Spondyloarthropathy

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DISCLOSURES/ CONFLICT OF INTEREST

None

Spondyloarthropathy (SpA)

OBJECTIVES

1. Diagnose, or identify patients at risk for a SpA
2. General principles of SpA management
3. Monitor for complications

SpA - Overview

- Ankylosing spondylitis (AS)
- Psoriatic arthritis (PsA)
- Enteropathic arthritis (IBD-associated SpA)
- Reactive arthritis (ReA)
- Undifferentiated SpA (ex. uveitis + HLAB27)
- ?SAPHO syndrome (association with psoriasis)
- Juvenile forms (enthesitis related JIA, juvenile AS)

axial (spine, SI joint)
enthesitis
dactylitis
HLA-B27
seronegative

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#

#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

n=649 patients with back pain;
Sensitivity: 82.9%, Specificity: 84.4%
Imaging alone: Sensitivity: 66.2%. Specificity: 97.3%

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

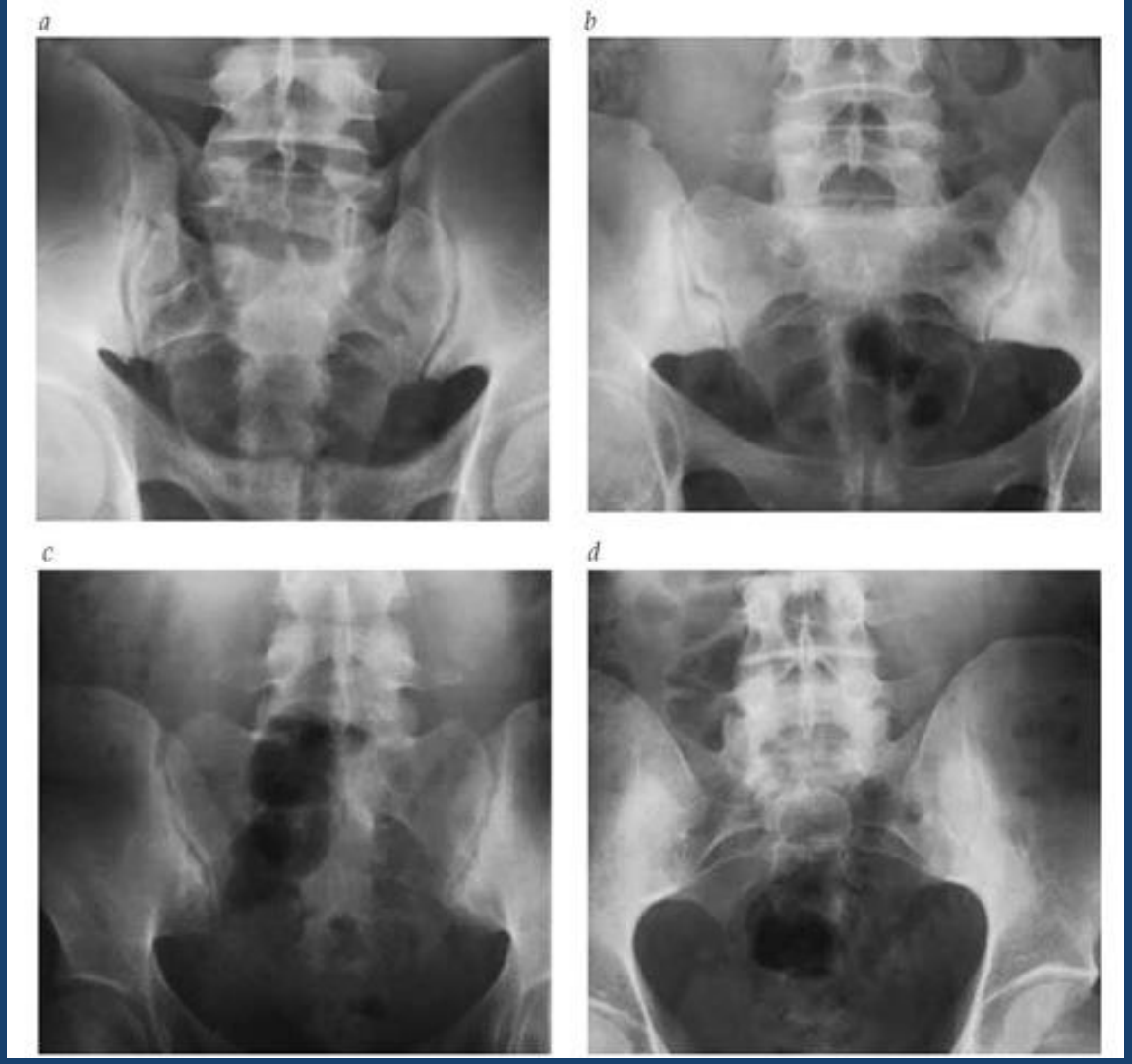
ASAS

Table 2 Inflammatory back pain (IBP) parameters, according to experts

Parameter	Criteria
1	Age at onset <40 years
2	Insidious onset **(> 3 months)**
3	Improvement with exercise
4	No improvement with rest
5	Pain at night (with improvement upon getting up)

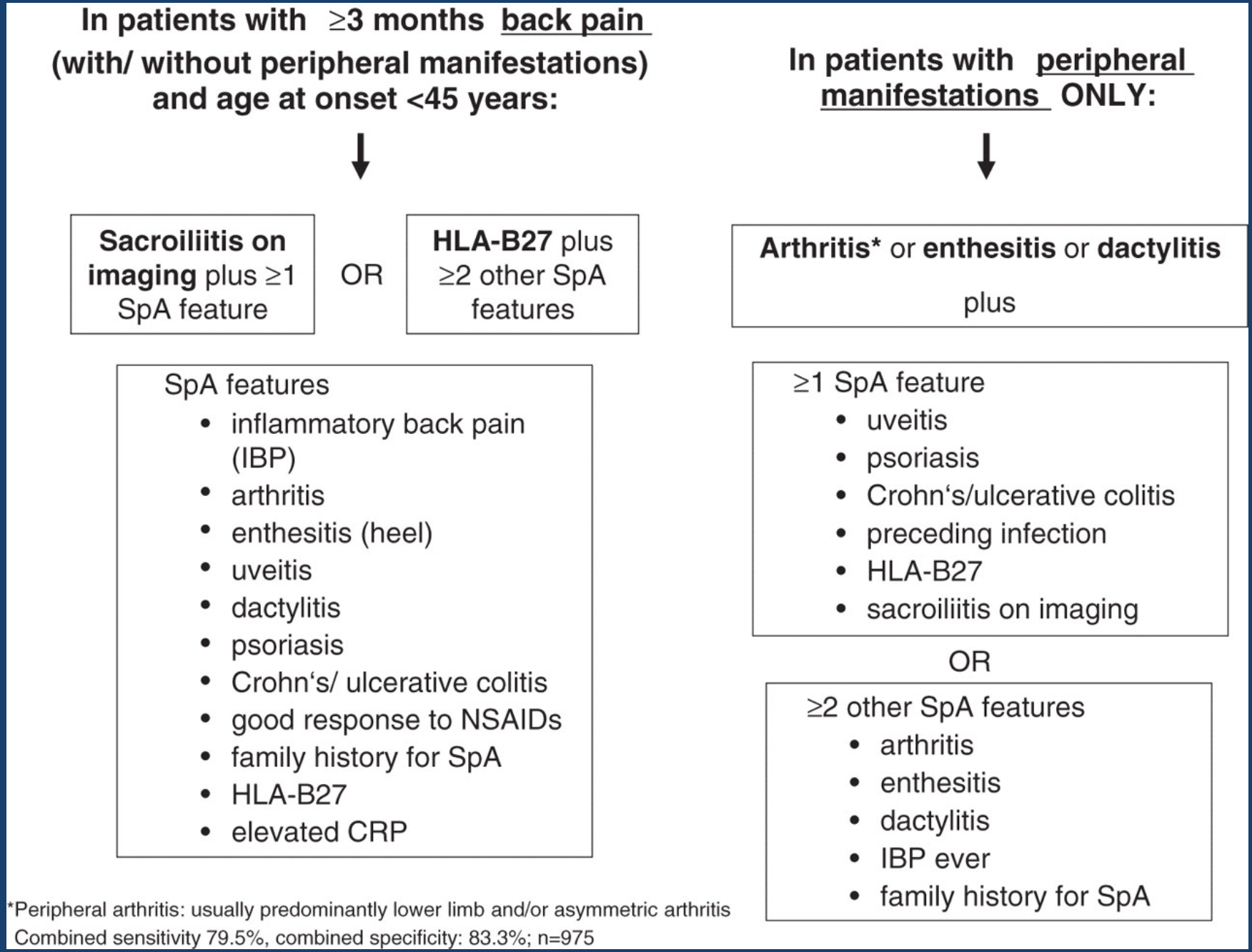
Sensitivity 77.0% and specificity 91.7% if at least four out of five parameters are present. Note that sensitivity and specificity refer to the presence of IBP, not to diagnosis.

Sieper J et al. *Ann Rheum Dis* 2009;68(6):784-788



Modified NY Grading: 0 - normal, 1 - suspicious changes (*a*),
2 - minimal definite changes (sclerosis, erosions) without change to joint space (*b*),
3 - definite changes, joint space narrowing/pseudo-widening, partial ankylosis (*c*),
4 - ankylosis (*d*)

van der Linden S et al. *Arthritis Rheum* 1984;27(4):361–68



ASAS criteria for axial and peripheral SpA

M Rudwaleit et al. *Ann Rheum Dis* 2011;70:25-31

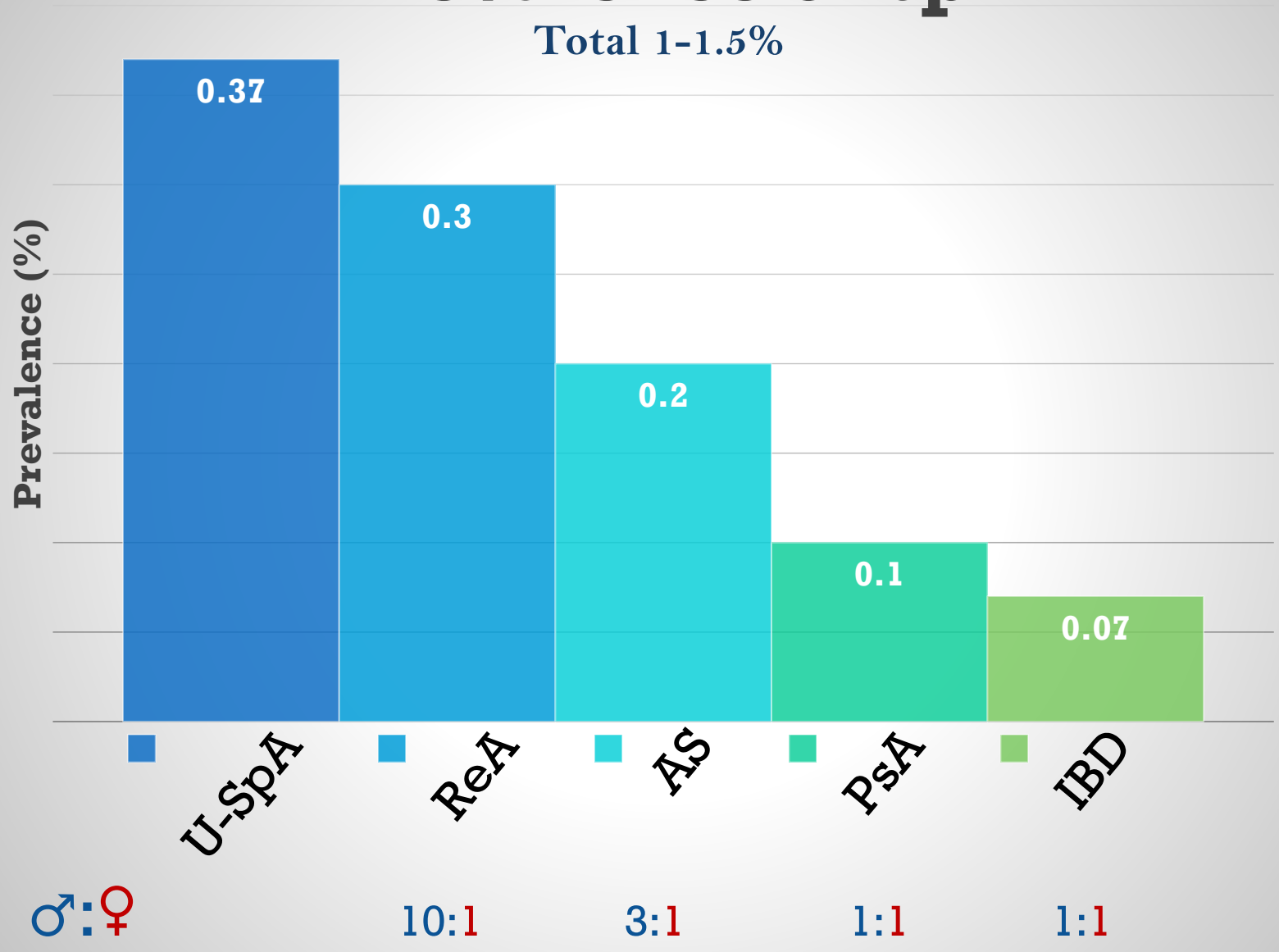
Table 4 Comparison of the combined criteria for axial SpA and for peripheral SpA (set 2D), ESSG criteria and Amor criteria in the entire ASAS study population (n=975)

Sets of criteria for SpA	Sensitivity (%)	Specificity (%)
ESSG	66.7	72.0
Modified ESSG (with MRI)*	79.1	68.8
Amor	55.6	86.7
Modified Amor (with MRI)†	67.5	86.7
Combination of ASAS criteria	79.5	83.3

ASAS superior to European Spondyloarthropathy Study Group (ESSG) and Amor criteria, which were developed in 1990s as classification criteria for all SpA, including peripheral.

Rudwaleit M et al. *Ann Rheum Dis* 2011;70:25-31

Prevalence of SpA



Am J Med Sci. 2011; 341(4):284-286

Table 1

CASPAR criteria for PsA[17]

To meet the CASPAR criteria for PsA, the patient should have inflammatory joint disease (peripheral, axial or enthesitis) and achieve three or more points, based on the following categories

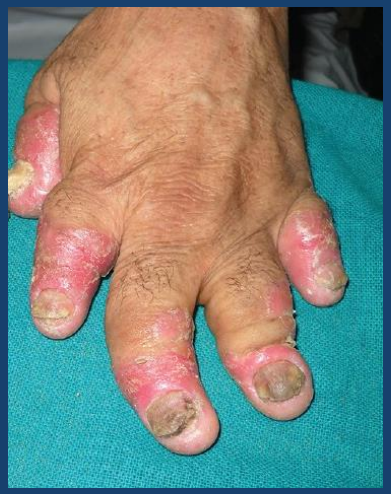
1. Evidence of psoriasis	
Current	2 points
Personal history	1 point
Familial history	1 point
2. Psoriatic nail dystrophy	
Pitting, onycholysis, hyperkeratosis	1 point
3. Negative test result for rheumatoid factor	1 point
4. Dactylitis	
Current inflammation of an entire digit	1 point
History of dactylitis	1 point
5. Radiological evidence of juxta-articular new bone formation	
Well-defined ossification close to joint margins on plain radiographs of hands and feet	1 point

Sensitivity: 91%; specificity: 99%.

Taylor W et al. *Arthritis Rheum* 2006; 54(8):2665–73

Psoriasis & PsA

- PsA prevalence 0.04 - 0.1%
- Psoriasis (Ps) prevalence 2-3% → arthritis in 6 - 47%
  → PsA prevalence 1%



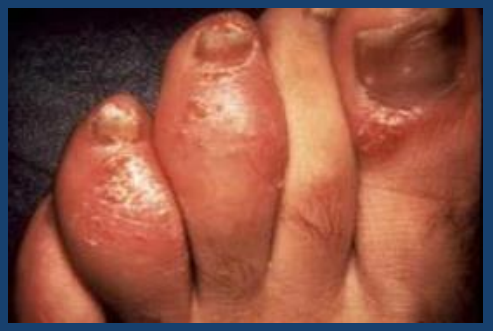
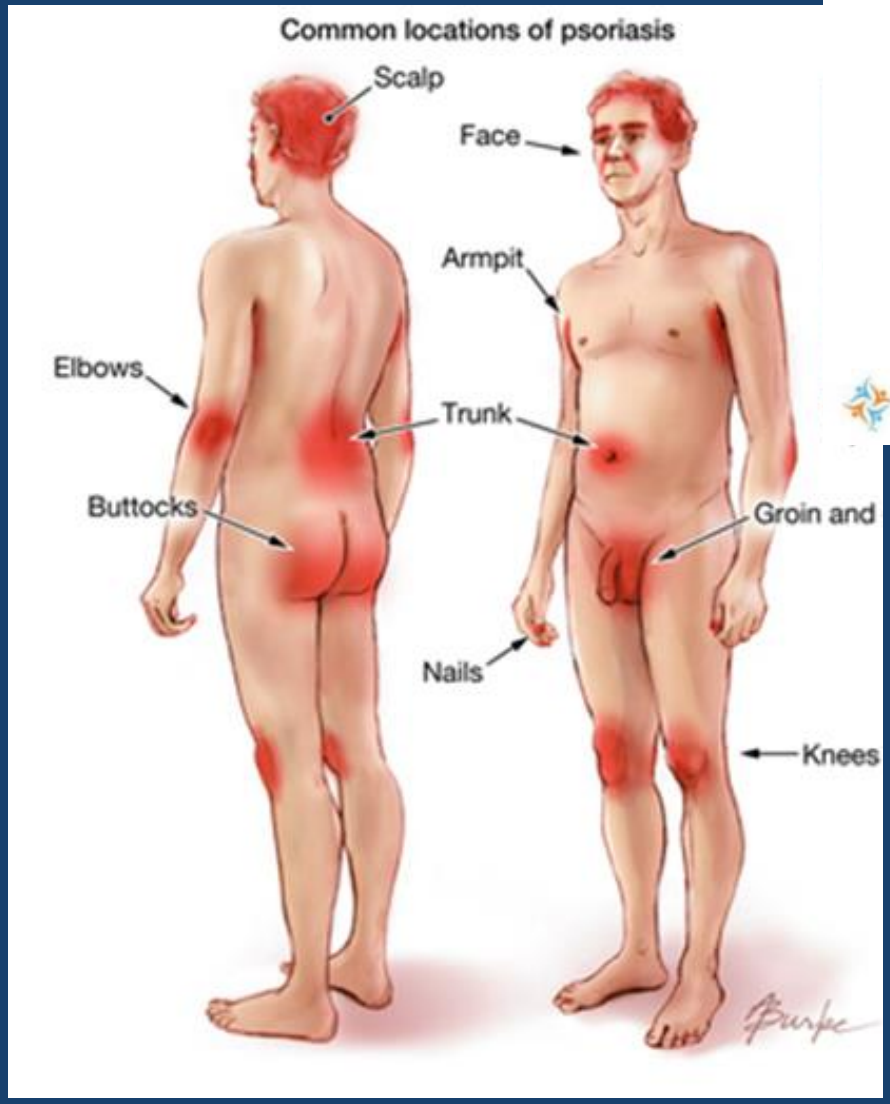


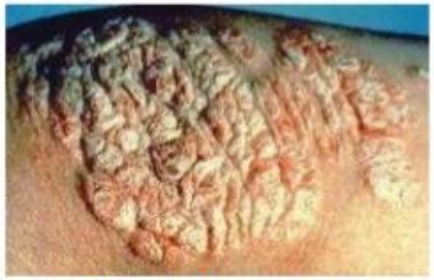
Table 2. Classification of the study patients (*N*=352) according to Moll and Wright[1] PsA subtypes*

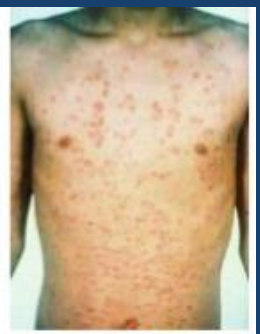
PsA subtype	Patients, *n*	M/F ratio
Polyarticular	208	95/113 (1:1.2)
DIP	67	44/23 (1.9:1)
Oligoarticular	42	31/11 (2.8:1)
Spondylitis predominant	32	22/10 (2.2:1)
Arthritis mutilans	3	1/2 (1:2)

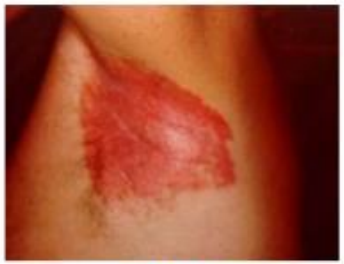
Moll JM, Wright V. *Semin Arthritis Rheum* 1973;3(1):55-78
Maharaj AB et al. *S Afr Med J* 2016;106(6):630-633
Gladman DD et al. *Ann Rheum Dis* 2005;64(Suppl II):ii14–ii17

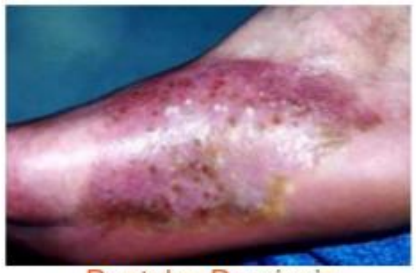
PsA diagnosis before Ps in 15-20%, concurrent in 10%

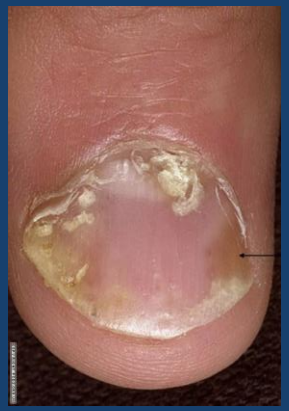


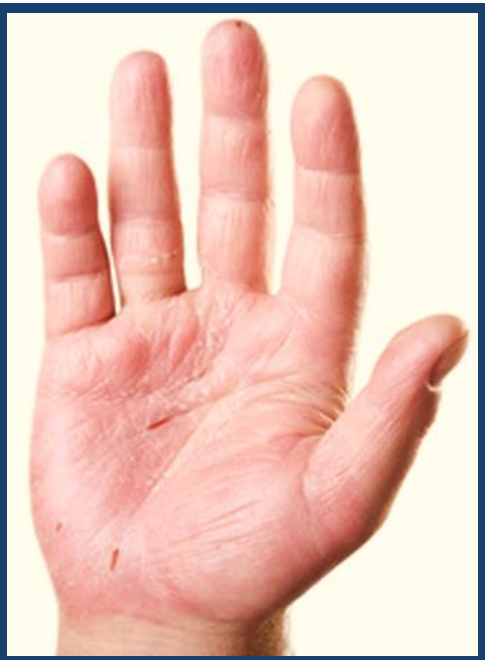

Plaque Psoriasis


Guttate Psoriasis


Inverse Psoriasis


Pustular Psoriasis





Risk factors/Predictors of PsA

- Nail lesions - in 87% PsA patients vs. 40% Ps without arthritis
- HLA-B27 - PsA, axial disease, extra-articular manifestations
  - HLA-B38 & 39 predict peripheral arthritis; HLA-B22 protective
- More severe psoriasis (>3 sites), ?scalp & perianal involvement
- Koebner phenomonen
- Higher BMI
- Female
- Family history of Ps, PsA
- ?Trauma, infections
- Smoking – no or inverse association

Azivido V et al. *An Bras Dermatol. 2013;88(2):233-36*
Eastmond CJ, Wright V. *Ann Rheum Dis* 1979;38:226–8
Soltani-Arabshahi R et al. *Arch Dermatol* 2010;146:721-6
Eder L, et al. *Arthritis Care Res* 2011;63:1091-7

HLA-B27 & SpA

Table 2. **Association of Spondyloarthropathies with HLA-B27 in White Persons***

Disease	Approximate Prevalence of HLA-B27, %
Ankylosing spondylitis	90
Reactive arthritis	40–80
Juvenile spondyloarthropathy	70
Enteropathic spondyloarthritis	35–75
Psoriatic spondyloarthritis	40–50
Undifferentiated spondyloarthropathy	70
Acute anterior uveitis (acute iritis)	50
Aortic incompetence with heart block	80

* Persons of western European extraction. The prevalence in the general healthy population is approximately 8%. 4% of African Americans, 1% of Asians

Risk of developing AS if HLA-B27+: 1 - 2%
Risk if 1st degree relative has AS: 20 - 30%

Khan MA. *Clin Rheumatol* 1996;15 Suppl 1:10-2

PsA: Prognosis

- ? not as severe/symptomatic as RA (ex. back pain reported by 19% with axial lesions on radiographs)
- 67% have erosive disease; ≥ 5 deformed joints by 10y in 55%
- Predictors of progression: polyarticular disease (≥ 5 joints), HLA-B27, female, delay in treatment
- Extra-articular manifestations in up to 40%
- Quality of life, functional capacity (HAQ, SF-36) similar to RA
- Standardized mortality ratio: 1.62 (mostly cardiovascular disease)

Gladman DD et al. *Ann Rheum Dis* 2005;64(Suppl II):ii14 -17
Queiro R et al. *Joint Bone Spine* 2008;75: 544-7

SpA:
Extra-articular Manifestations

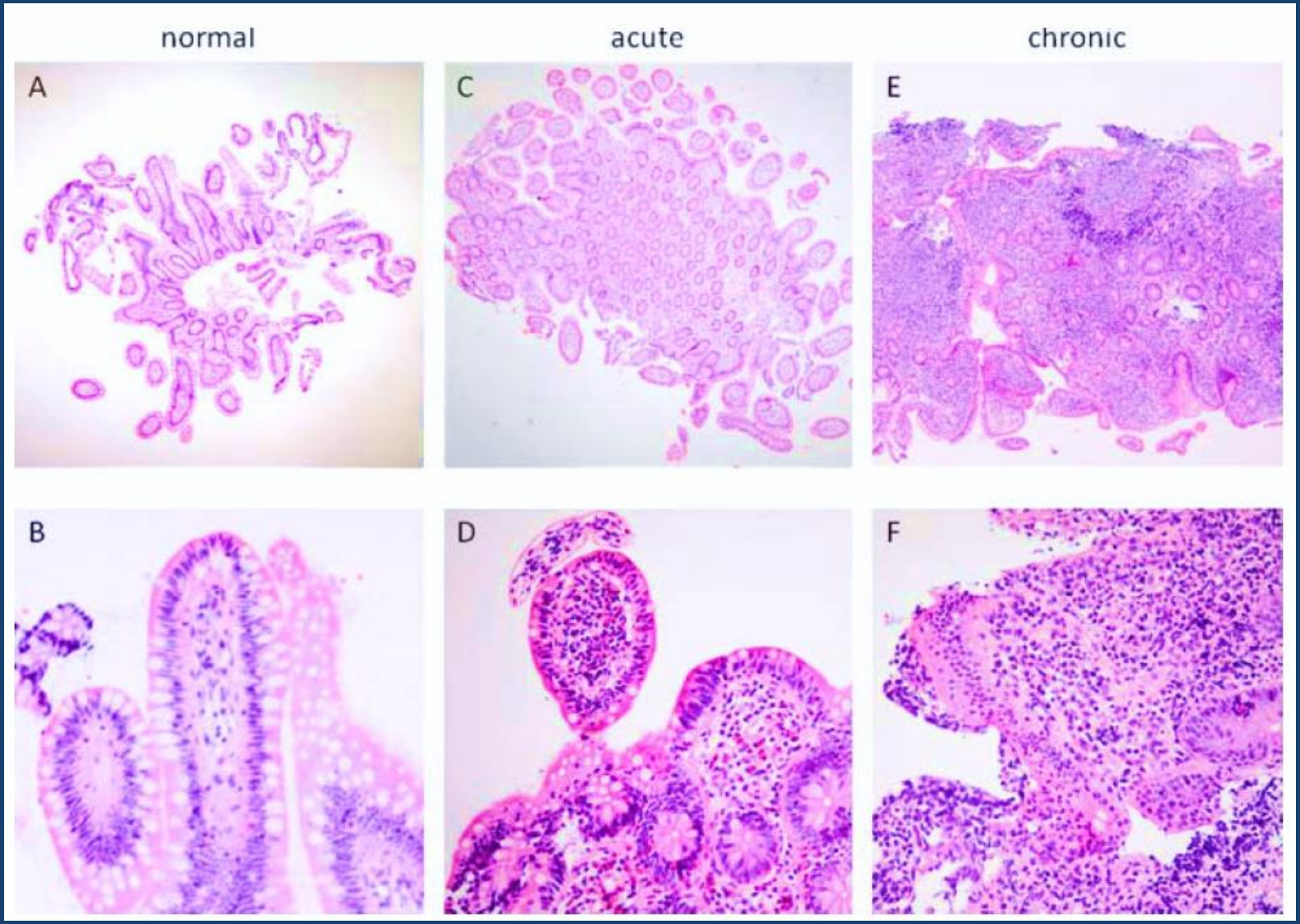
Microscopic Colitis in SpA

- 5 – 10% with SpA have Inflammatory Bowel Disease (IBD)
- Arthritis in 9 - 53% with IBD, esp. large intestine involvement
- Microscopic colitis in 50% of SpA without GI Sx or IBD

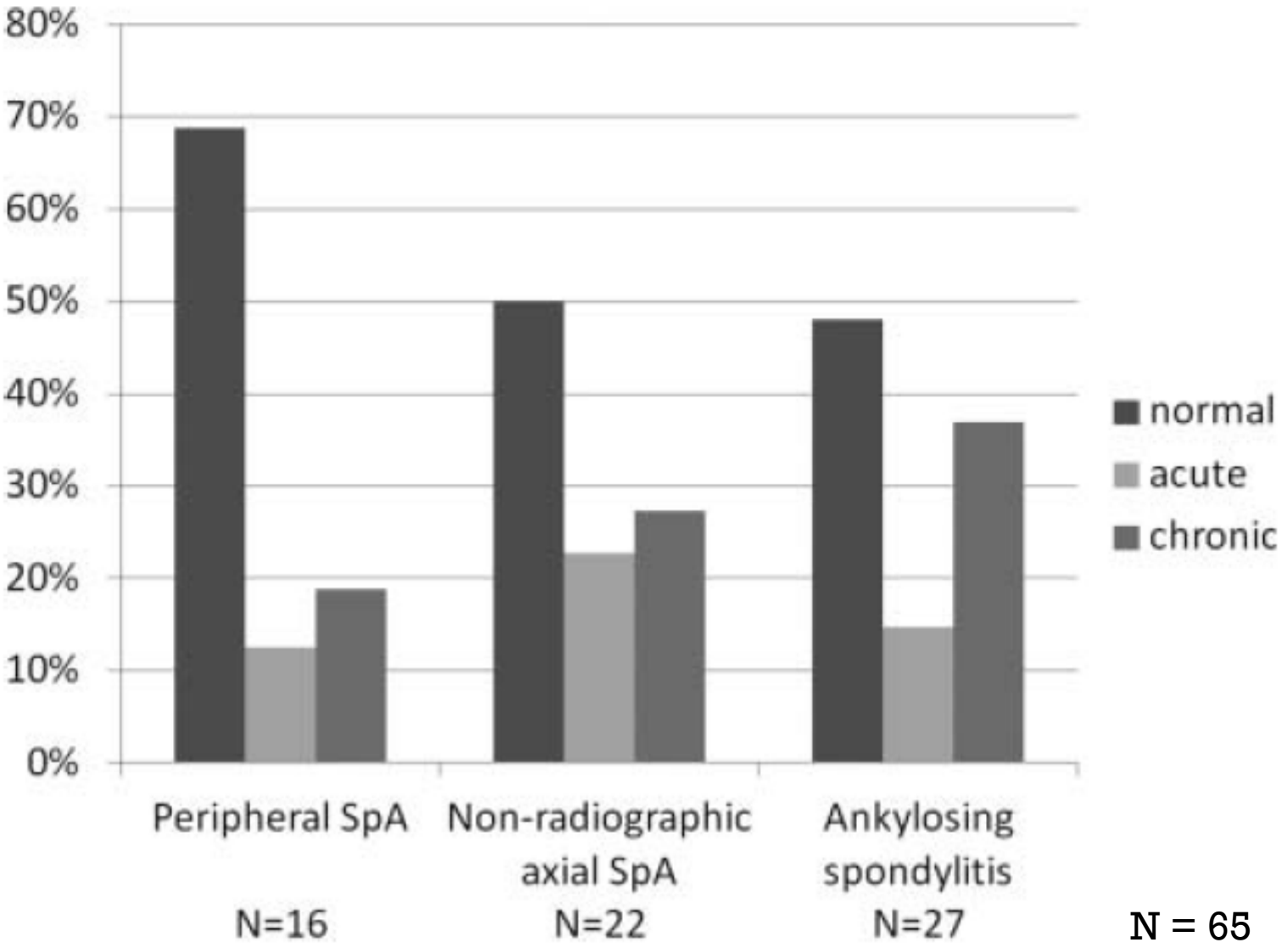
  → 6% progress to Crohn's disease over 5 years
- Parallels bone marrow edema (SPARCC score) in axial SpA
- Joint inflammation ←→ gut inflammation
- Predicts increased need for biologicals (HR 2.5)

Van Praet, L et al. *Ann Rheum Dis* 2013;72:414–417

Microscopic Colitis in SpA



Van Praet, L et al. *Ann Rheum Dis* 2013;72:414–417



17%

30%

N = 65

Figure 2 Prevalence of gut inflammation according to classification.

Van Praet, L et al. *Ann Rheum Dis* 2013;72:414–417

Table 2 Multivariate analysis of microscopic gut inflammation in axial SpA

Model variable	OR	CI	p Value
Age	0.85	0.75 to 0.97	**0.013**
Sex, male	8.90	1.18 to 67.37	**0.035**
BASMI	1.94	1.18 to 3.19	**0.009**
BASDAI	2.05	1.06 to 3.95	**0.032**
Presence or history of enthesitis	0.32	0.04 to 2.40	0.27

Sensitivity of 81.8% and a specificity of 78.3% for detecting microscopic gut inflammation in axial SpA.

Van Praet, L et al. *Ann Rheum Dis* 2013;72:414–417

Progression to axial ankylosing SpA associated with colitis at disease onset. Remission of joint inflammation associated with disappearance of gut inflammation.

Mielants H et al. *J Rheumatol* 1995;22:2279–84

Calprotectin as biomarker for colitis in SpA

Marker	Cut-off	Sens (%)	Spec (%)	Odds ratio for bowel inflammation	AUC (%)
CRP (mg/dl)	0.4	67.3	54.4	2.46 (p=0.019)	60.9
Serum calpro (ng/mL)	3340	60.4	61.1	2.4 (p=0.018)	60.7
Faecal calpro (μg/g)	85	64.3	73.3	4.95 (p=0.021)	68.8

CRP and serum Calprotection both elevated	⇨	High risk		
Either serum Calprotection or CRP elevated	↗	Fecal calprotection < 85µg/g	⇨	Low Risk
	↘	Fecal calprotection > 85µg/g	⇨	High Risk
CRP and serum Calprotection both low	⇨	Low Risk		

Cypers H, et al. *Ann Rheum Dis* 2015;0:1–6

Extra-articular Manifestations

PsA

- conjunctivitis (20%), uveitis (5% -10%), mainly in axial disease
- oral aphthae; GI involvement; rarely lung fibrosis, aortitis/ AI

SpA

- Uveitis - typically acute, anterior, recurrent, but can be chronic, bilateral, & posterior with IBD & PsA; of a series of 175 patients with HLA-B27 uveitis, SpA in 50%, mostly AS
- CV – aortitis ascending aorta & arch, late in disease
- In one series of 52 patients with AS, 40% noted to have pulmonary abnormalities on CT
- Renal: amyloidosis, IgA nephropathy

Pereira et al *Rheumatol Curr Res* 2012;2(3):1-5

SpA Management

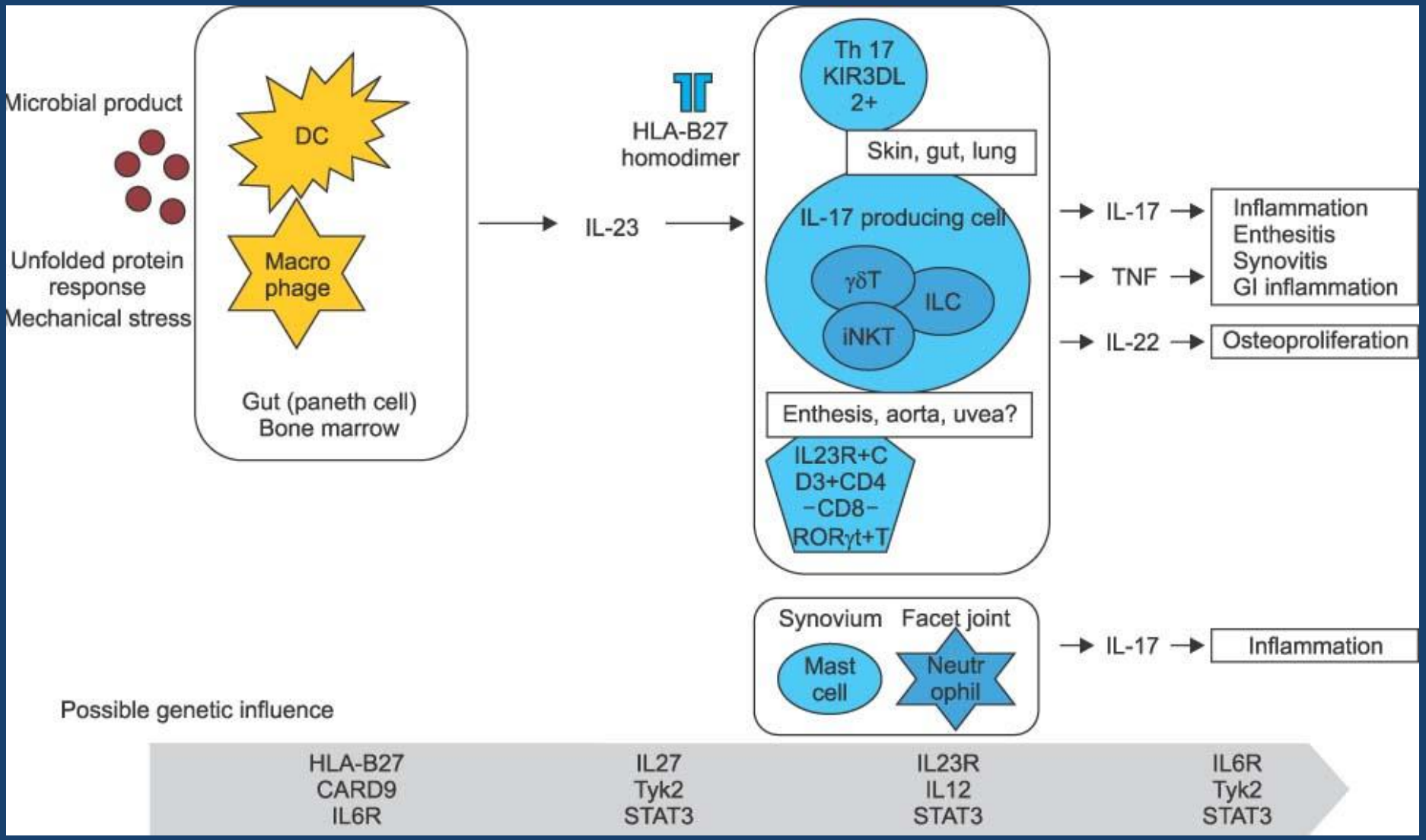
Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, RCT

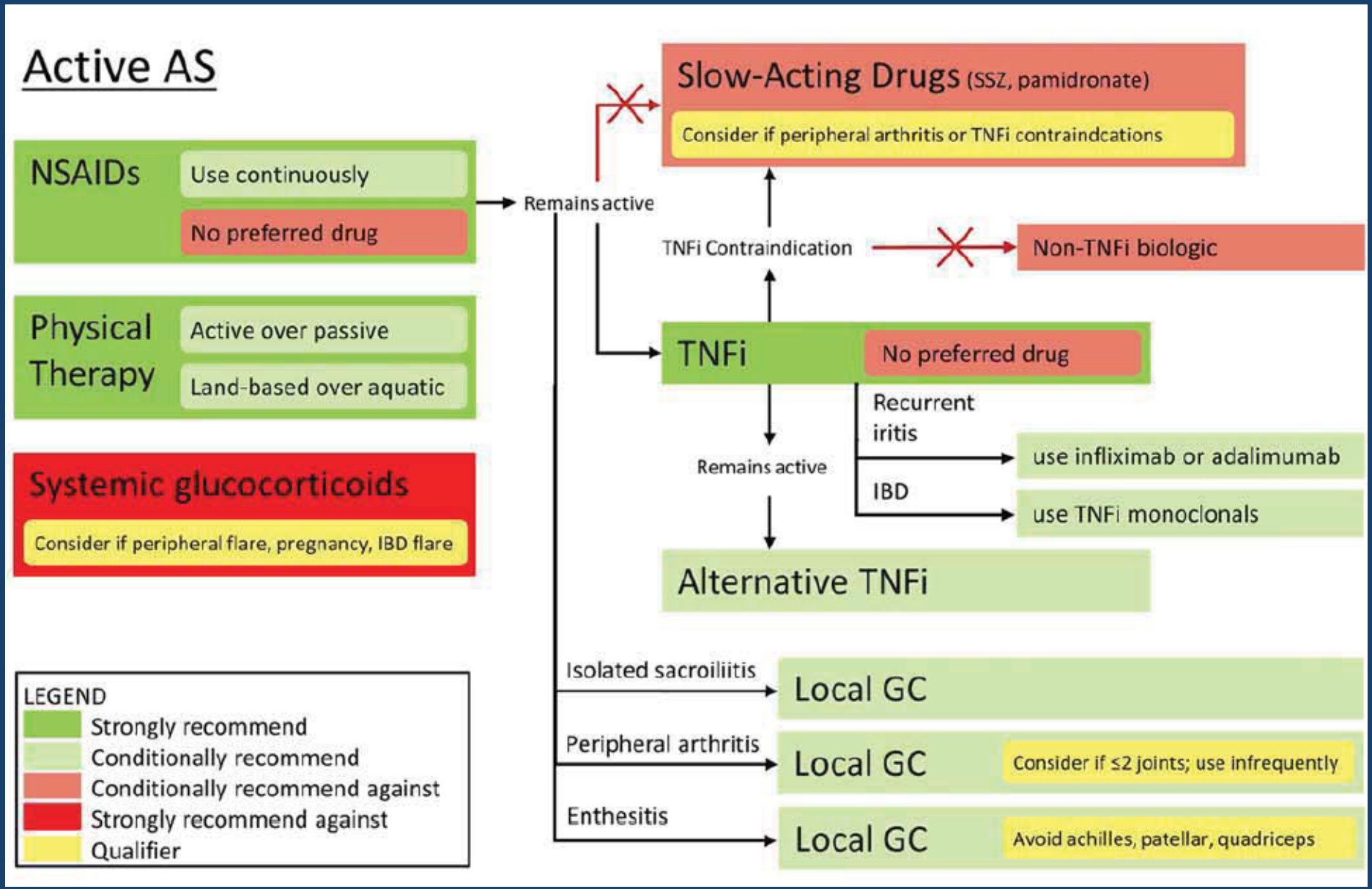
Coates L et al. *Lancet* 2015; 386: 2489–98

- Adults with PsA Sx <24 mos, no prior DMARD
- N=206: 101 to tight control (f/u q4 weeks, escalate Rx if minimal disease activity criteria not met); 105 to standard care (as per treating clinician, review q12 weeks)
- Outcome: Proportion achieving ACR 20 response at 48 weeks
- Analysis: ITT, multiple imputation for missing components

RESULTS:

- ACR20 response at 48 weeks higher in tight control (OR 1·91, 95% CI 1·03–3·55; p=0·04); no difference in radiographic progression
- Serious AE > in tight control (25 events in 14 vs. 8 in 6 patients)
- Tight control group also more likely to be on Rx, including biologicals


Microbial product
Unfolded protein response
Mechanical stress
DC
Macro phage
Gut (paneth cell)
Bone marrow
IL-23
HLA-B27 homodimer
Th 17 KIR3DL 2+
Skin, gut, lung
IL-17 producing cell
γδT
ILC
iNKT
Enthesis, aorta, uvea?
IL23R+C D3+CD4 −CD8− RORγt+T
IL-17
TNF
IL-22
Inflammation
Enthesitis
Synovitis
GI inflammation
Osteoproliferation
Synovium
Facet joint
Mast cell
Neutr ophil
IL-17
Inflammation
Possible genetic influence
HLA-B27
CARD9
IL6R
IL27
Tyk2
STAT3
IL23R
IL12
STAT3
IL6R
Tyk2
STAT3



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

SpA: Pharmacotherapy

For peripheral arthritis:

- non-biological DMARDs (methotrexate, sulfasalazine, leflunamide)

For axial disease, enthesitis:

- NSAIDs
- TNFi
- IL-17i (Sekukinumab), FUTURE 1 & 2

Others:

- IL-17i (Ixekizumab)
- IL-12/23i (Ustekinumab)
- IL-17/23i (Guselkumab)
- Jak/stat pathway (Tofacitinib)

Table 5 Assessment of SpondyloArthritis international Society (ASAS) core set for symptom modifying antirheumatic drugs (SM-ARD) and physical therapy[17]

Domain	Instrument
Function	BASFI
Pain	NRS/VAS (last week/spine/at night due to AS)
	NRS/VAS-last week-spine-due to AS
Spinal mobility	Chest expansion
	Modified Schober
	Occiput to wall
	Cervical rotation
	Lateral spinal flexion or BASMI
Patient global	NRS/VAS (global disease activity last week)
Stiffness	NRS/VAS (duration of morning stiffness/spine/last week)
Fatigue	Fatigue question BASDAI

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; NRS, numerical rating scale 0–10; VAS, visual analogue scale 0–100.

ASAS Handbook. *Ann Rheum Dis* 2009;68(Suppl II):ii1–ii44

SUMMARY

- SpA likely underestimated
- SpA associated with significant comorbidity & mortality
- Early treatment and treat to target beneficial
- Management includes pharmacotherapy, monitoring for complications, and managing co-morbid conditions
- Multidisciplinary team approach (GI specialists, rheumatologist, dermatologist, ophthalmologists, general practitioners)