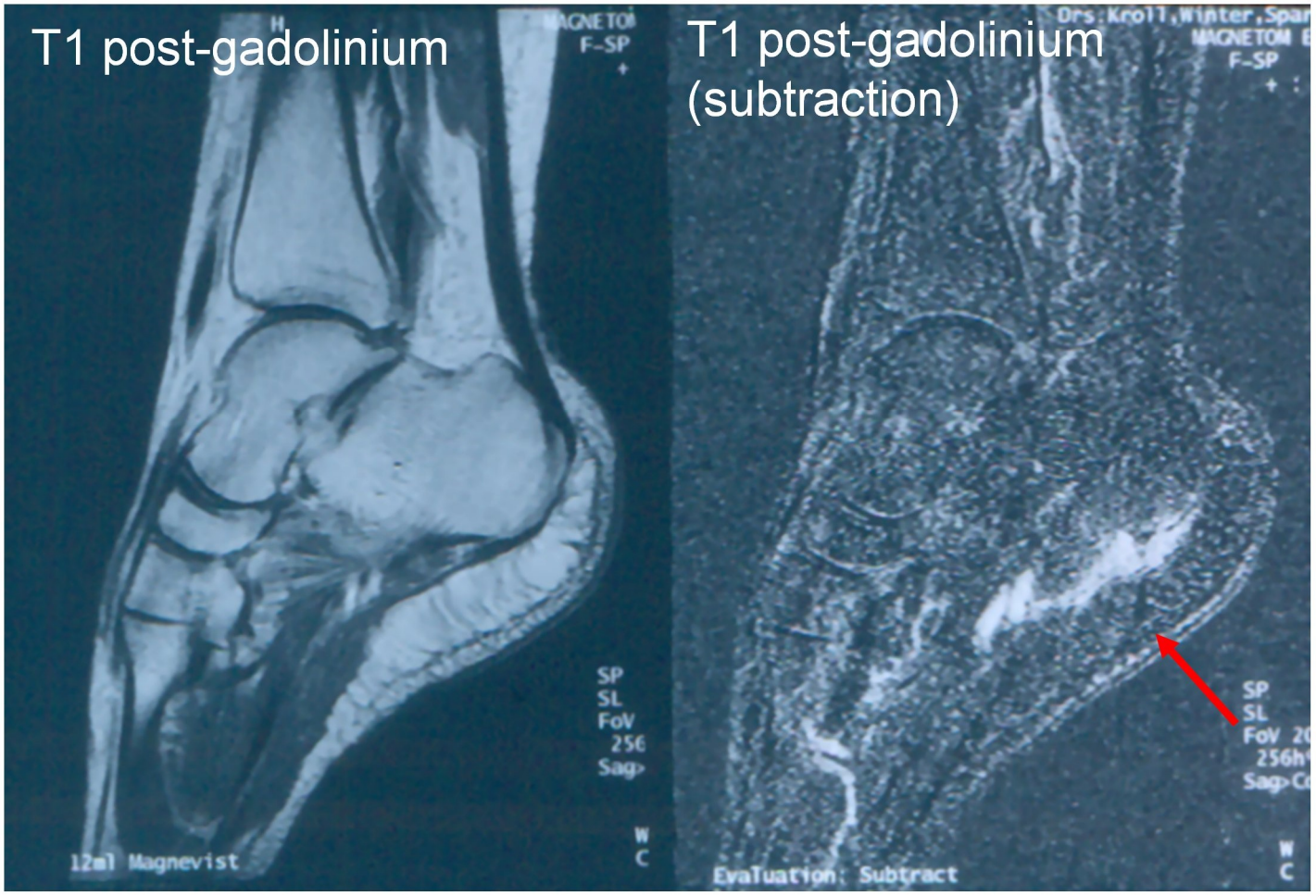
Enthesitis as a Manifestation of Spondyloarthritis by Scintigraphy

Acute Inflammation of both heels and of the MTP-joints I+II of the left foot as shown by scintigraphy

Right heel: Achilles tendon enthesitis

Left heel: Fascia plantaris enthesitis

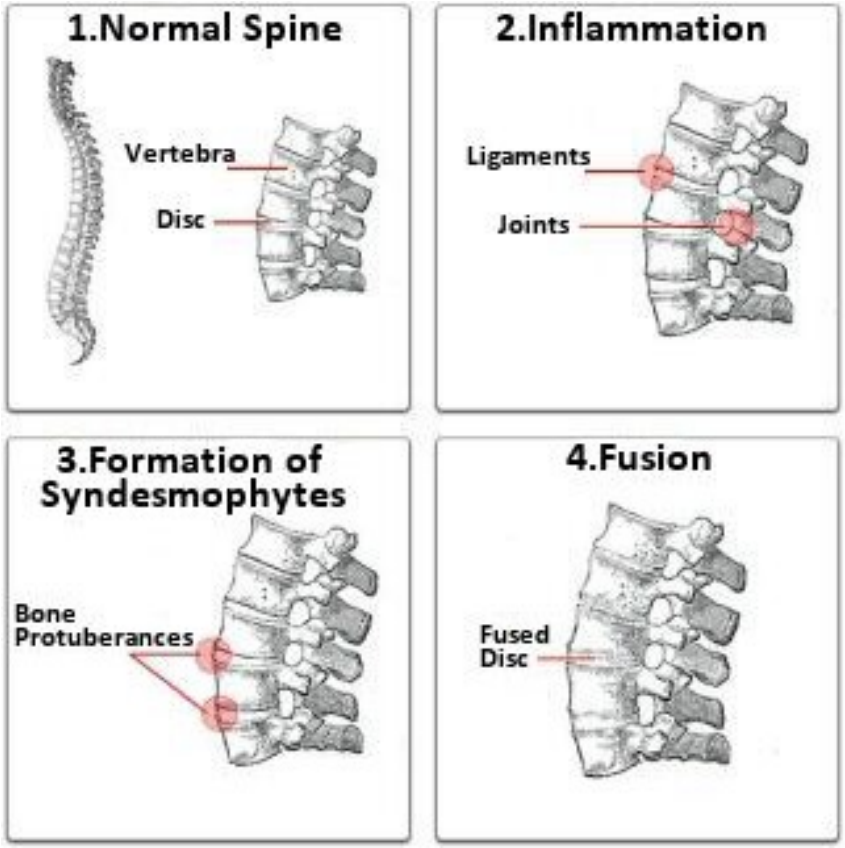
Enthesitis of the Plantar Fascia by MRI



Axial skeleton arthritis

-Arises from enthesitis

-Includes spondylitis and sacroiliitis



<u>Spondylitis</u>

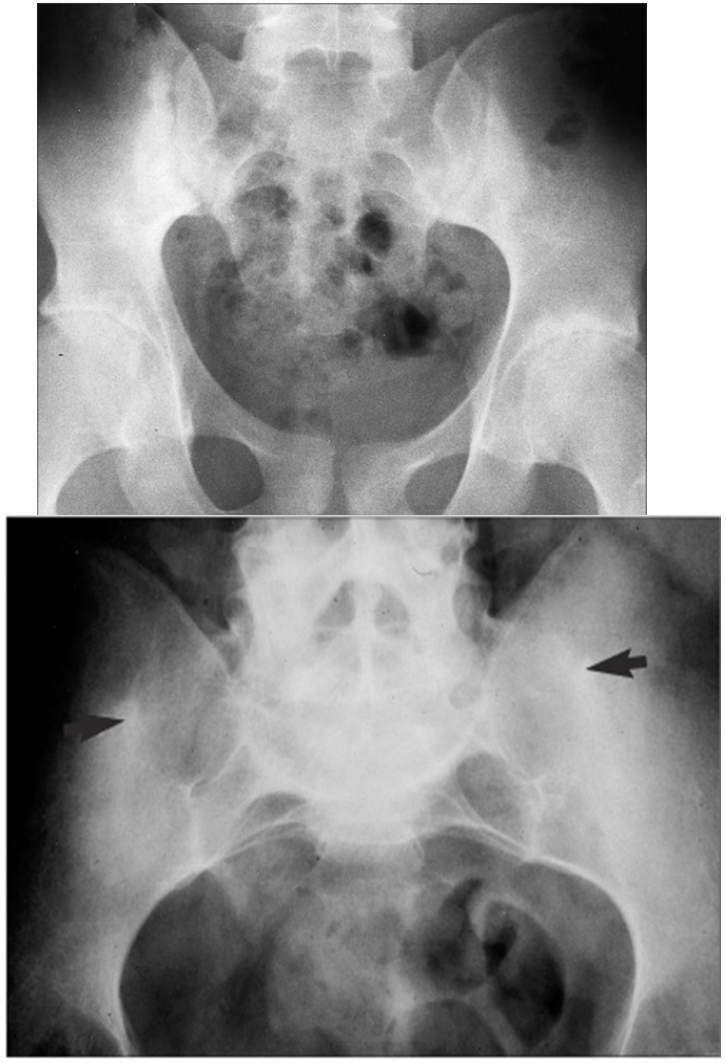
CD8 T cells invade the junction of the annulus fibrosis and the vertebral body (an enthesis)

Annulus fibrosis is replaced by bone (syndesmophytosis)

Vertebral bodies assume a square shape, and ultimately a bamboo spine

Sacroiliitis

- CD8 T cells invades the subchondral area at the junction of the bones and the cartilage (an enthesis)
- Cartilage on iliac side is replaced by bone, obliterating the joint



SPA: bone erosion and bone formation

- The major hallmark of AS is syndesmophyte formation that leads to fusion of the spine.

- Three-stages:

✓ Acute inflammatory reaction at the fibro-cartilagenous enthesis, leading to

✓ erosions which are followed by

✓ new bone formation or enthesopathy at the site

- Osteoporosis of the spine with risk of vertebral fractures.

Features of SpA
Dactylitis (sausage digits)

- The entire digit is swollen related to inflammation in the flexor tendon, sheath, and marked adjacent soft tissue involvement.

- Joints do not show the discrete palpable fusiform swelling of synovitis,

- There may be little pain or tenderness.

- **Differential of Dactylitis in addition to SpA**: tuberculosis, syphilis, sarcoidosis, sickle cell disease, and tophaceous gout.

Dactylitis

* Psoriasis plaque lesions

Arthritis of Several Joints (in one row) by Scintigraphy

Digitum III (right hand) and Digitum II (left hand).
Typical for Psoriatic Arthritis.

Inflammatory eye disease

- **Conjunctivitis** : non-purulent and transient
- **Anterior uveitis** : Acute onset of unilateral redness, pain, and photophobia

✓ -Can be recurrent.

✓ -50 % of patients with acute recurrent unilateral anterior uveitis have a form of SpA

✓ -10 % can become chronic and threaten permanent impairment of vision

Inflammation of the bowel mucosa and Psoriasis

- Up to 7% of patients with Ankylosing spondylitis have inflammatory bowel disease.

- Musculoskeletal symptoms are the most common extra-intestinal symptoms in patients with inflammatory bowel disease

- Psoriasis is associated with all forms of SpA (approximately 10 % of patients with AS have psoriasis).

Ankylosing Spondylitis / Axial Spondyloarthritis
Typical Manifestations

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

*** best estimate**

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

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

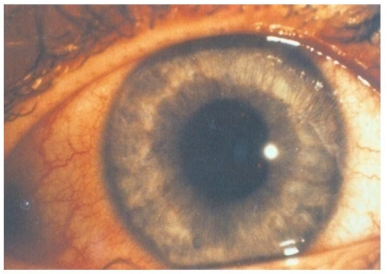
Modified from: Rudwaleit M et al. Ann Rheum Dis 2006;65:1251-2

ASAS

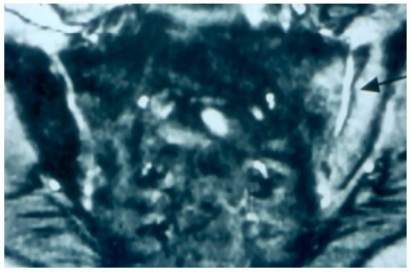
Spondyloarthritis: Characteristic Parameters Used for Diagnosis I

Symptoms

Inflammatory back pain



Imaging



Lab

ESR/CRP

Patient‘s history

Good response to NSAIDs

ASAS

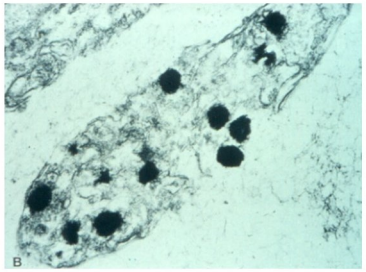
Spondyloarthritis: Characteristic Parameters Used for Diagnosis II

Genetics

HLA-B27 positive

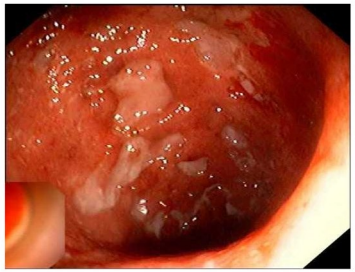
family history

Predisposing/ concomitant diseases



Infection*

psoriasis



Crohn‘s

*positive staining for Chlamydia in synovial membrane[1]

1. Schumacher HR et al. Arthritis Rheum 1988;31:937-946

Ankylosing spondylitis

- A chronic inflammatory disease that characterized by enthesitis and subsequent syndesmophytes in spinal joints and peripheral joints.
- More common in men 2:1
- Classic age 16-40

- Inflammatory back pain with alternating pain in the buttocks region due to sacroillitis
- Fatigue (impaired sleep)
- Oligoarthritis
- Acute unilateral anterior uveitis
- Enthesitis

Ankylosing spondylitis

- Cardiovascular involvement with conduction defects and aortitis with dilatation of the aortic valve ring and aortic regurgitation

- Pulmonary involvement: upper lung fibrosis
- Restrictive lung disease due to rigid chest wall.

Case 1

- 24 y/o man with low back pain x 3 years. Had alternating buttock pain, worse in the morning with 25 min stiffness. Wakes up from sleep late at night because of pain. Pain got better with ibuprofen and exercise at the gym.

Modified Criteria (Berlin) for Inflammatory Back Pain

(chronic back pain, onset < 45 yrs)

Ankylosing Spondylitis n=101; mechanical back pain n=112

- morning stiffness > 30 min
- improvement with exercise, not with rest
- awakening at 2nd half of the night because of pain
- alternating buttock pain

Sensitivity: 70.3%; Specificity: 81.2%

Inflammatory back pain present if at least 2 of the above 4 parameters are fulfilled.

Rudwaleit M et al. Arthritis Rheum 2006;54:569-78

ASAS

Inflammatory Back Pain Criteria (Calin)

Ankylosing Spondylitis n=42; mechanical low back pain n=21

- age at onset < 40 years
- duration of back pain > 3 months
- insidious onset
- morning stiffness
- improvement with exercise

Sensitivity: 95%; Specificity: 76%

Inflammatory back pain if 4/5 criteria are present.

Calin A et al. JAMA 1977;237:2613-4

ASAS

Inflammatory back pain

- The highest predictive value for true inflammatory back pain:

✓ pain at night and

✓ improvement with exercise.

Case 1, cont., your next step

- 1- check HLA B27
- 2-Check ESR/CRP
- 3- Order imaging study
- 4- Obtain additional history

Case 1, cont., your next step

- 4- obtain additional history

✓ **Evaluate for other symptoms**: peripheral joint pain, heel pain, bloody stools. Diarrhea, rashes

✓ **Evaluate for other diagnoses** : acute anterior uveitis, IBD, psoriasis

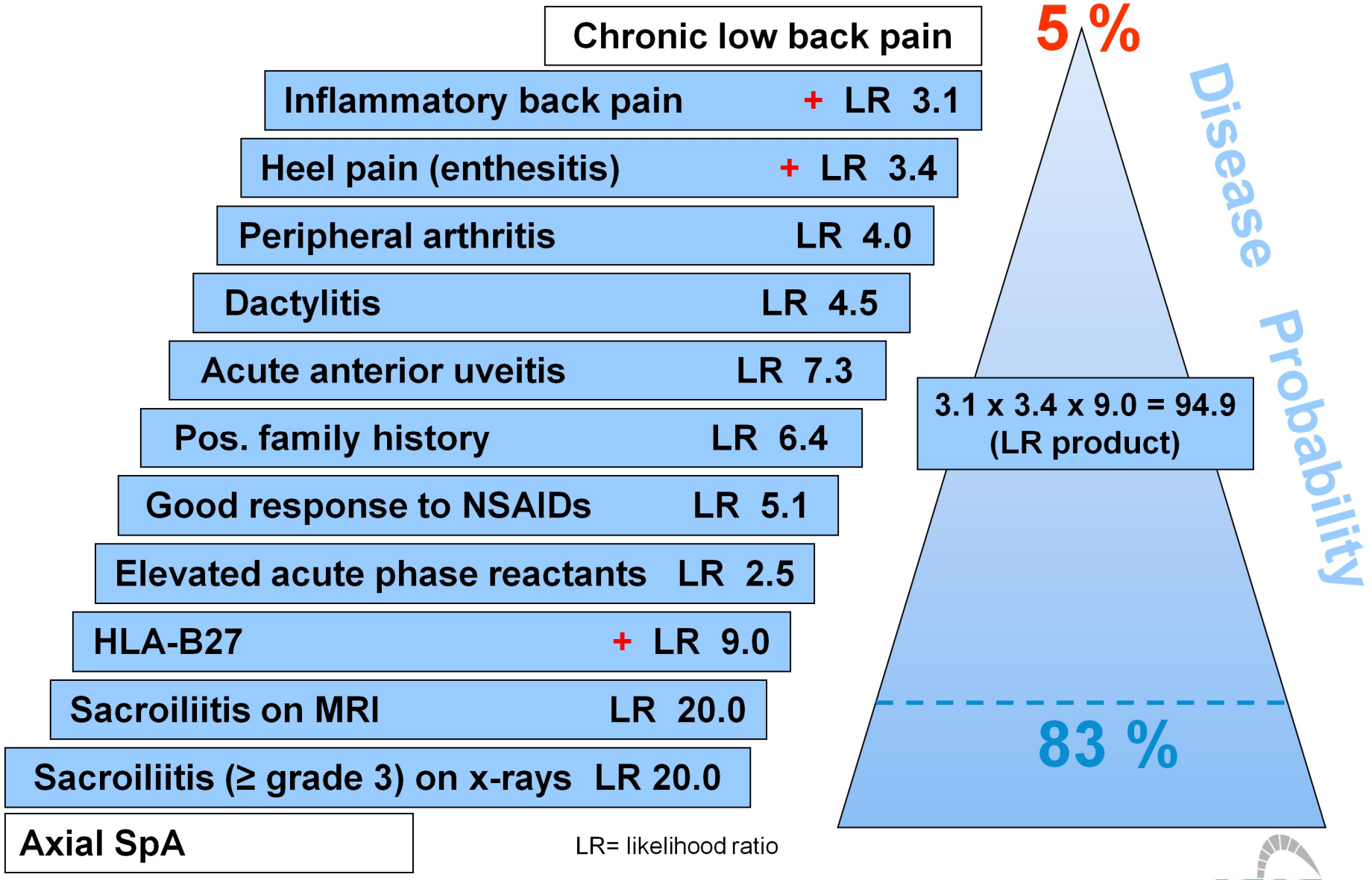
✓ **Assess Family history**: 20 % of AS pts will have a first degree relative with AS.

Case 1, cont.,

- The patient tells you his father has AS

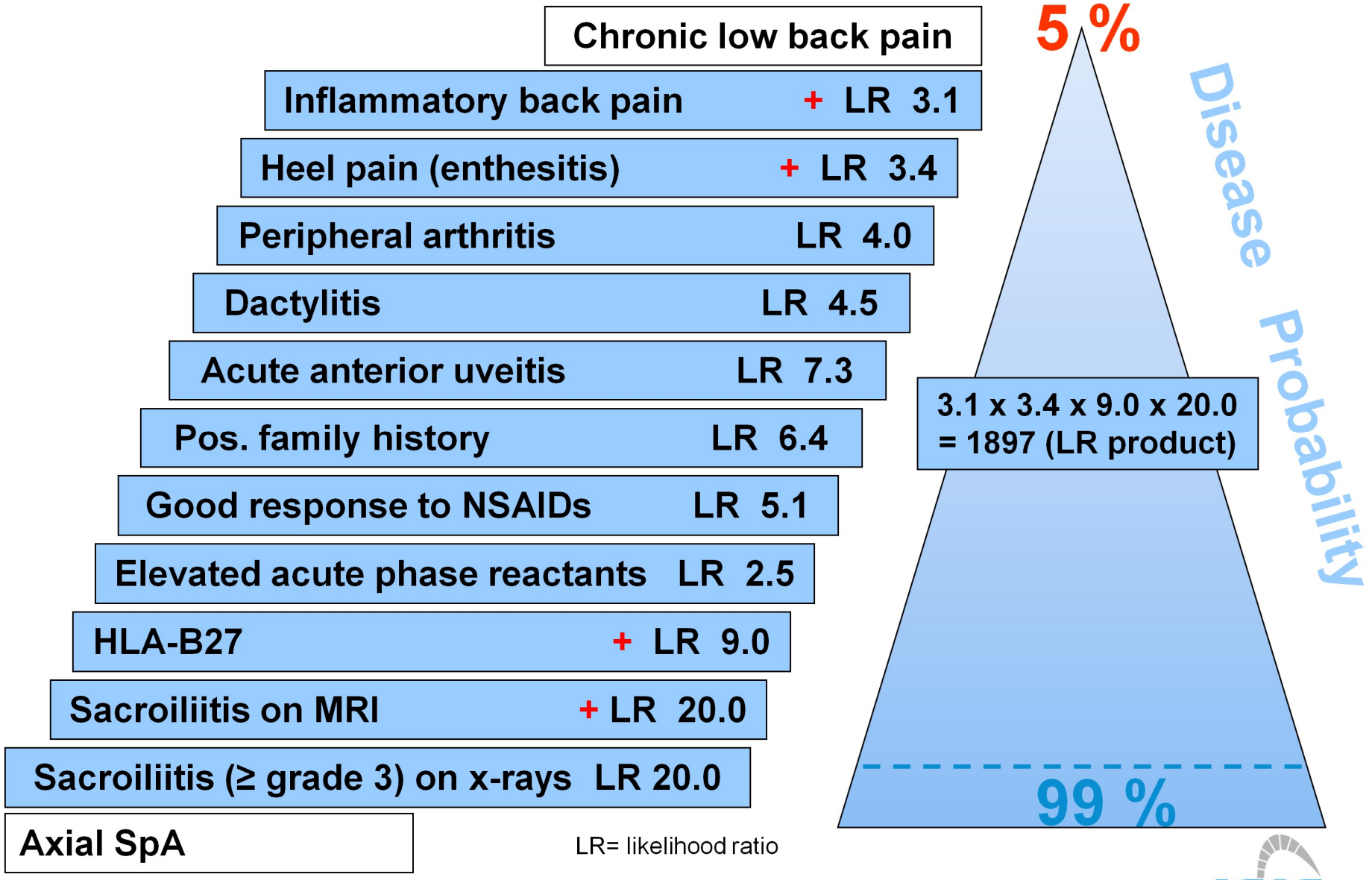
- Next step?

Diagnostic Pyramid for Axial Spondyloarthritis



Modified from: Rudwaleit M et al. Arthritis Rheum 2005;52:1000-8

Diagnostic Pyramid for Axial Spondyloarthritis



Modified from: Rudwaleit M et al. Arthritis Rheum 2005;52:1000-8

The Incidence of Ankylosing Spondylitis

- The annual incidence of AS requiring antirheumatic medication was 6.9 per 100,000 adults (95% CI = 6.0 to 7.8) in Finland[1].
- The incidence of AS was shown to be 7.26 per 100,000 inhabitants in northern Norway[2].
- The overall age- and sex-adjusted incidence of AS was 7.3 per 100,000 person years (95% CI = 6.1 to 8.4) in the U.S[3].

No data available for axial spondyloarthritis (proportion AS/nr-axSpA about 50/50).

1. Kaipiainen-Seppanen O et al. J Rheumatol 1997;24:496-499
2. Bakland G et al. Arthritis Rheum 2005;53:850-855
3. Carbone LD et al. Arthritis Rheum 1992;35:1476-82

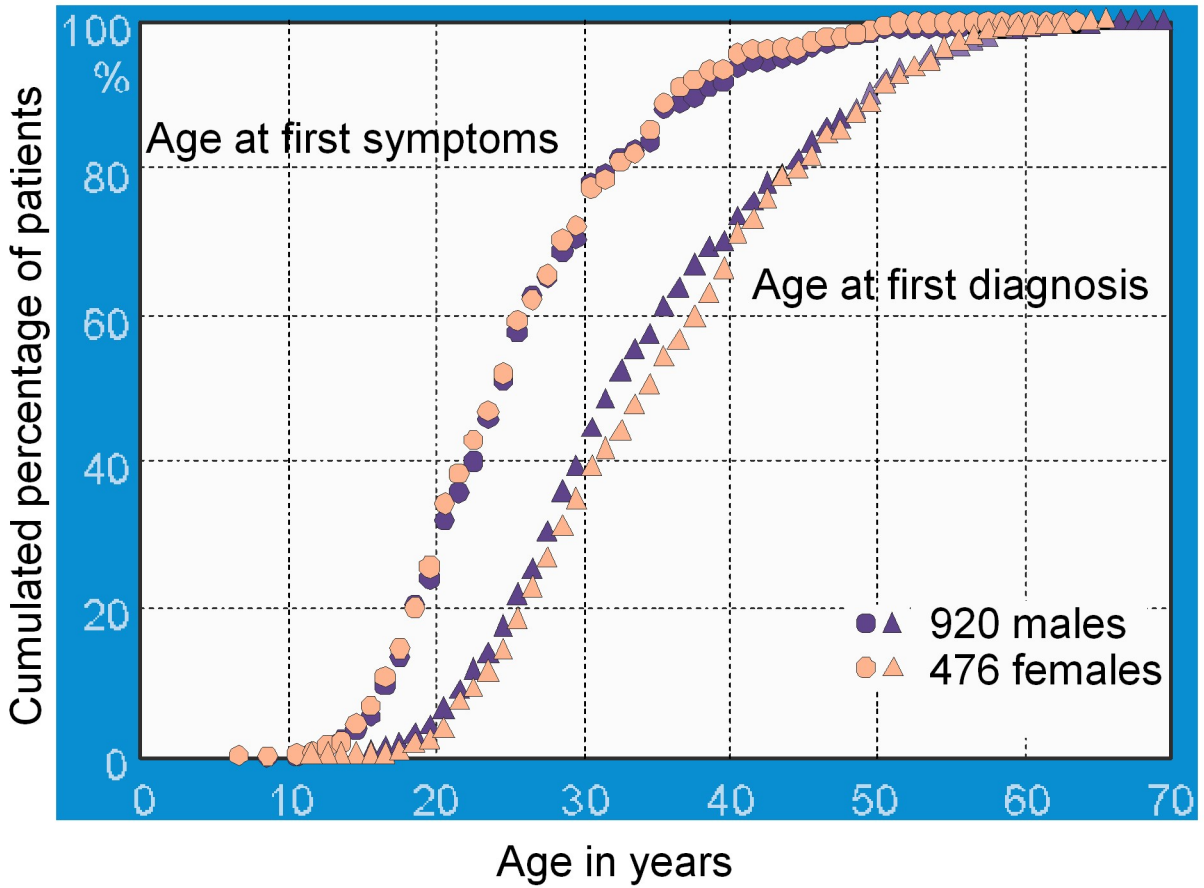
ASAS

Ankylosing Spondylitis - Prevalence

Country	AS Prevalence	HLA-B27 Prevalence
US[1, 2]	0.52%	6%
The Netherlands[3]	0.1%	8%
Germany[4]	0.55%	9%
Norway[5]	1.1 – 1.4%	14%
Haida Indians[6]	6.1%	50%

[1]Helmick CG et al. Arthritis Rheum 2008;58:15-25; [2] Reveille JD et al. Arthritis Rheum 2012;64:1407-11;
[3]van der Linden S et al. Arthritis Rheum.1984;27:241-9; [4]Braun J et al. Arthritis Rheum 2005;52:4049-50;
[5]Gran T et al. Ann Rheum Dis 1985;44:359-67; [6]Gofton JP et al. Ann Rheum Dis 1966;25:525-7

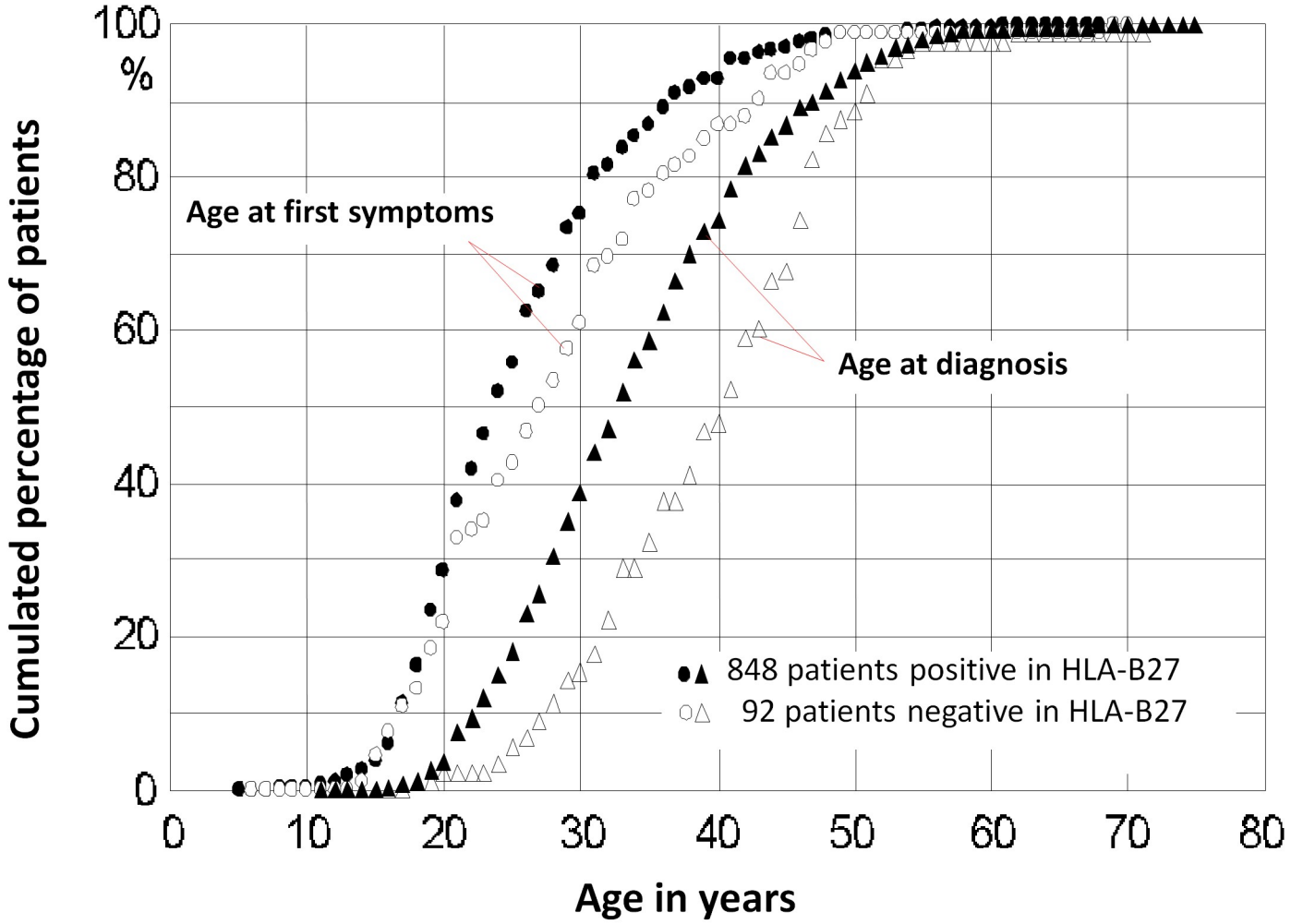
Age at First Symptoms and at First Diagnosis in Ankylosing Spondylitis Patients



Average delay in diagnosis: 9 years

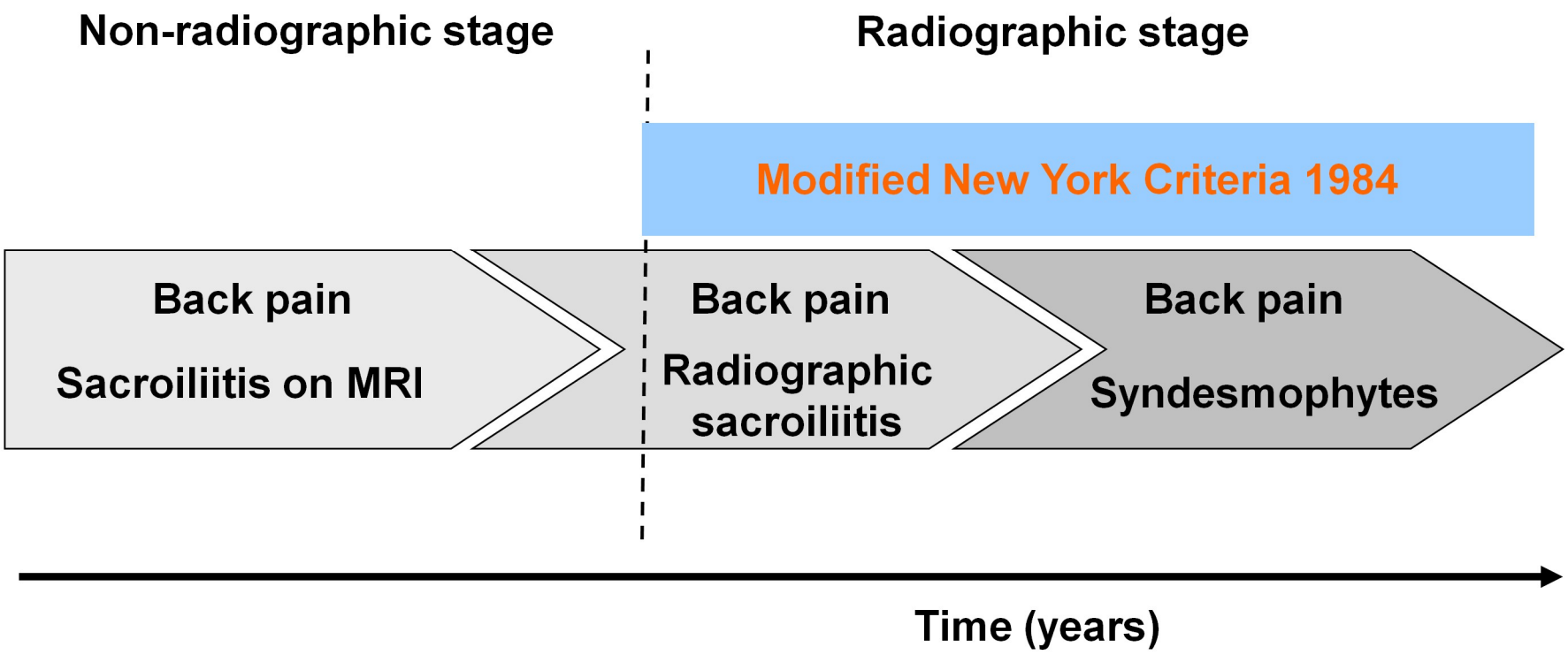
Feldtkeller E et al. Curr Opin Rheumatol 2000;12:239-247 (with permission)

Age at First Symptoms and Age at Diagnosis in HLA-B27 (+) and (-) Patients with Ankylosing Spondylitis



Feldtkeller E et al. Rheumatol Int 2003;23:61-66 (with permission)

Axial Spondyloarthritis



Rudwaleit M et al. Arthritis Rheum 2005;52:1000-8 (with permission)

Case 1 cont., what to order

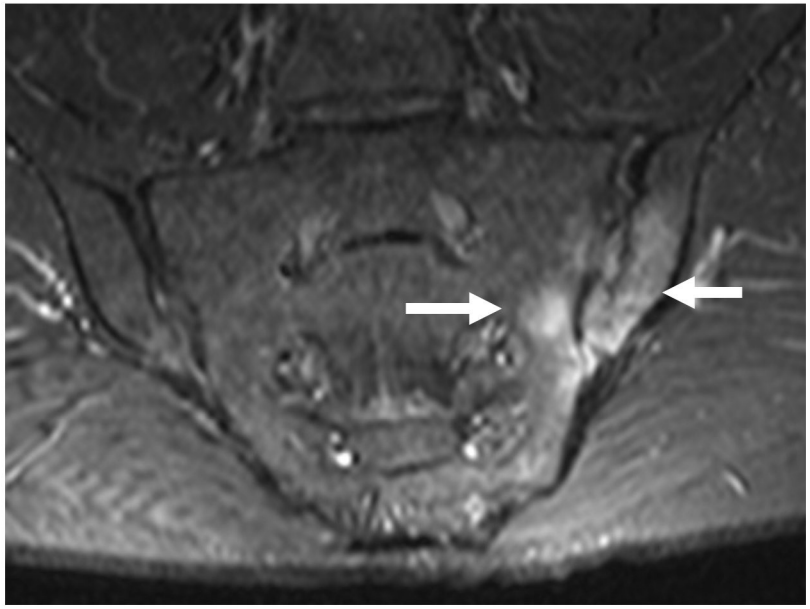
- Labs: HLA B27, ESR, CRP
- Imaging: start with AP pelvis.
- If negative pelvis x ray: MRI with STIR of the pelvis for evaluation of sacroiliac joints
- MRI spine:+/-

Grading of Radiographic Sacroiliitis (1966)

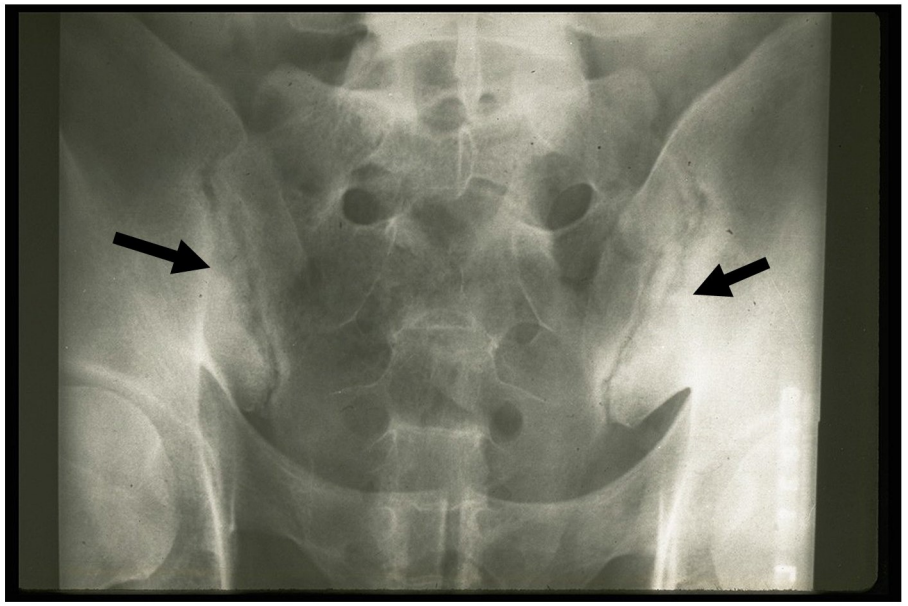
- **Grade 0** **normal**
- **Grade 1** **suspicious changes**
- **Grade 2** **minimal abnormality – small localized areas with erosion or sclerosis, without alteration in the joint width**
- **Grade 3** **unequivocal abnormality – moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis**
- **Grade 4** **severe abnormality – total ankylosis**

Bennett PH, Burch TA: Amsterdam.Excerpta Medica Foundation International Congress Series 148, 1966:456-457

Sacroiliitis by MRI and X-ray in Patients with Axial Spondyloarthritis



Active inflammatory sacroiliitis without bony changes



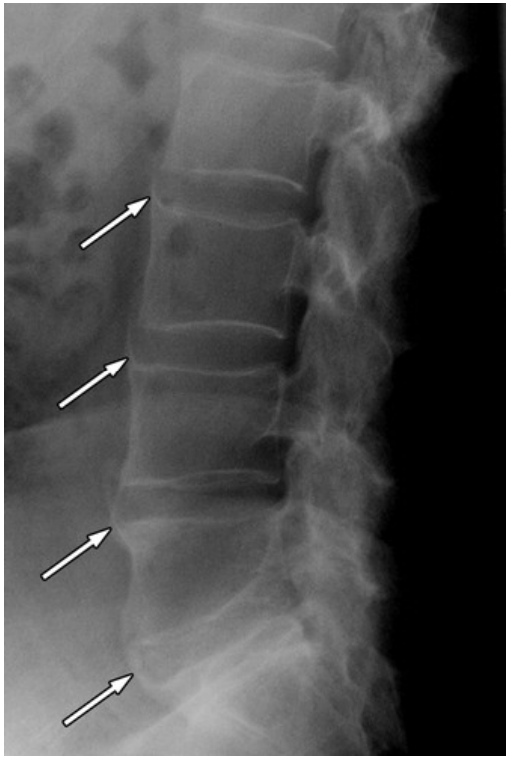
Sacroiliitis with bony changes (grade II)

Radiographic features in Ankylosing spondylitis

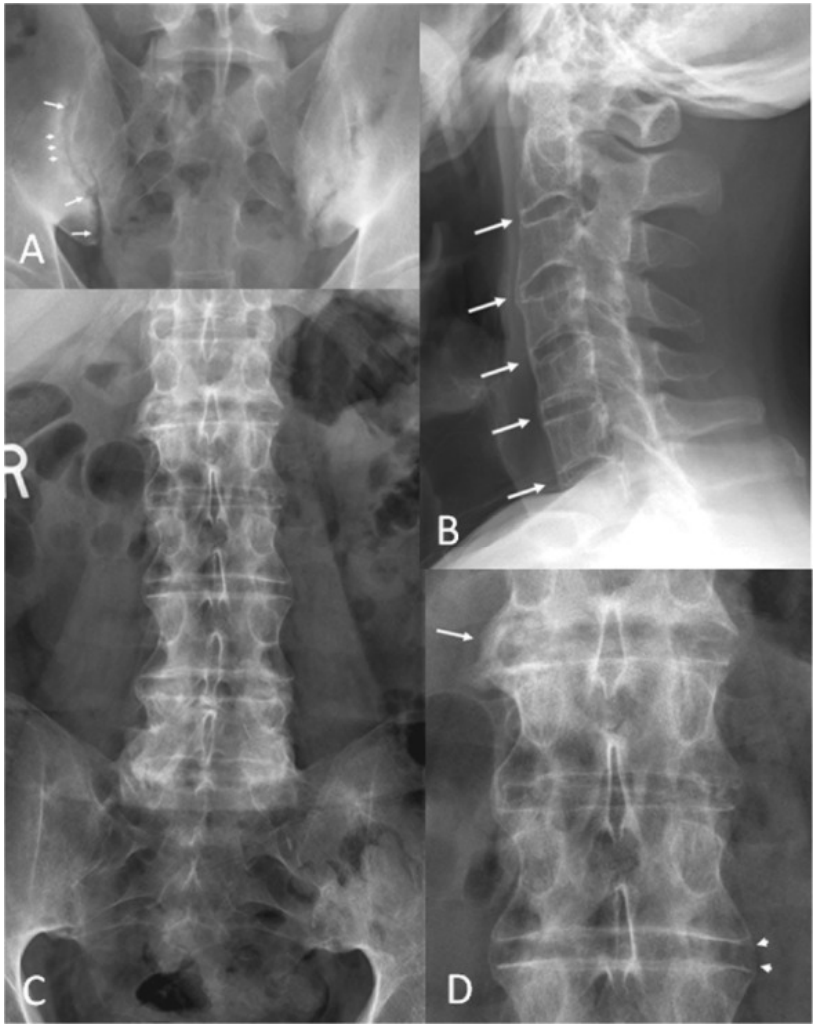
Spine

- Early spondylitis is characterized by small erosions at the corners of vertebral bodies with reactive sclerosis (Romanus lesions and shiny corner sign)

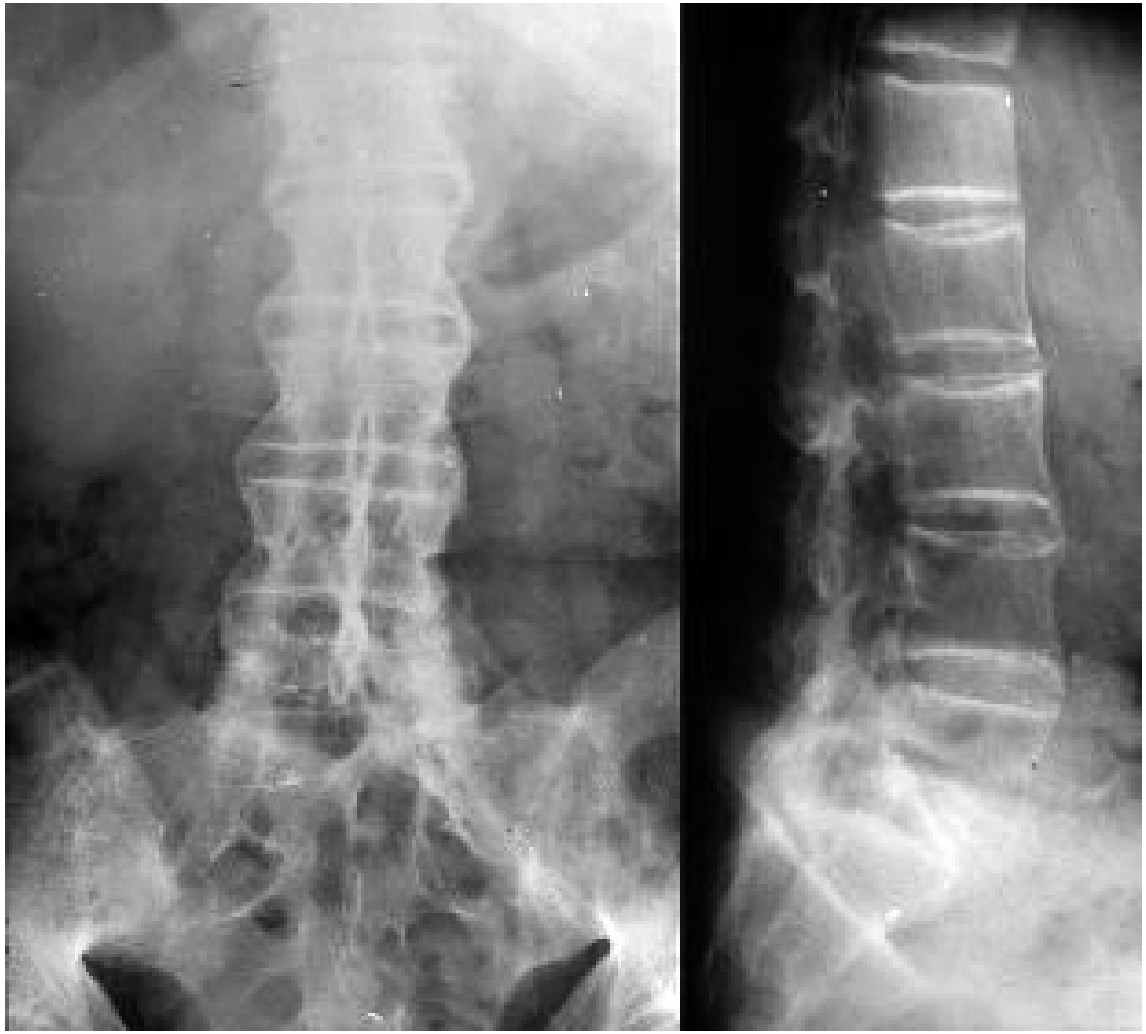
- Diffuse syndesmophyitic ankylosis can give a "bamboo spine" appearance



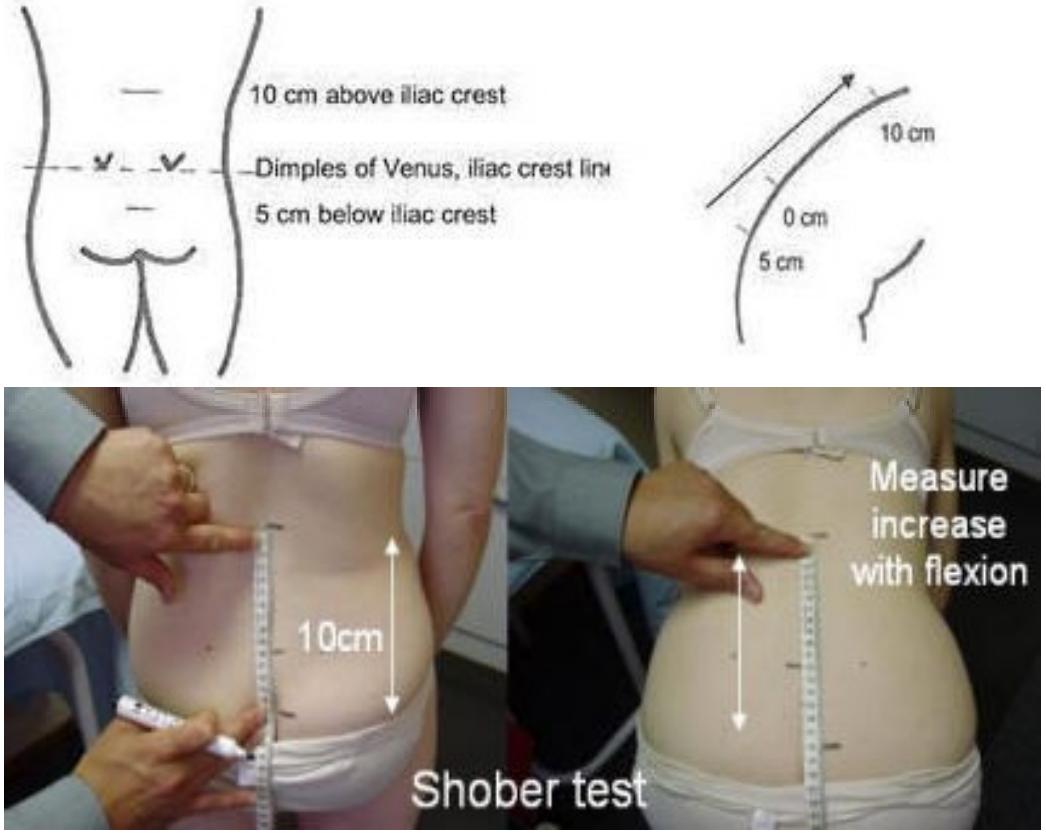
Ankylosing spondylitis



Bamboo spine



Shober’s test



Final Stage of AS with Severe Kyphosis of Thoracic and Cervical Spine

Unable to look ahead while walking
(‚patient cannot see the sun‘)

AS Patient with no Flexibility of the Lumbar Spine on Bending Forward (Flat Back)

AS Patient with Disappearance of the Lordosis of the Lumbar Spine

Modified New York Criteria for Ankylosing Spondylitis (1984)

1. Clinical criteria:

a.Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.

b.Limitation of motion of the lumbar spine in both the sagittal and frontal planes.

c.Limitation of chest expansion relative to normal values correlated for age and sex.

2. Radiological criterion:

Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally

Definite ankylosing spondylitis if the radiological criterion is associated with at least 1 clinical criterion.

van der Linden S et al. Arthritis Rheum 1984;27:361

ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

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

Sacroiliitis on imaging*

plus

≥1 SpA feature

OR

HLA-B27

plus

≥2 other SpA features

***Sacroiliitis on imaging**

- **active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA**
- **definite radiographic sacroiliitis according to the modified New York criteria**

SpA features:

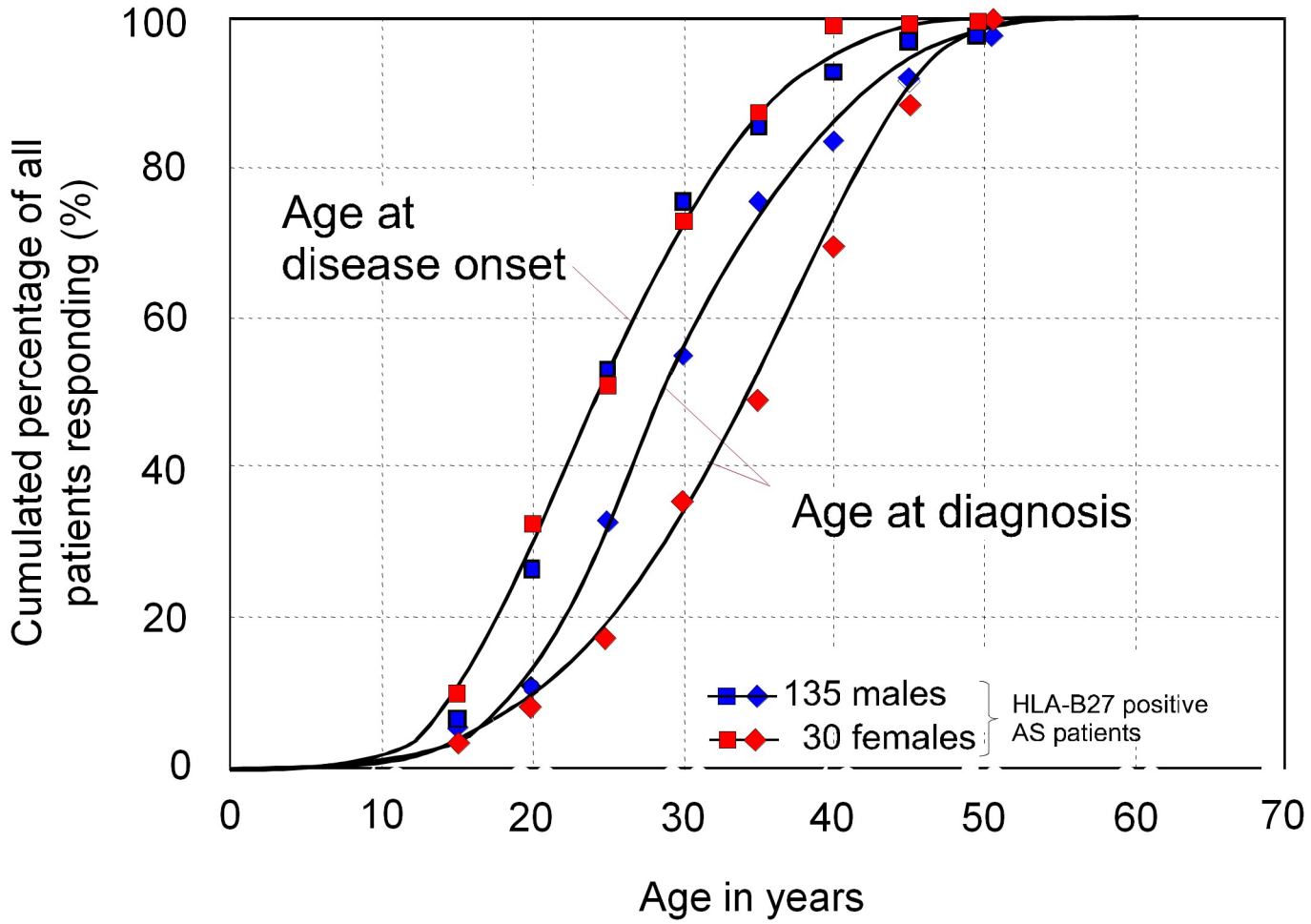
- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

n=649 patients with back pain;

Overall
Sensitivity: 82.9%, Specificity: 84.4%
Imaging arm alone
Sensitivity: 66.2%, Specificity: 97.3%
Clinical arm alone
Sensitivity: 56.6%, Specificity: 83.3%

Rudwaleit M et al. Ann Rheum Dis 2009;68:777-783 (with permission)

Age at Onset and Time of Ankylosing Spondylitis-Diagnosis



van der Linden SM et al. Arthritis Rheum 1984;27:241-249 (with permission)

Psoriatic arthritis

- Psoriasis :

✓ Present prior to arthritis 70 % of the time.

✓ Presents with the arthritis 10-15% of the time

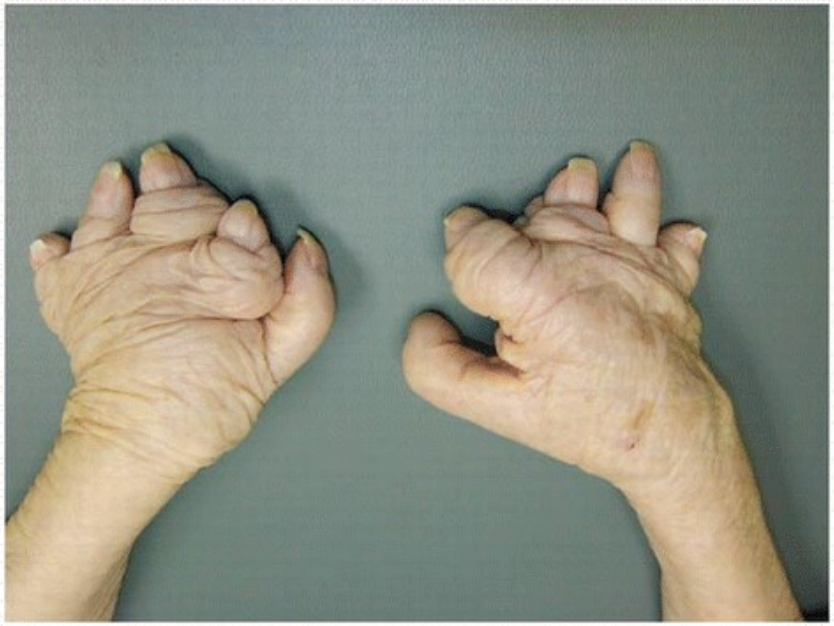
✓ Presents after the arthritis 10-15% of the time

- 5 patterns of arthritis

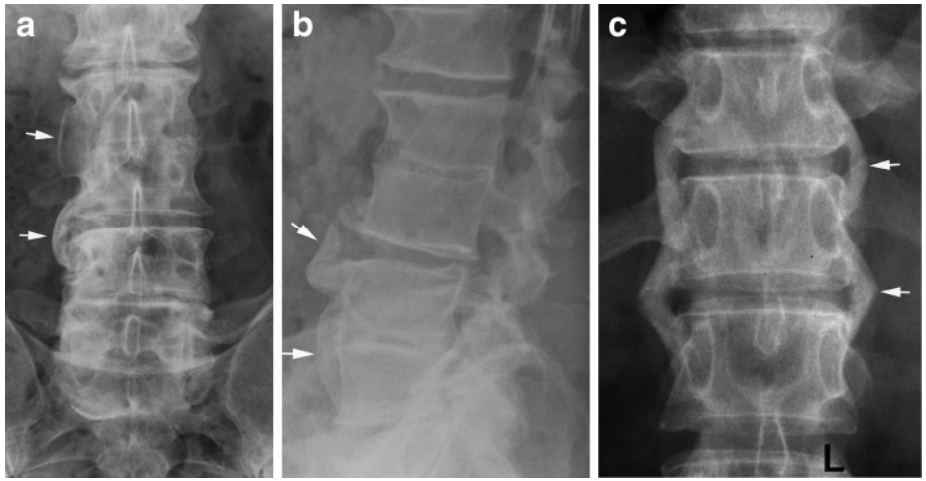
1. Distal
2. Arthritis mutilans
3. Polyarticular
4. Oligoarticular and
5. Axial Asymmetric sacroiliitis

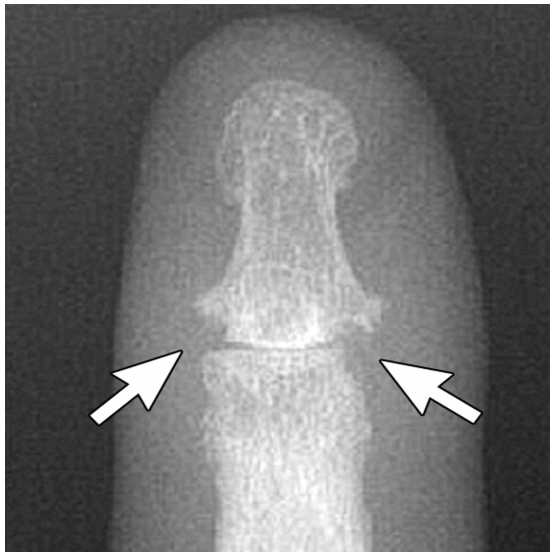
Psoriatic arthritis

Arthritis mutilans



Psoriatic arthritis





CASPER criteria for PsA

Joint, Spine or entheseal inflammatory disease with 3>= of the following:

TABLE 1: CLASSIFICATION OF PSORIATIC ARTHRITIS (CASPAR) STUDY CRITERIA

Criteria	Point Value
Skin Psoriasis Present Previously present Family history (if patient not affected)	2 1 1
Nail lesions (oncholysis, pitting, hyperkeratosis)	1
Dactylitis (present or past with documentation by rheumatologist)	1
Negative rheumatoid factor	1
Juxtaarticular new bone formation on radiograph	1

Adapted from reference 4.

Reactive arthritis

- An arthritis that arises following an infection, although the pathogens cannot be cultured from the affected joints.
- Infections occur often in the gastrointestinal or urogenital tract.
- The diagnosis is mainly clinical: acute oligoarticular arthritis of larger joints developing within 2-4 weeks of the preceding infection.
- Annual incidence of ReA is 0.6-27/100,000

Reactive arthritis

- Keratoderma blenorrhagica
  - A papulosquamous skin rash
  - Comprises vesicles that become hyperkeratotic, forming crusts before disappearing
    - Palms/soles
    - Penis (causing circinate balanitis)

- Oral ulcers (usually shallow and painless)
- Inflammatory back pain (50% of patients)
- Enthesitis (40%)
- Dactylitis (40%)
- Anterior uveitis (20% of patients)

Reactive arthritis diagnostic criteria

Diagnostic criteria for reactive arthritis. A "definite" diagnosis of reactive arthritis is based on the fulfillment of both major criteria and a relevant minor criterion, while a "probable" diagnosis is characterized by both major criteria but no relevant minor criterion or one major criterion and one or more of the minor criteria. The identification of the trigger infection is also required.

Major criteria	1) Arthritis with 2 of 3 of the following findings: - Asymmetric - Mono or oligoarthritis - Lower limb involvement 2) Preceding symptomatic infection with 1 or 2 of the following findings: - Enteritis (defined as diarrhea for at least 1 day, and 3 days to 6 weeks before the onset of arthritis) - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
Minor criteria	At least one of the following: 1) Evidence of triggering infection: - Positive urine ligase reaction or urethral/cervical swab for *Chlamydia trachomatis* - Positive stool culture for enteric pathogens associated with reactive arthritis 2) Evidence of persistent synovial infection (positive immunohistology or PCR for *Chlamydia*)

Infectious agents commonly and less frequently associated with reactive arthritis.

Gastrointestinal tract	*Yersinia*
	Salmonella
	Shigella
	Campylobacter jejuni
Urogenital tract	*Chlamydia trachomatis*
	Neisseria gonorrhoea
	Mycoplasma genitalium
	Ureaplasma urealyticum
Less frequent agents	*Clostridium difficile*
	Campylobacter lari
	Chlamydia psittaci
	Chlamydia pneumoniae

Enteropathic arthritis

- IBD-related arthritis happens more frequently in crohn's colitis than crohn's ileitis.
- Type 1 arthritis: runs with the GI disease activity, so treat underlying IBD to treat the arthritis
- Type 2 arthritis: spondylitis runs independently of the GI disease activity

	AS	PsA	ReA	IBD arthritis
Gender	M:F 2-3:1	M=F	M:F 1:1 GI, 8:1 GU	M=F
Age at onset	16-40	30-55	20-40	any
HLA B 27	85-95%	25-60%	30-70%	7-70%
Peripheral pattern	Uncommon (oligo)	Varies	Asym mono/oligo	Asym oligo/poly
Sacroillitis	symmetric	asymmetric	asymmetric	symmetric
Skin	Ps 10-20%	Ps, nail changes	KB, CB	EN, PG, Ps
Eye	AAU??	Uveitis	AAU, conjunctivitis	AAU
Syndesmophytes	Marginal	Non -marginal, bulky	Non -marginal, bulky	Marginal

Treatment of SPA

- Axial Vs peripheral disease
- Physical therapy: improves function, flexibility and disease activity
- NSAIDs: first line therapy. Less progression.? DMARD?
- Glucocorticoids not recommended in AS.
- DMARDs: sulfasalazine, methotrexate: peripheral arthritis only not in axial disease.

Treatment of spondyloarthropathies

Nonsteroidal antiinflammatory agents

Naproxen sodium, indomethacin, meloxicam, diclofenac sodium ,,etc

Disease modifying anti-rheumatic drugs (DMARDs)

Sulfasalazine
Methotrexate

Tumor necrosis factor antagonists

Infliximab
Etanercept
Adalimumab
Certolizumab pegol
Golimumab

IL-17 antagonist:

secukinumab

For axial arthritis, exercises to maintain posture and flexibility

Thank you