Juvenile Spondyloarthropathies

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Objectives

- Definition
- Classification of spondyloarthritides
- Epidemiology of juvenile spondyloarthritis and psoriatic arthritis
- Clinical manifestations and course
- Imaging and labs
- Treatment

The name…

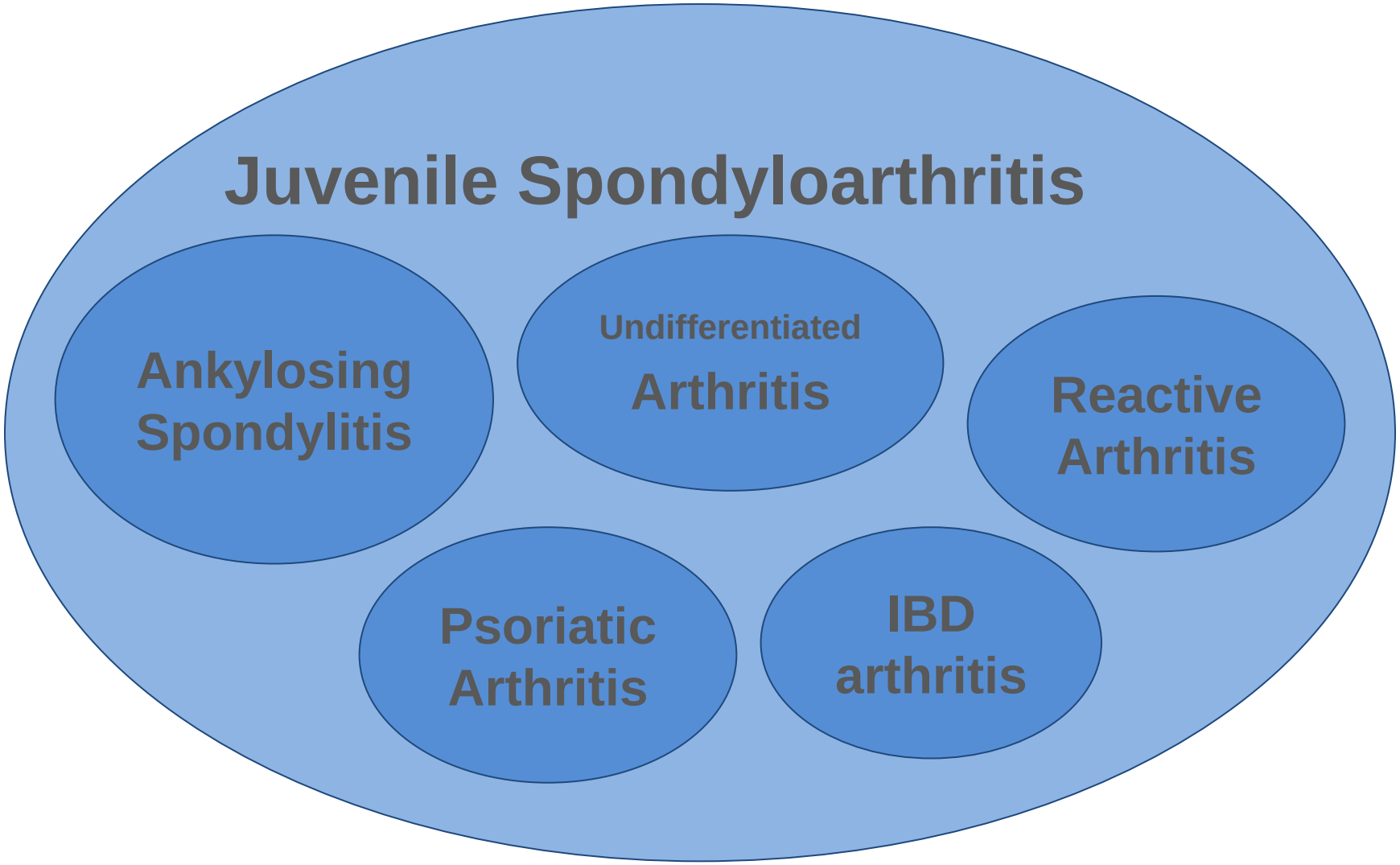
- Spondyloarthropathy
- Spondyloarthritis
- Spondyloarthritides
- Seronegative enthesopathy and arthropathy syndrome
- Pelvispondylopathy

Definition

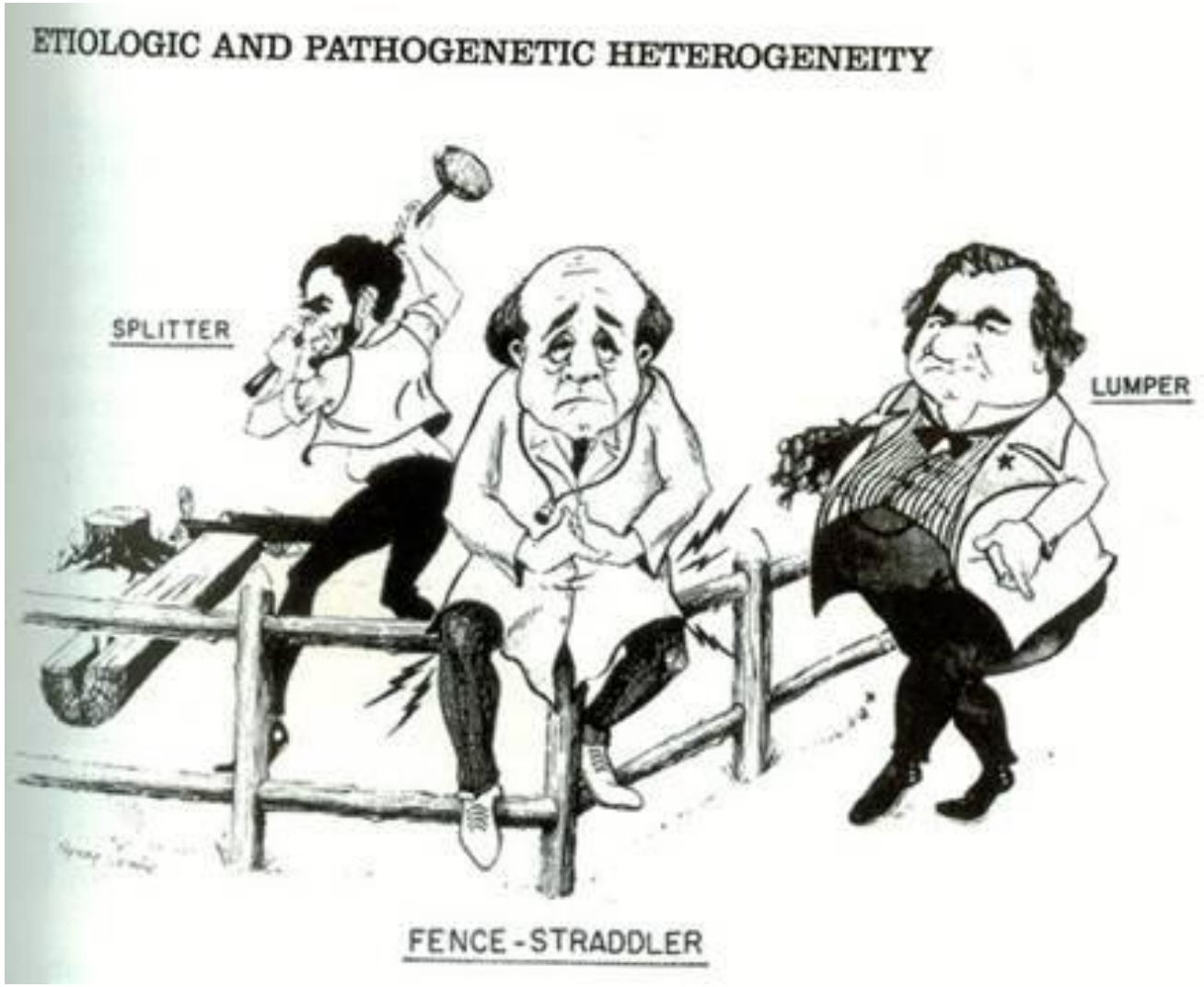
Group of pediatric rheumatic diseases characterized by enthesitis and arthritis involving in most cases, the lower extremities in the initial years, and, in a variable proportion of cases, the sacroiliac and spinal joints some years later.

Burgos-Vargas R. Rheum Dis Clin North Am. 2002

Types of Spondyloarthritides



Lumpers vs. Splitters



Lumpers vs. Splitters

Who has SpA?

- Depends on who you ask:
  - NY criteria for ankylosing spondylitis
  - Modified NY criteria for ankylosing spondylitis
  - European Spondyloarthropathy Study Group (ESSG) criteria
  - Modified ESSG criteria
  - Amor criteria
  - ILAR JIA enthesitis-related arthritis or psoriatic arthritis criteria
  - Garmisch–Partenkirchen criteria
  - SEA syndrome criteria
  - Atypical SpA in children criteria
  - Vancouver juvenile psoriatic arthritis criteria

Classification Warfare

Much of rheumatology remains mired in the 19th century when it comes to classifying autoimmune and inflammatory disorders….we revisit classification criteria every few years to determine whether they can be improved, but are these revisions necessary and useful?

Robert P. Sundel

Sundel RP. Nat Rev Rheumatol. 2012

Inflammatory back pain (ASAS 2009 definition)

- Age at onset <40 years
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night (with improvement on rising)

Modified NY criteria for Ankylosing Spondylitis

Table 1 Modified New York criteria for ankylosing spondylitis ref. [3]

A. Diagnosis*
1. Clinical criteria
a) Low back pain and stiffness for more tan three months, which improves by 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
B. Grading
1. Definite ankylosing spondylitis is considered if the radiologic criteria is associated with at least one clinical criterion
2. Probable ankylosing spondylitis if:
a) Three clinical criteria are present
b) The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered)
Radiographic criteria
Grade 0 = normal
Grade 1 = suspicious changes
Grade 2 = minimal abnormality – small localized areas with erosions or sclerosis, without alteration in the joint width
Grade 4 = severe abnormality –total ankylosis.

The proportion of children and adolescents that fulfill these criteria before they reach the age 17 years is probably <15%.

Burgos-Vargas R. Pediatr Rheumatol. 2012

ASAS classification criteria for axial spondyloarthritis

Back pain of ≥3 months' duration and age at onset <45 years

PLUS

Sacroiliitis on imaging and ≥1 feature of SpA

OR

HLA-B27 and ≥2 other features of SpA

#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

*Sacroiliitis on imaging

- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to mod NY criteria

ASAS classification criteria for peripheral spondyloarthritis

In patients with ≥3 months back pain (with/ without peripheral manifestations) and age at onset <45 years:

↓

Sacroiliitis on imaging plus ≥1 SpA feature

OR

HLA-B27 plus ≥2 other SpA features

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

In patients with peripheral manifestations ONLY:

↓

Arthritis* or **enthesitis** or **dactylitis**

plus

≥1 SpA feature
- uveitis
- psoriasis
- Crohn's/ulcerative colitis
- preceding infection
- HLA-B27
- sacroiliitis on imaging

OR

≥2 other SpA features
- arthritis
- enthesitis
- dactylitis
- IBP ever
- family history for SpA

*Peripheral arthritis: usually predominantly lower limb and/or asymmetric arthritis
Combined sensitivity 79.5%, combined specificity: 83.3%; n=975

Rudwaleit M, et al. Ann Rheum Dis 2011

ESSG classification criteria

Table 5 European Spondylarthropathy Study Group classification criteria and results of their validation in children

Inflammatory back pain *or* synovitis –symmetric or predominantly in the lower limbs *plus*
one of the following
• Positive family history
• Psoriasis
• Inflammatory bowel disease
• Urethritis, cervicitis, or acute diarrhea within one month before arthritis
• Buttock pain alternating between right and left gluteal areas
• Enthesopathy
• Sacroiliitis

Validated in 361 adults with SpA and 455 controls, such criteria showed a sensitivity of 86.7% and specificity of 87.0% ref. [38].
Validated in 2,982 rheumatic children ref. [74], the diagnostic properties of those criteria were 78.7% for sensitivity, 92.2% for specificity, 58.8% and 96.8% for positive and negative predictive values, respectively, 85.3% for positive likelihood ratio, and 90.3 for diagnostic accuracy. Sensitivity of the criterion "inflammatory back pain" was only 9.1% in children.

Enthesitis-related arthritis (ILAR)

- Arthritis and enthesitis

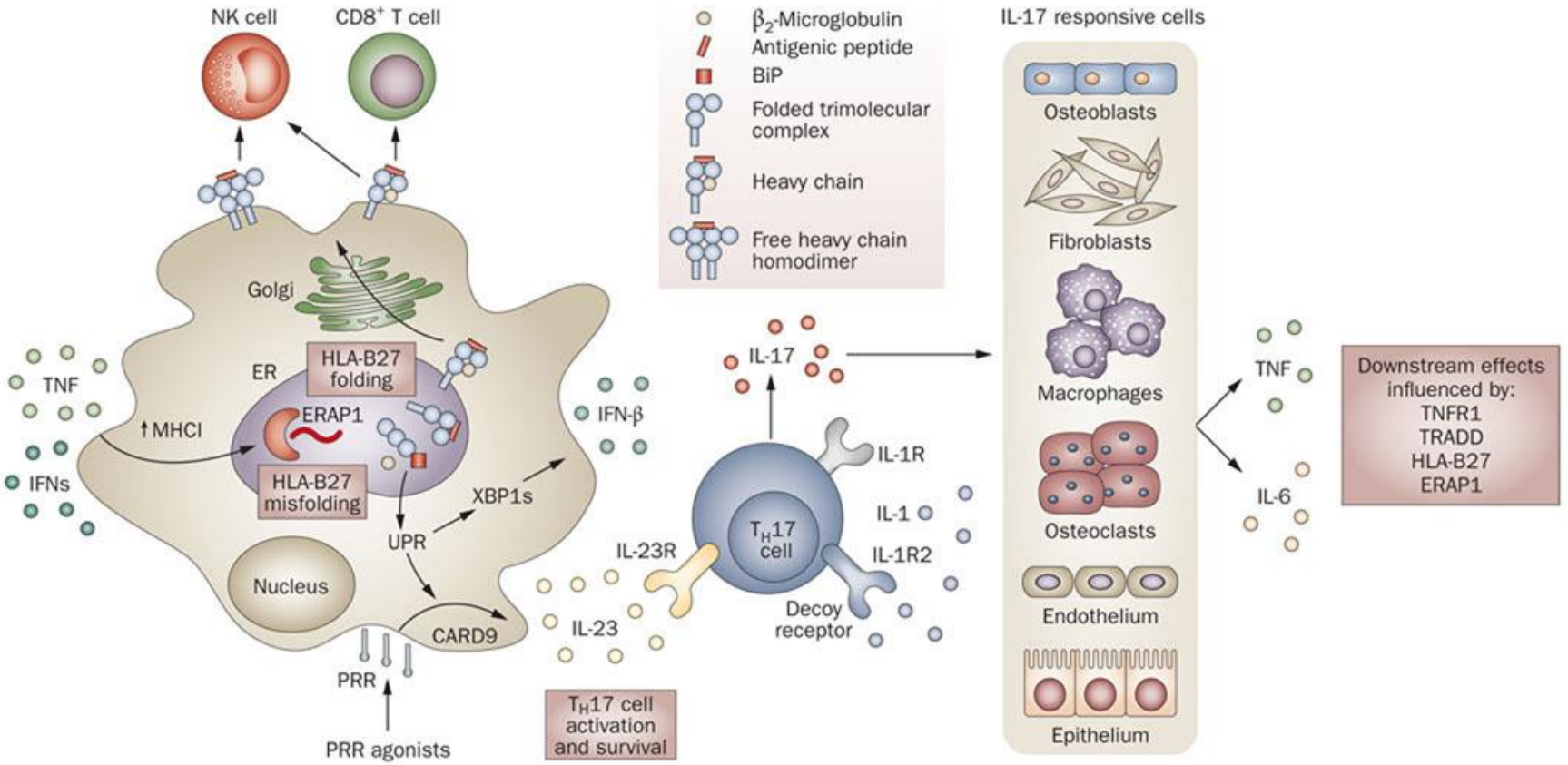
- Arthritis or enthesitis and at least 2 of the following:
  - Sacroiliac joint tenderness and/or inflammatory spinal pain
  - Family history of HLA-B27-associated disease in a 1st degree relative
  - Acute anterior uveitis
  - Onset of arthritis in a boy ≥6 years

- ERA exclusions: psoriasis in patient or 1st degree relative; IgM RF; systemic arthritis; arthritis fulfilling two JIA categories

Genetics of Spondyloarthritis

- 60-80% of children with spondyloarthritis have HLA B27.
- 5% of the HLA B27-positive population develop AS.
- 20% of HLA B27-positive relatives of patients with spondyloarthritis develop disease
- Variations in other genes such as *ERAP*1 y *IL23R* are associated with AS.

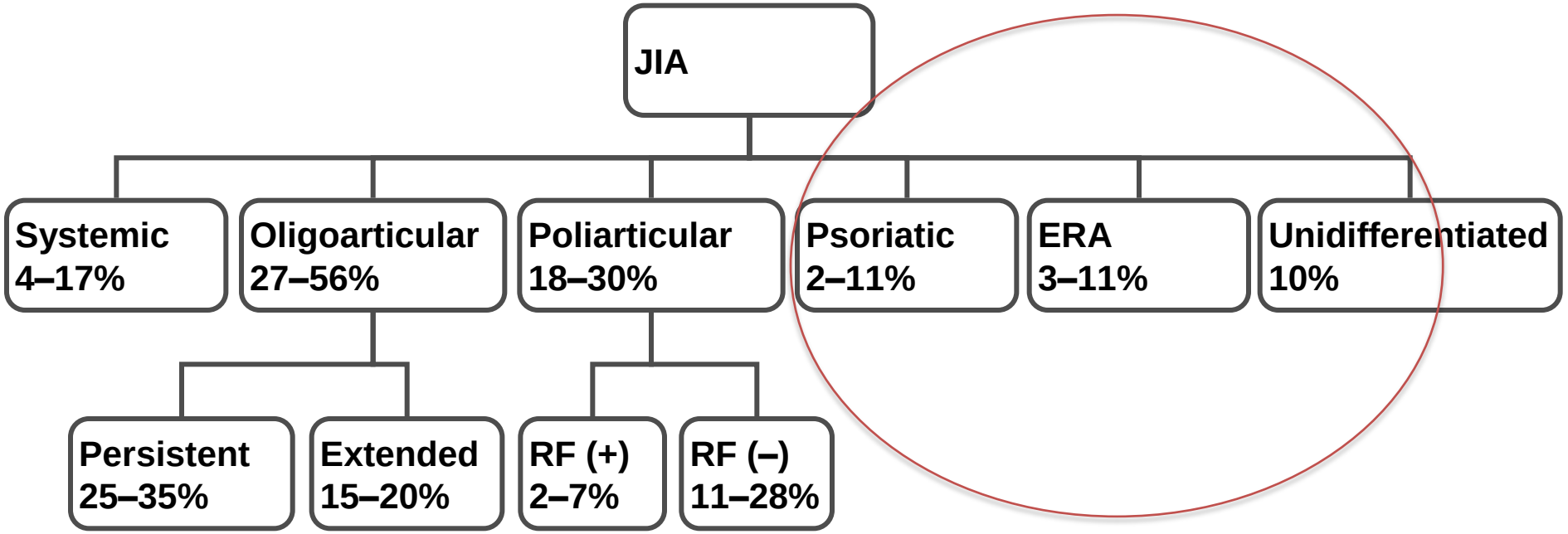
A brief look into pathogenesis



Epidemiology of juvenile spondyloarthritis

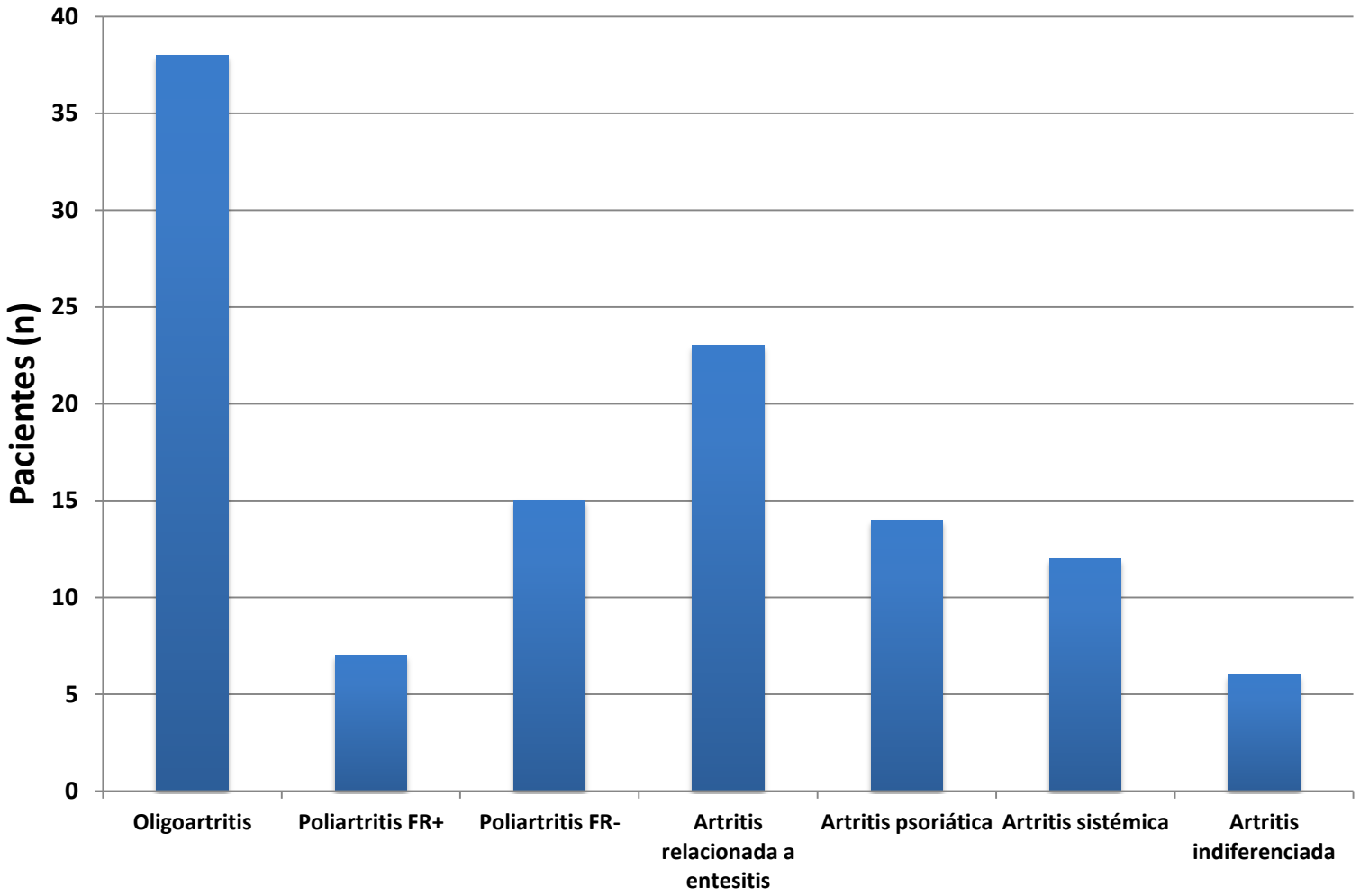
- Its a different animal than adult AS.
- ERA+PsA = 10-20% of JIA
- 10-20% of adult patients with spondyloarthritis begin with symptoms before age 16.

JIA subtypes



Petty RE, *et al. J Rheumatol* 2004; **31**:390–392.
Ravelli A & Martini A. *Lancet* 2007; **369**:767–778.

JIA in Chilean cohort

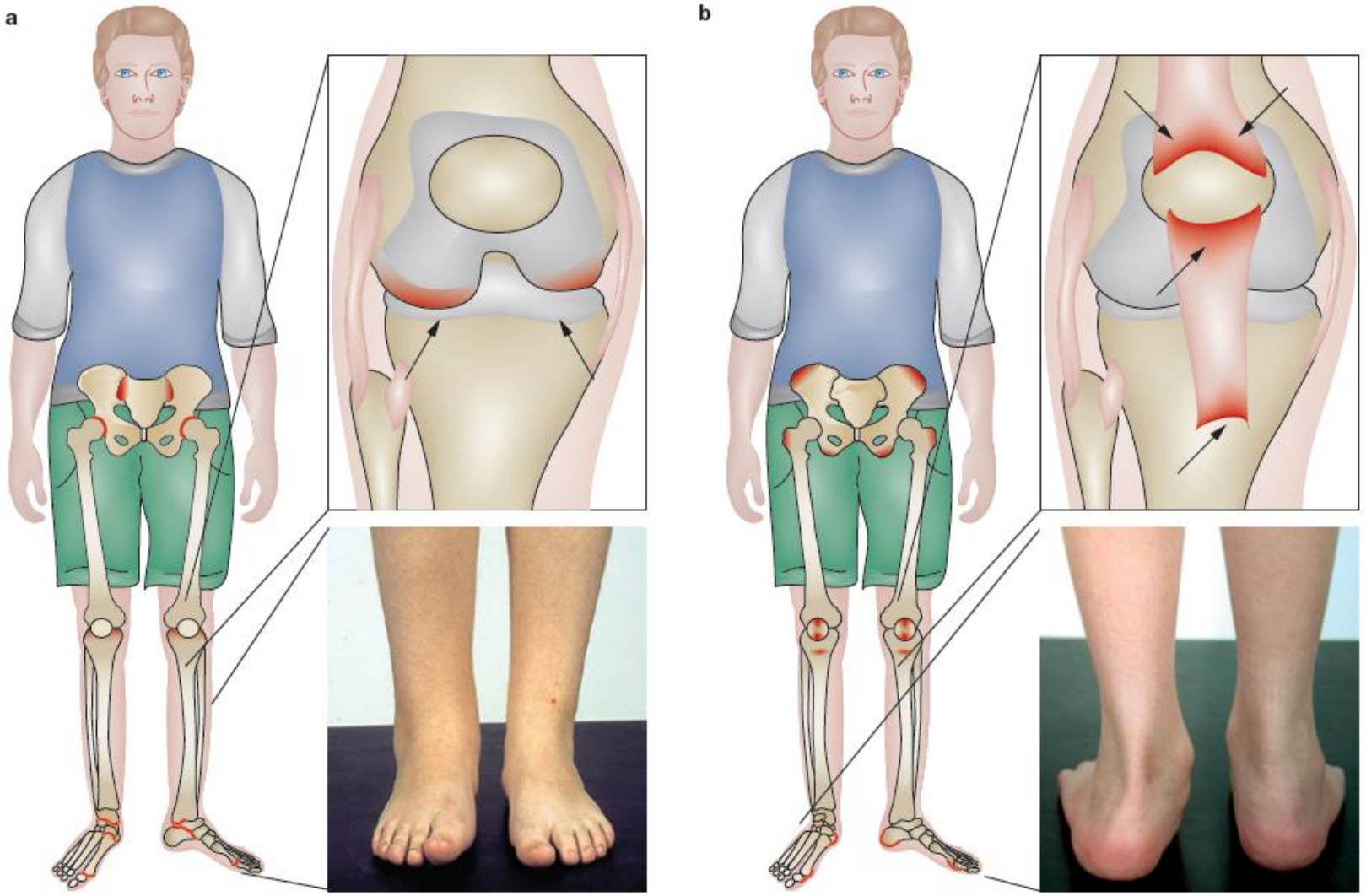


Clinical Characteristics

- Arthritis in juvenile SpA is predominantly peripheral (except for the hip) and usually affects lower>>upper limbs.
- Asymmetric oligoarthritis of the lower limbs is the form of the disease most prevalent at presentation, but polyarthritis occurs in up to 25% of patients at onset
- Spine and sacroiliac joint involvement at presentation is rare but can develop 5-10 years from disease onset.
- Tarsitis is a unique characteristic of SpA.
- Enthesitis occurs in 60-80% of patients.
- Uveitis and gastrointestinal manifestations are the most common extra-articular features.

Tse S, Laxer RM. Nat Rev Rheumatol 2012.

Anatomy of arthritis and enthesitis in SpA



Tse S, Laxer RM. Nat Rev Rheumatol 2012.

Frequency of peripheral enthesitis

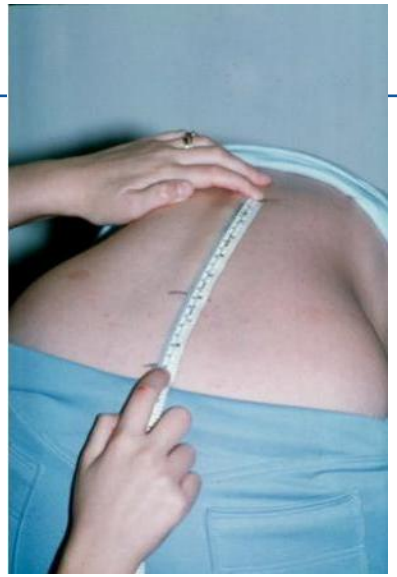
Table 3. Frequency (%) of peripheral entheses involved in patients with juvenile-onset SpA at different intervals[45,47,51].

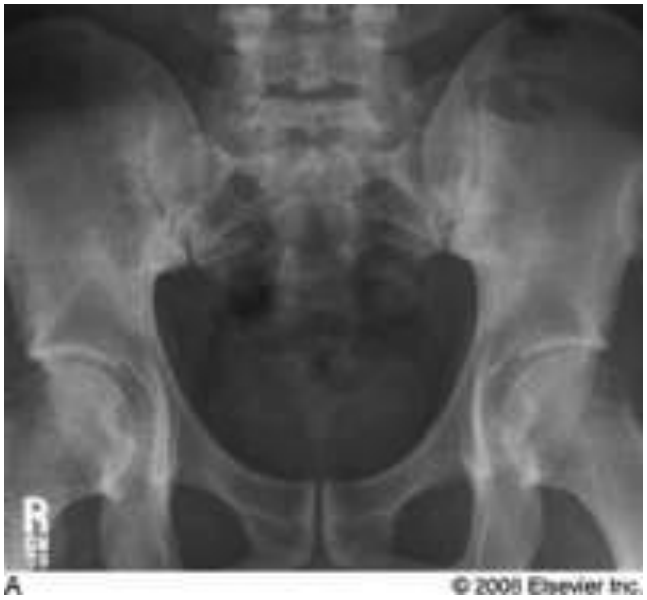
	6 months	12 months	Cumulative
Plantar fascia/calcaneus	20–40	34–64	54–86
Achilles tendón/calcaneus	11–29	20–50	34–71
Tibial tuberosity	0–23	3–29	7–40
Greater trochanter	7–11	7–14	14–32
Ischial tuberosity	0	0–6	0–9
Iliac crest	0	0–3	0–6
Tarsus, various sites	57–71	83–86	80–100

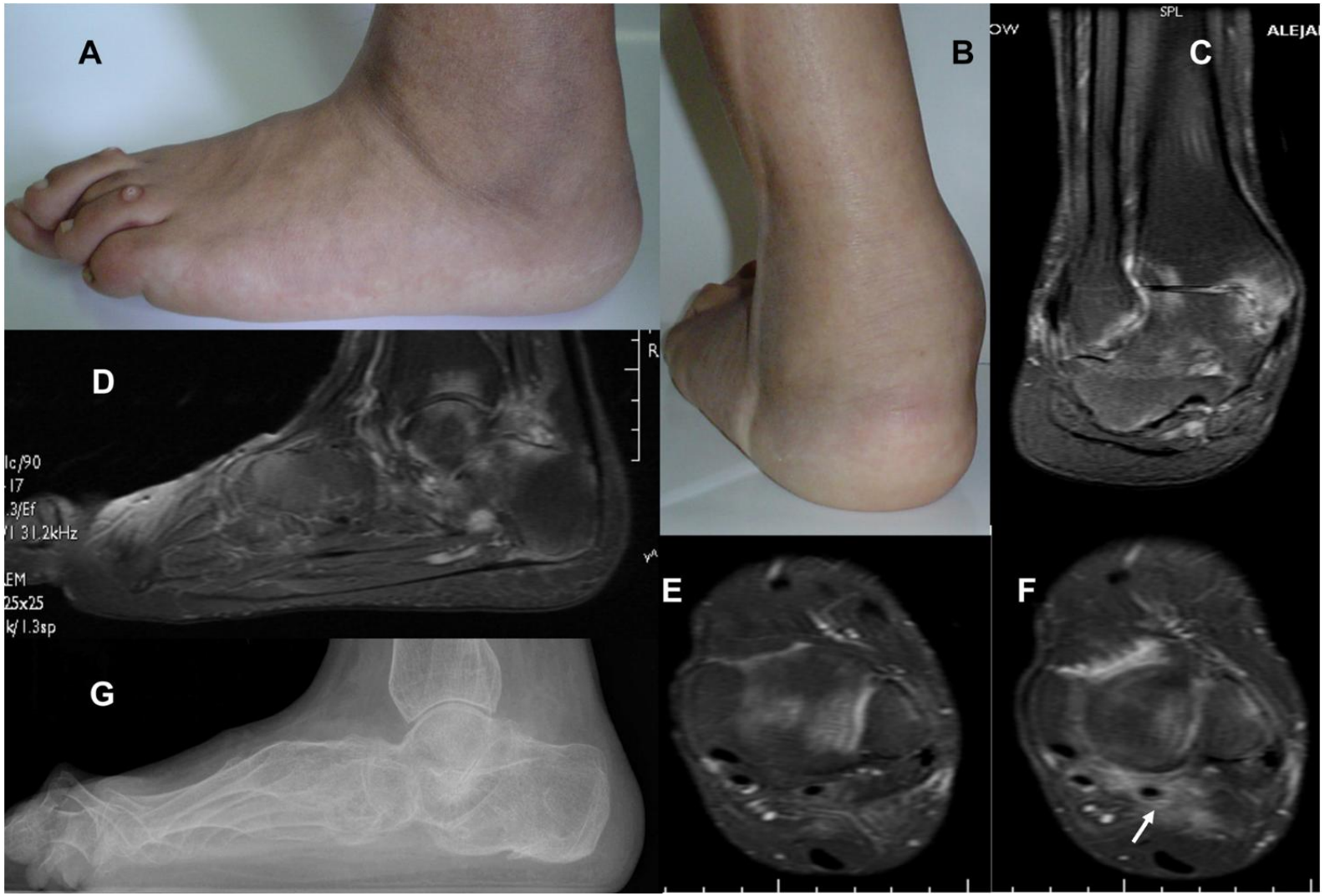
Burgos-Vargas R. Best Pract Res Clin Rheumatol. 2002

Spine and sacroiliac joint arthritis

- Inflammatory back pain
- Alternating buttock pain
- Schober test

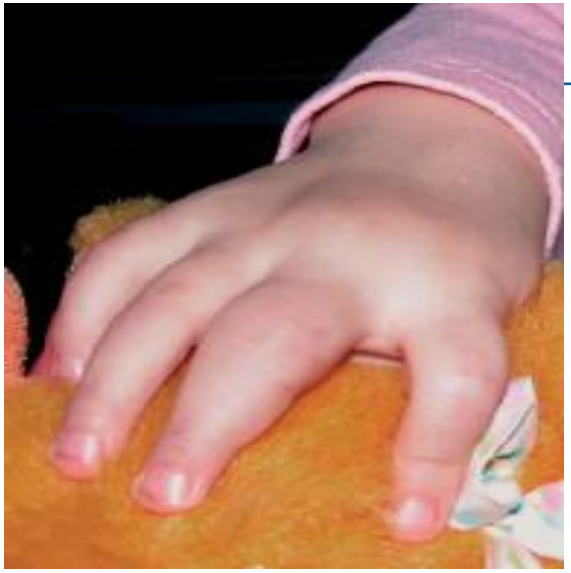


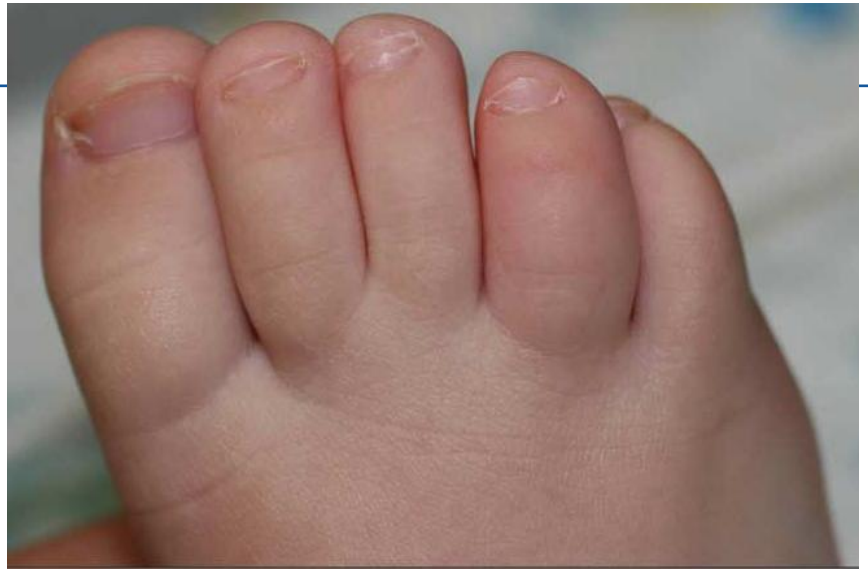


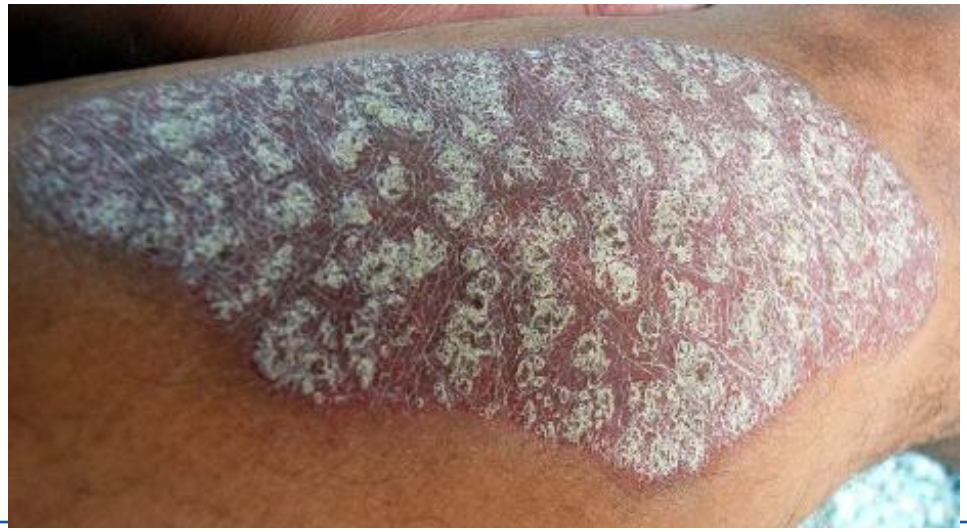

A
B
C
SPL
D
E
F
G

Psoriatic arthritis

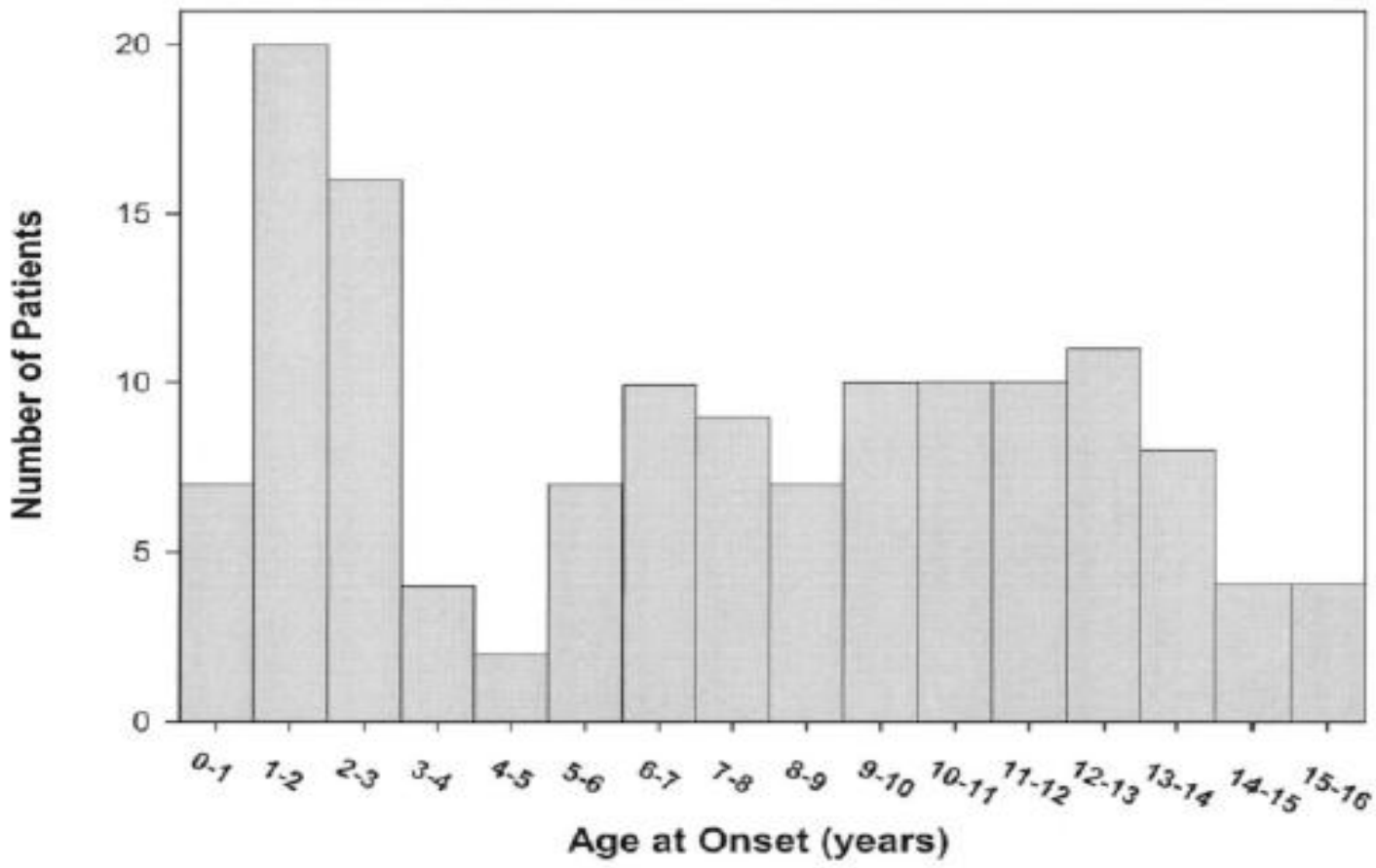
- Arthritis associated to psoriasis
- Frequent dactylitis and nail pitting.
- First-degree relatives with psoriasis.
- Can begin years before psoriasis.
- Variable joint count, usually asymmetric.
- Axial involvement usually appears in older children.





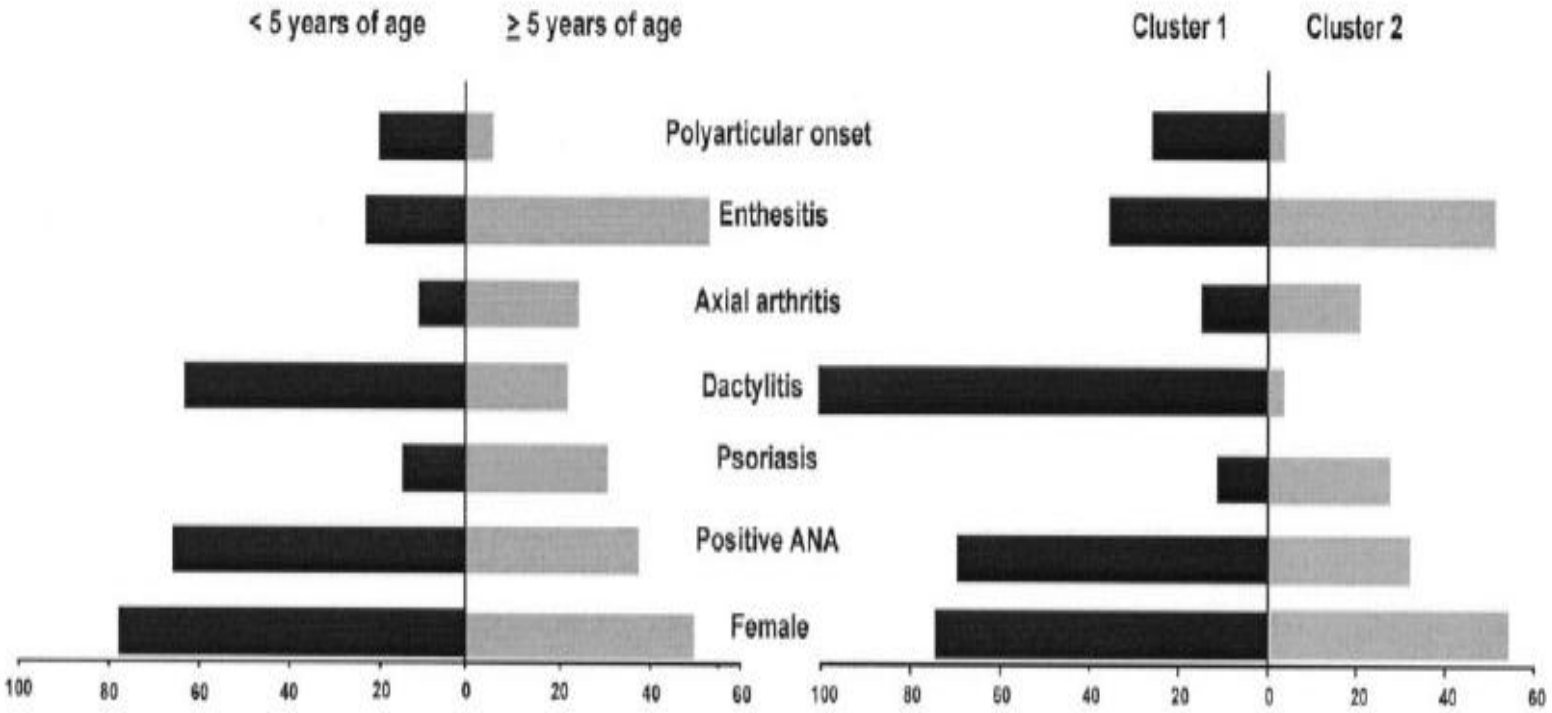


Age distribution of psoriatic arthritis



Stoll M. Arthritis Rheumatol. 2006.

Clinical characteristicis of jPsA



Stoll M. Arthritis Rheumatol. 2006.

In favor of the splitters, not all jSpA are created equal

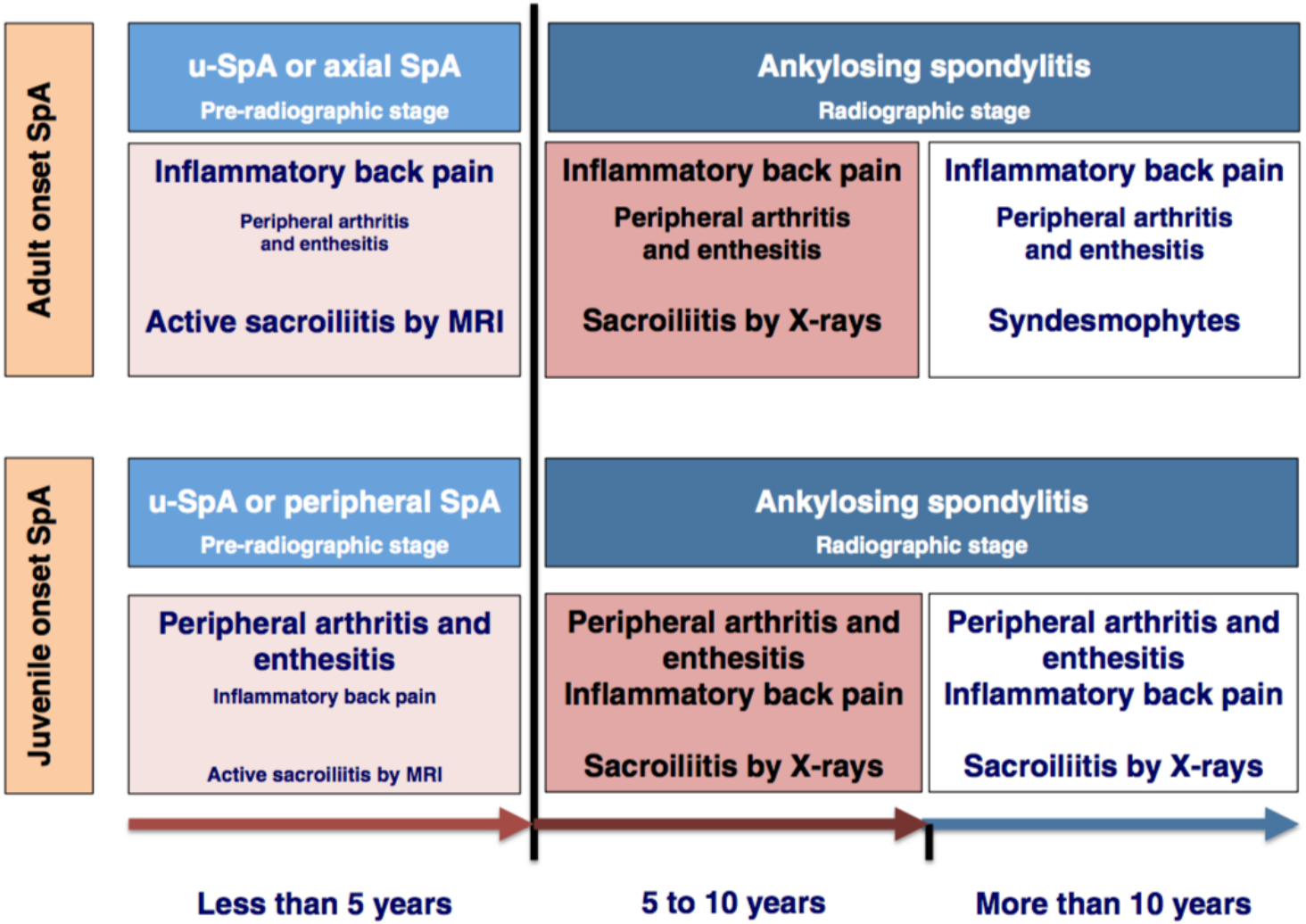
Table 6 Estimated prevalence of each of the items listed in the Assessment of Spondyloarthritis International Society classification criteria for axial and peripheral spondyloarthritis in the different categories of juvenile onset disease in children and adolescents*

	Ankylosing spondylitis	Undifferentiated spondyloarthritis	Enthesitis related arthritis	Psoriatic spondyloarthritis	Psoriatic arthritis not related to spondyloarthritis
Sacroiliitis on MRI	+++	+	+	+	-
Sacroiliitis on X-rays	++++	-	+	+	-
Inflammatory back pain	++++	+	+	+	-
Arthritis	++++	++++	++++	++++	++++
Enthesitis (heel pain)	+++	+++	+++	++	-
Uveitis	++	+	+	+	-
Dactylitis	+	++	++	++	+++
Psoriasis	+	-	-	++++	++++
Crohn's/colitis	+	-	-	+	-
Good response to NSAIDs	+++	NA	NA	NA	NA
Family history for SpA	++	+	+	++	-
HLA-B27	+++	++	++	++	-
Elevated C reactive protein	+++	+++	+++	+++	++
Previous infection	+	-	-	-	-

*Based on the literature and on the opinion of local experts in the care of these children.
The presence of such items excludes the undifferentiated spondyloarthritis and enthesitis related arthritis as diagnosis.
MRI = magnetic resonance imaging. NSAIDs = Non-Steroidal Antinflammatory Drugs. NA = data not available. SpA = Spondyloarthritis.

Burgos-Vargas R. Pediatr Rheumatol. 2012

Clinical Course



Burgos-Vargas R. Pediatr Rheumatol. 2012

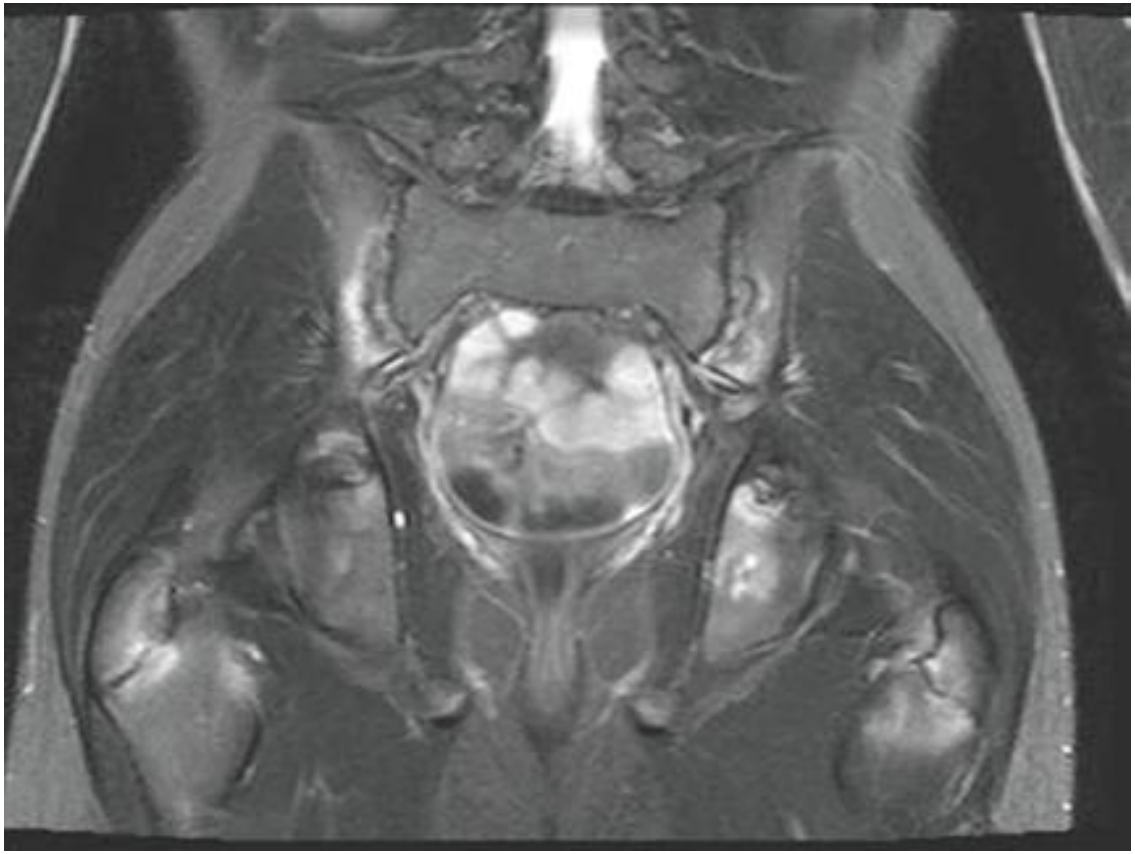
Imaging in spondyloarthritis

- Sacroiliac joint x-rays rarely shows changes at diagnosis nowadays.

- MRI is most sensitive in showing bone edema, erosions and synovitis of the sacroiliac joint and spine.
  - STIR sequences are sufficient to detect bone marrow edema reflecting active inflammatory lesions.
  - Synovitis, capsulitis and enthesitis are more reliably detected on T1 post-IV gadolinium sequences.

- Ultrasound has better sensitivity than physical exam to demonstrate enthesitis but is operator-dependent.

Sacroiliac joint MRI



Labs

- Many patients with juvenile SpA have elevated platelet count, ESR and CRP, but labs can be totally normal.
- Young children can be ANA+ (particularly PsA)
- HLA B27 can determine progression to ankylosing spondylitis.

Treatment

- NSAIDs provide good symptomatic relief. Children with mild SpA could be treated only with NSAIDs.
- Sulfasalazine and methotrexate are an alternative in peripheral SpA, but are rarely effective in spondylitis.
- TNF inhibitors are the mainstay of treatment for moderate to severe cases and most cases with axial involvement.

Treatment recommendations (Go lumpers!!!)

Box 3 | Application of JIA treatment recommendations to juvenile SpA

Factors indicative of poor prognosis

- Radiographic damage of any joint (erosions or joint-space narrowing on plain radiographs)

Disease activity levels

- Low (must satisfy all criteria): normal back flexion; normal ESR or CRP levels; physician assessment score of <4 of 10; patient or parent assessment score of <2 or 10
- Moderate (does not satisfy either the low or high activity criteria): one or more features greater than low disease activity levels and <2 high disease activity features
- High (must satisfy >2 features): ESR or CRP >2 times the upper limit of normal; physician assessment score ≥7 of 10; parent or patient assessment score of ≥4 of 10

Initiation of TNF recommended

- Scenario 1: adequate trial of NSAIDs (up to 2 months); high disease activity; feature of poor prognosis present
- Scenario 2: methotrexate for 3 months; high disease activity; irrespective of poor prognosis features
- Scenario 3: methotrexate for 3 months; moderate disease activity; feature of poor prognosis present
- Scenario 4: methotrexate for 6 months; moderate disease activity; feature of poor prognosis absent
- Scenario 5: sulfasalazine for 3 months; moderate or high disease activity; irrespective of feature of poor prognosis
- Scenario 6: sulfasalazine for 6 months; low disease activity; feature of poor prognosis present

Adapted from 2011 ACR criteria for JIA.[67] Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis. Permissions obtained from Wiley © Beukelman, T. *et al. Arthritis Care Res.* **63**, 465–482 (2011).

Tse S, Laxer RM. Nat Rev Rheumatol 2012.

Outcomes

- Variable disease course.
- Disease remission is reported for 17-39% of patients with jSpA and up to 44% of patients with ERA.

Table 1 | Outcomes in juvenile SpA

Study	Population	HLA-B27 positive (%)	Mean follow-up (years)	Summary of outcomes for those with juvenile SpA
Undifferentiated juvenile SpA				
Minden *et al.* (2002)[30]	ERA (n=33) versus JIA (n=182)	24.0	16.0	Better HAQ Disease remission rate in 18% (2nd lowest) 39% developed AS (mNY criteria), 36% with probable AS
Flato *et al.* (2006)[29]	ERA (n=55) versus JIA (n=205: oligoarthritis or polyarthritis)	85.0	15.3	Worse HAQ Poorer physical health and increased body pain (SF-36) Disease remission in 44% 35% developed AS (mNY criteria, 75% had decreased spinal mobility
Selvaag *et al.* (2005)[77]	Juvenile SpA (n=12: 3 juvenile AS [mNY criteria], 4 SEA, 5 juvenile PsA) versus juvenile RA (n=185)	50.0	3.0	Worse CHAQ (physical function) Highest pain scores and patient/physician global assessment of disease
Oen *et al.* (2010)[79]	ERA (n=36) versus JIA (n=318)	59.0	0.5	50% ongoing active arthritis (median AJC=1) 31% ongoing active enthesitis, inactive disease activity in 19% (2nd lowest)
Sarma *et al.* (2008)[78]	ERA (n=49)	53.0	6.0 (median)	Abnormal HAQ in 75% (49% moderate to severe disability) 62.6% ongoing active enthesitis Disease remission in 8% 35% had evidence of radiologic damage (especially hips) 65.3% experienced lost years of education 28.6% had decreased spinal mobility

Tse S, Laxer RM. Nat Rev Rheumatol 2012.

Conclusions

- Juvenile spondyloarthropathies are heterogenous arthritides with predominant lower limb involvement and high risk of progression to axial involvement.
- It is characterized by arthritis and enthesitis and is different from adult SpA.
- A single diagnostic or classification system that is representative of the juvenile SpA population is still needed
- Frequently associated to HLA B27 +
- Not all juvenile psoriatic arthritis falls in the SpA group.
- As in all JIA reatment should be focused in achieving clinical remission (early use of TNFi!).

¡Muchas Gracias!