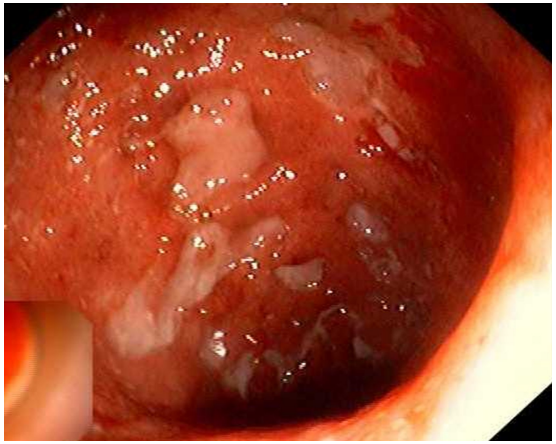
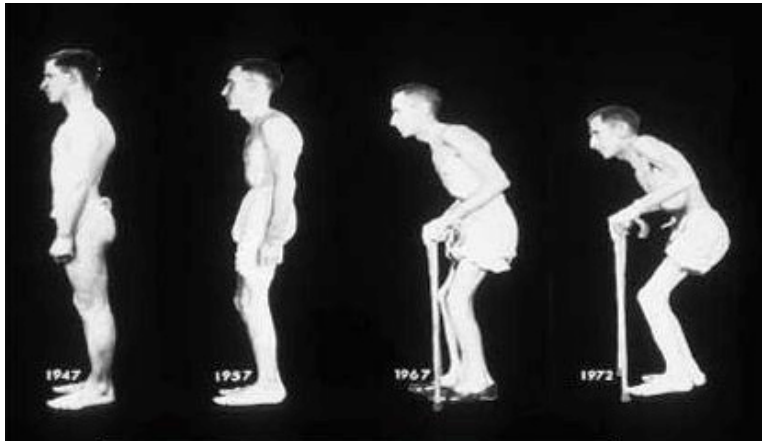
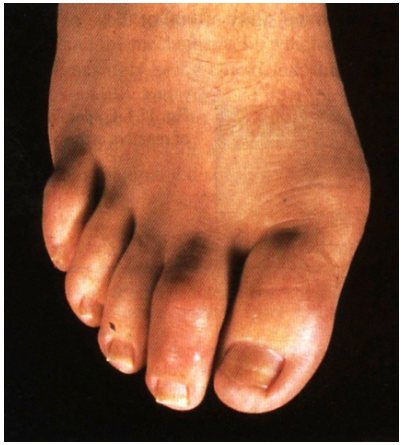
Update on extra-articular manifestations in axial Spondyloarthritis







RHEUMAZENTRUM RUHRGEBIET

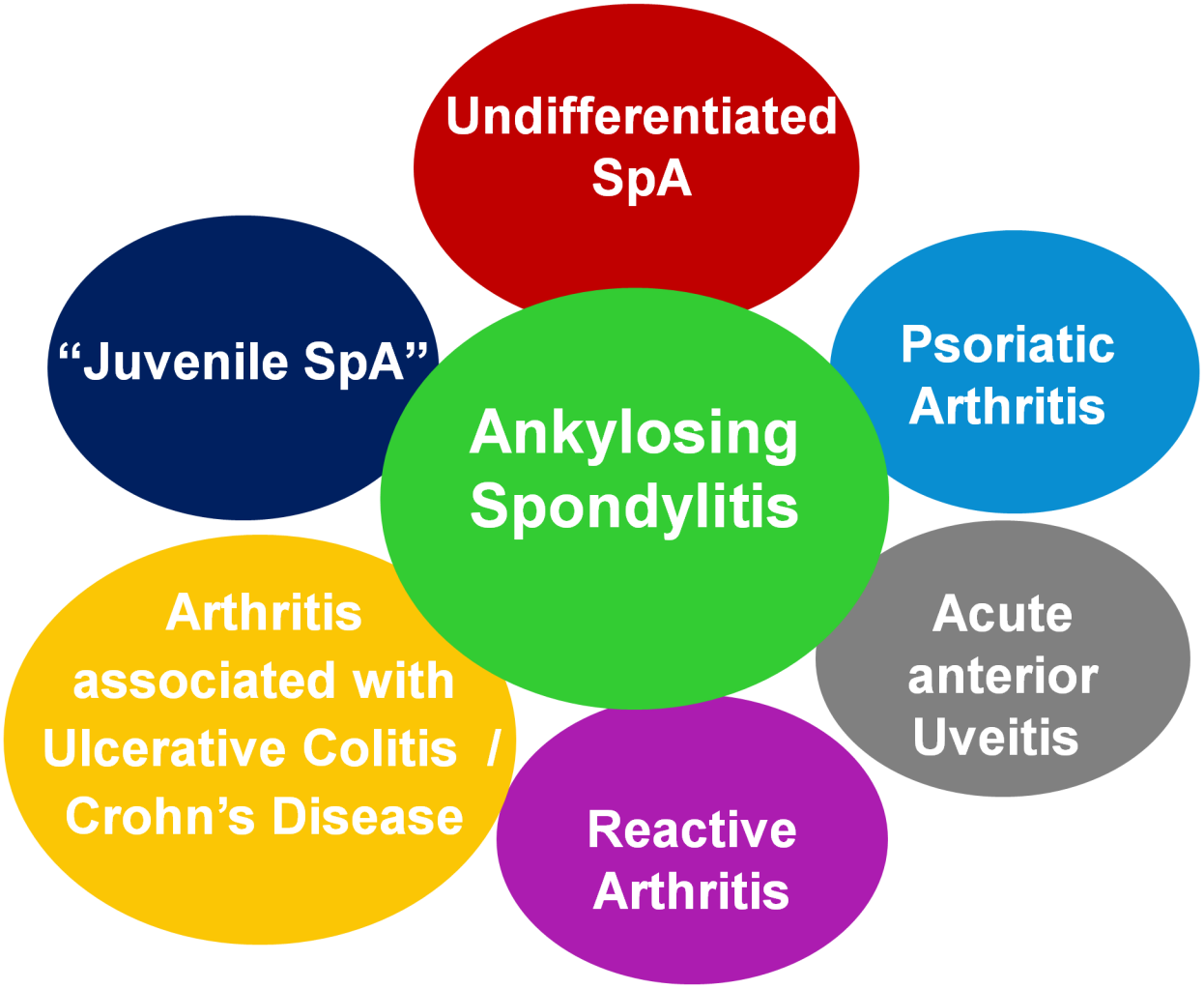
Genoa, 20.10.2016

Xenofon Baraliakos
Rheumazentrum Ruhrgebiet Herne
Ruhr-University Bochum
Germany

50 Jahre RUB

Question: What do ‚extraspinal' manifestations have to do with axial spondyloarthritis?

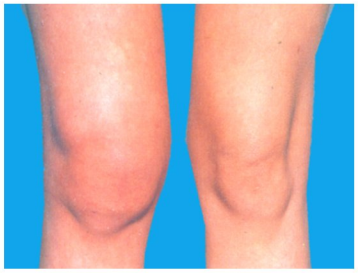
Concept of Spondyloarthritides

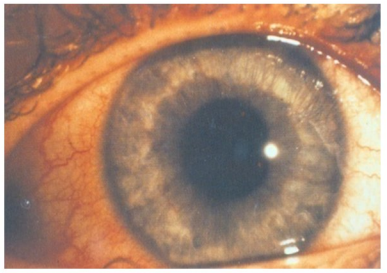


Spondyloarthritis: Characteristic Parameters Used for Diagnosis I

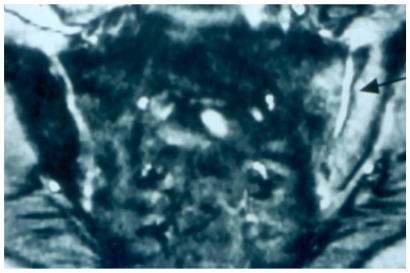
Symptoms

Inflammatory back pain





Imaging



Lab

ESR/CRP

Patient‘s history

Good response to NSAIDs

ASAS

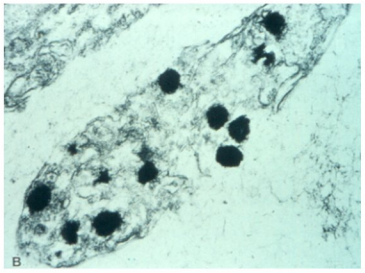
Spondyloarthritis: Characteristic Parameters Used for Diagnosis II

Genetics

HLA-B27 positive

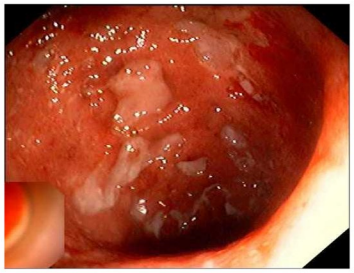
family history

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

ASAS Classification Criteria for 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 (IBP)
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

Sensitivity: 79.5%, Specificity: 83.3%; n=975

In patients with peripheral symptoms ONLY

Arthritis or enthesitis or dactylitis

plus

≥1 SpA feature

- uveitis
- psoriasis
- Crohn's/colitis
- preceding infection
- HLA-B27
- sacroiliitis on imaging

OR

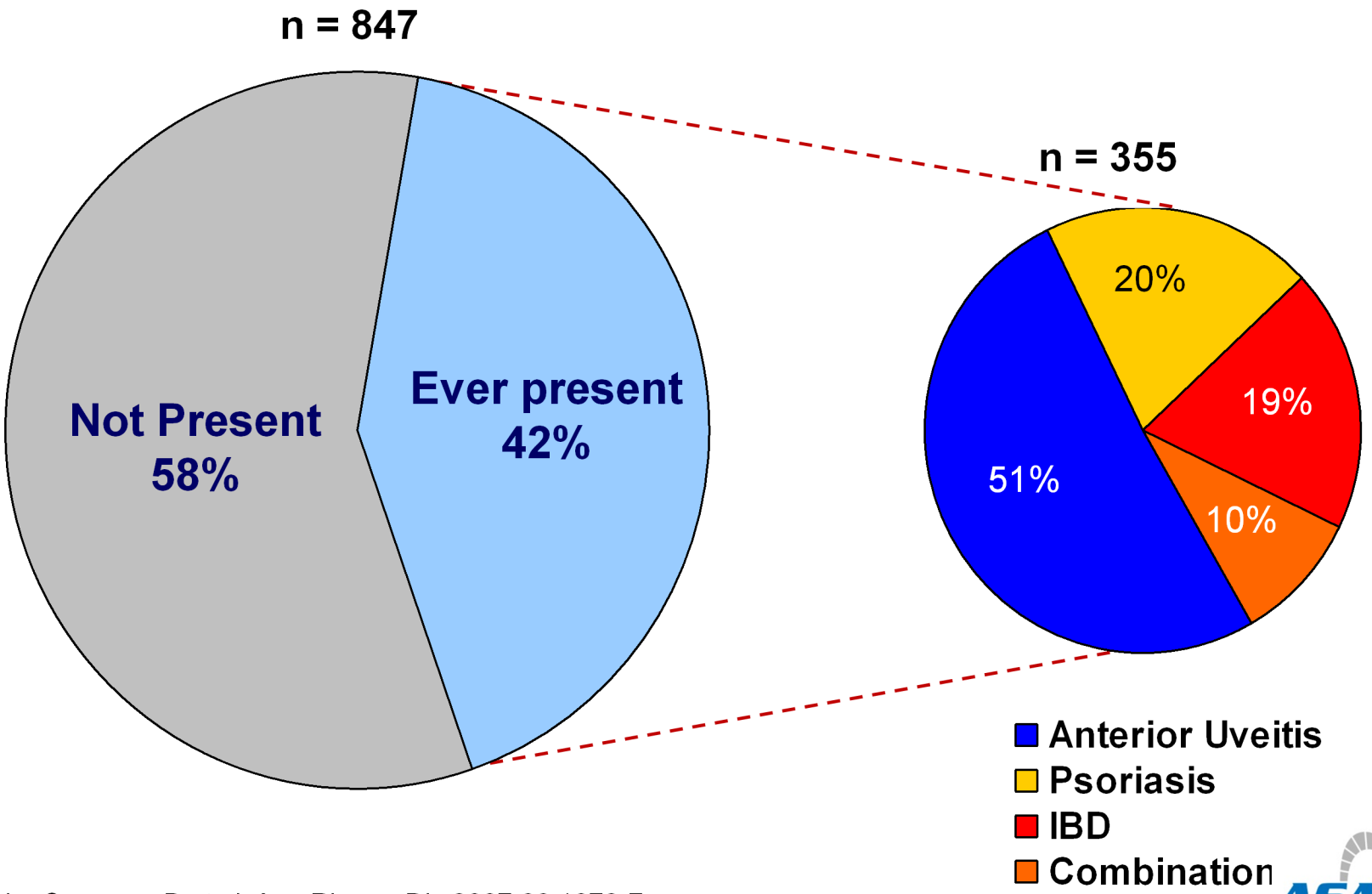
≥2 other SpA features

- arthritis
- enthesitis
- dactylitis
- IBP ever
- family history for SpA

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31 (with permission)

Question: **Are extraspinal manifestations frequent and relevant in the concept of axSpA?**

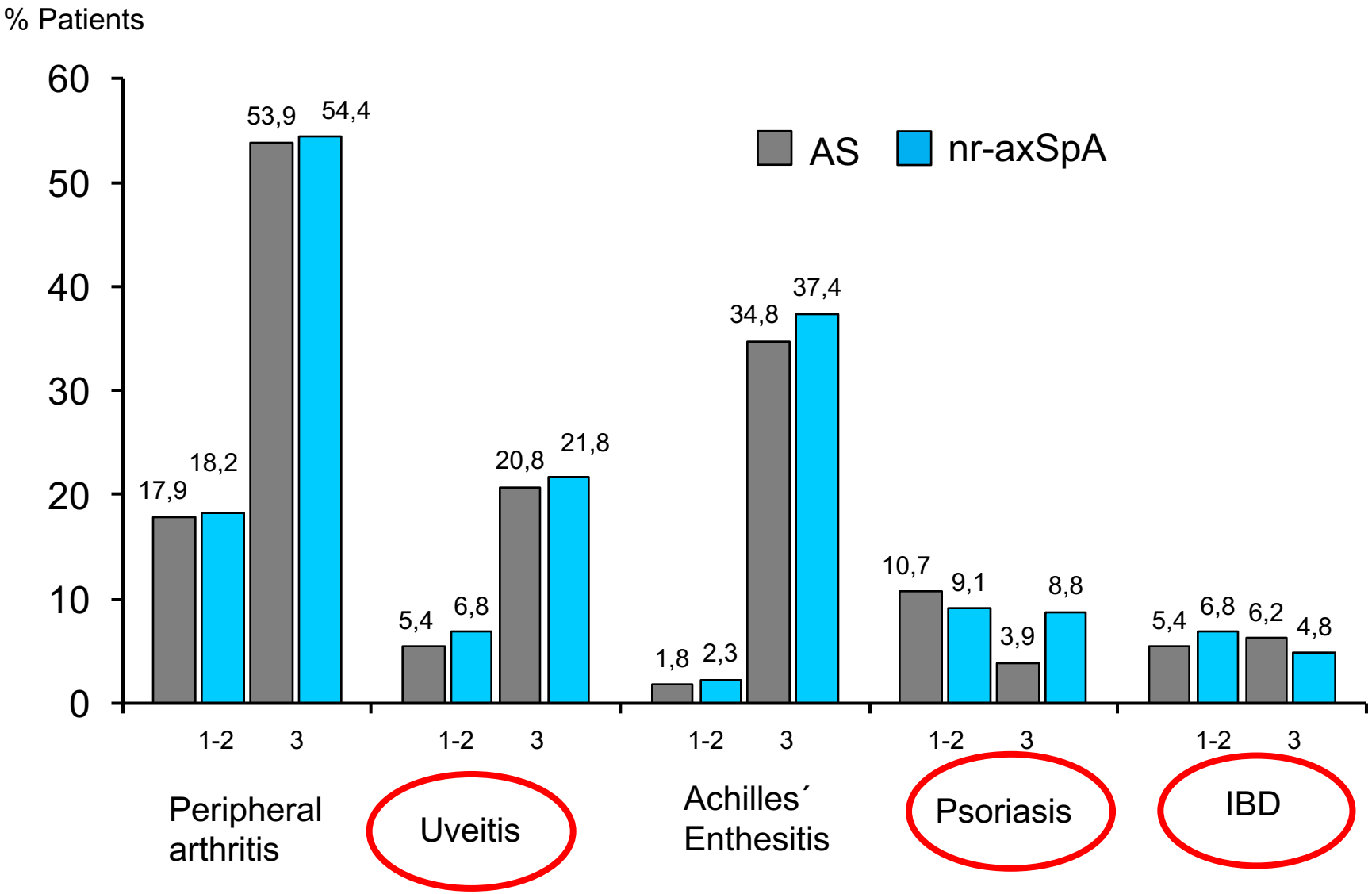
Extra-Articular Manifestations in Ankylosing Spondylitis



Vander Cruyssen B et al. Ann Rheum Dis 2007;66:1072-7

ASAS

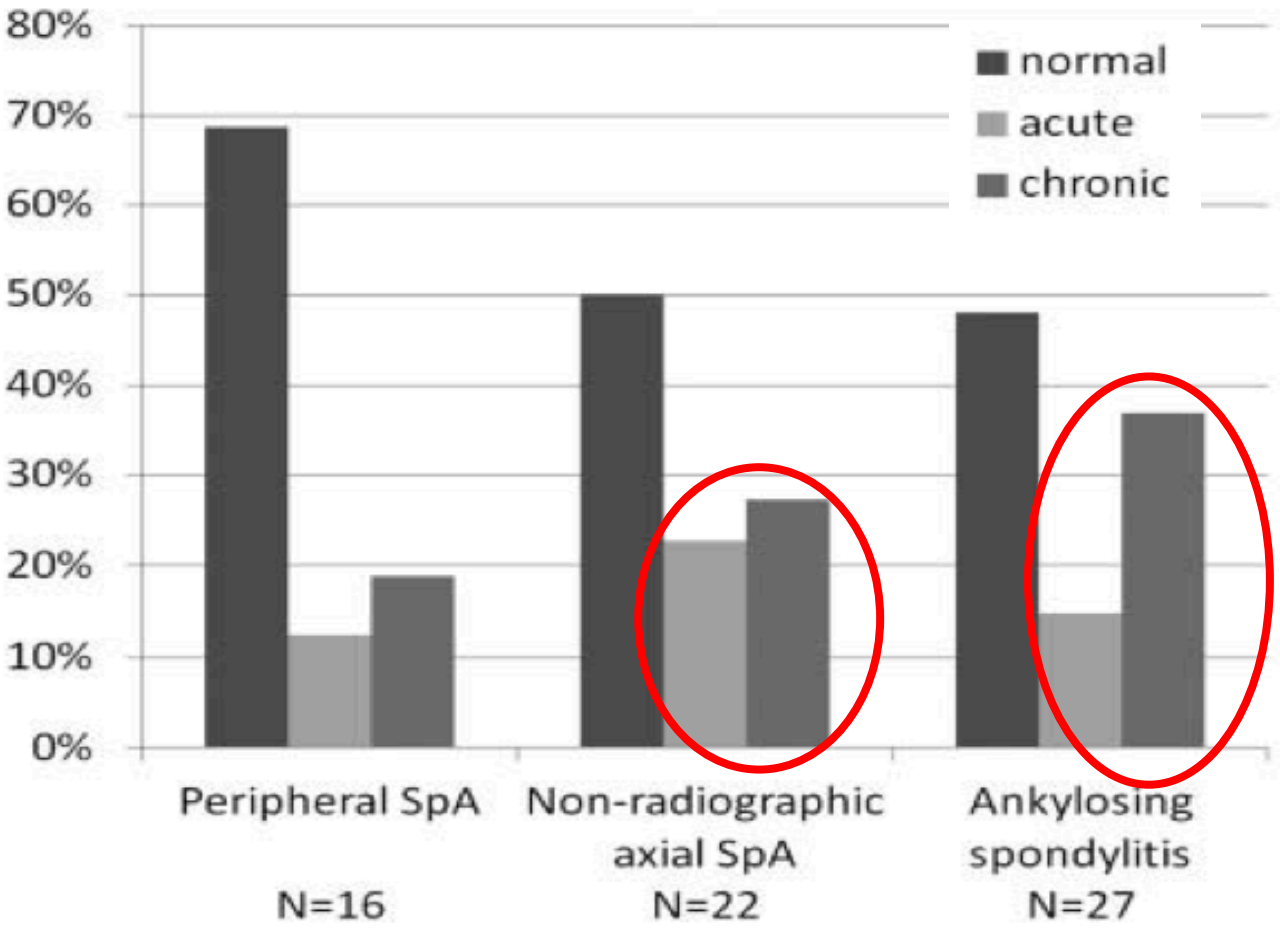
Similar prevalence of EAMS between AS and nr-axSpA



[1]Kiltz U et al. AC&R 2012, [2]Kiltz U et al. ARD 2012, [3]Landewe R, et al. ARD 2013

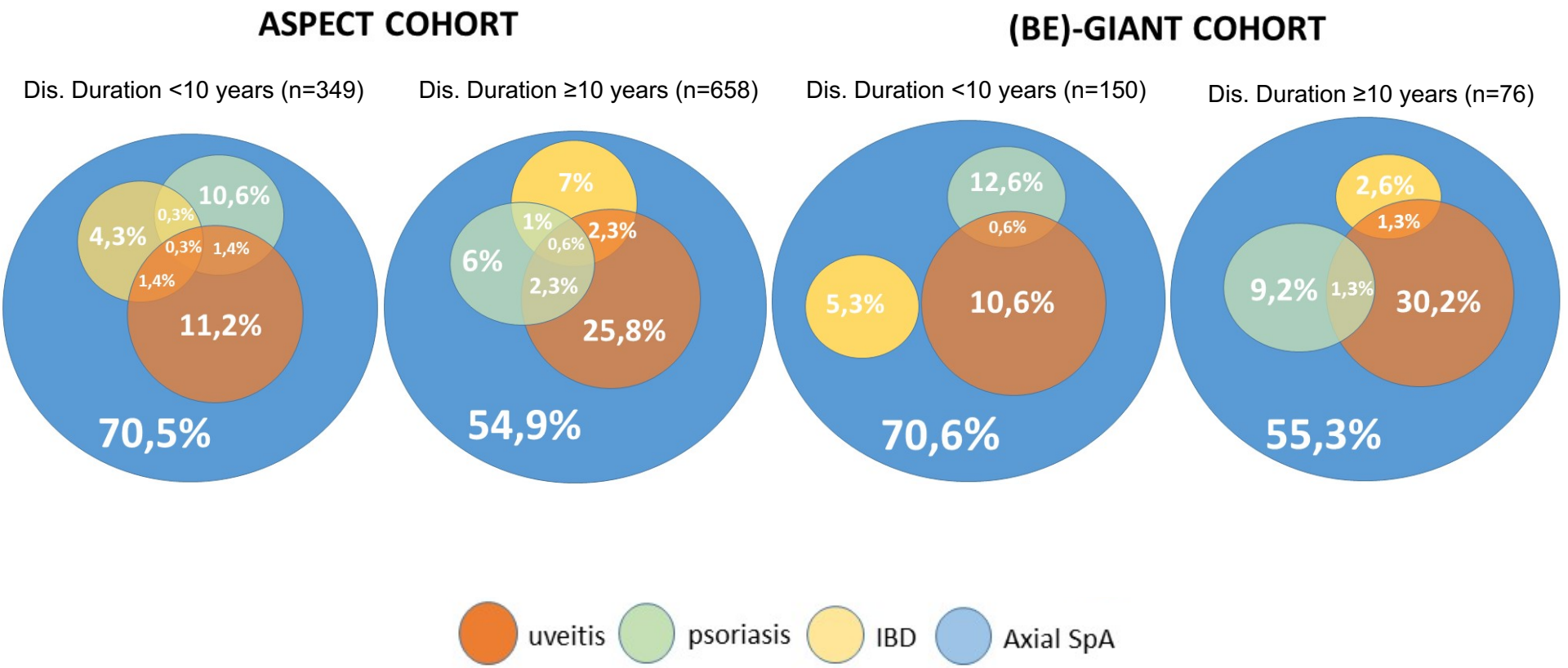
Different forms of IBD in different stages of axSpA

Prevalence of IBD:
46% of patients



van Praet E et al, Ann Rheum Dis 2013

Prevalence of extra-articular manifestations linked to longer cumulative exposure to inflammation



Varkas G et al, EULAR 2016

EAMs: High likelihood ratio for identifying SpA

	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

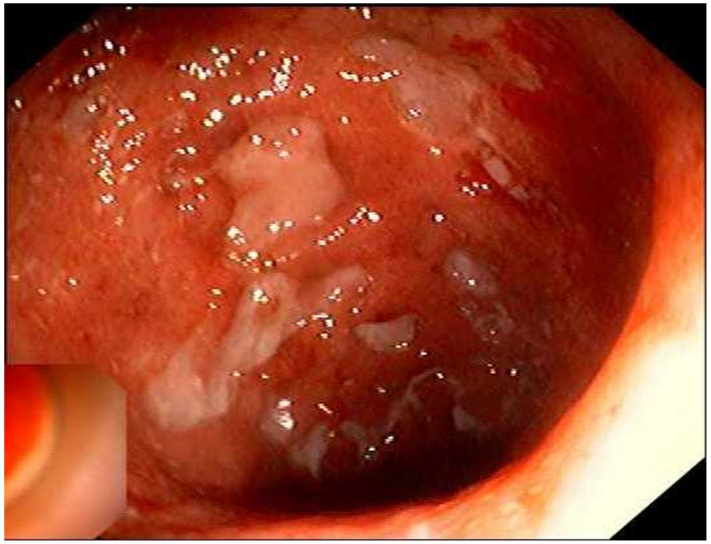
Modified from: Rudwaleit M et al. Ann Rheum Dis 2006;65:1251-2

ASAS

Question: How frequent is IBD in axSpA and how frequent is axSpA in IBD?

Focus on IBD

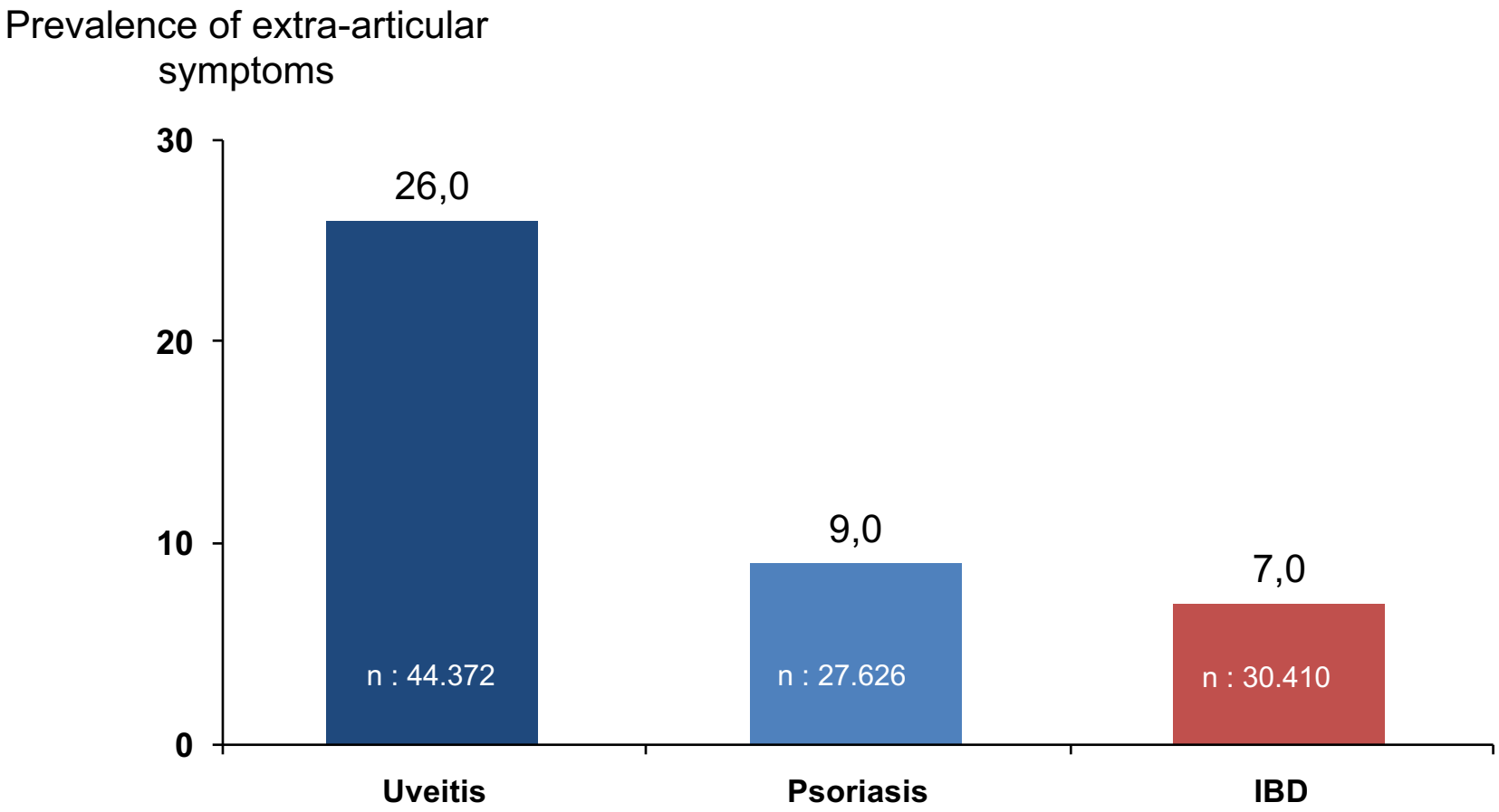
Typical Gut Lesions in Crohn‘s Disease



Crohn‘s disease lesions in the colon with deep ulcerations and islands of regenerative mucosa in between.

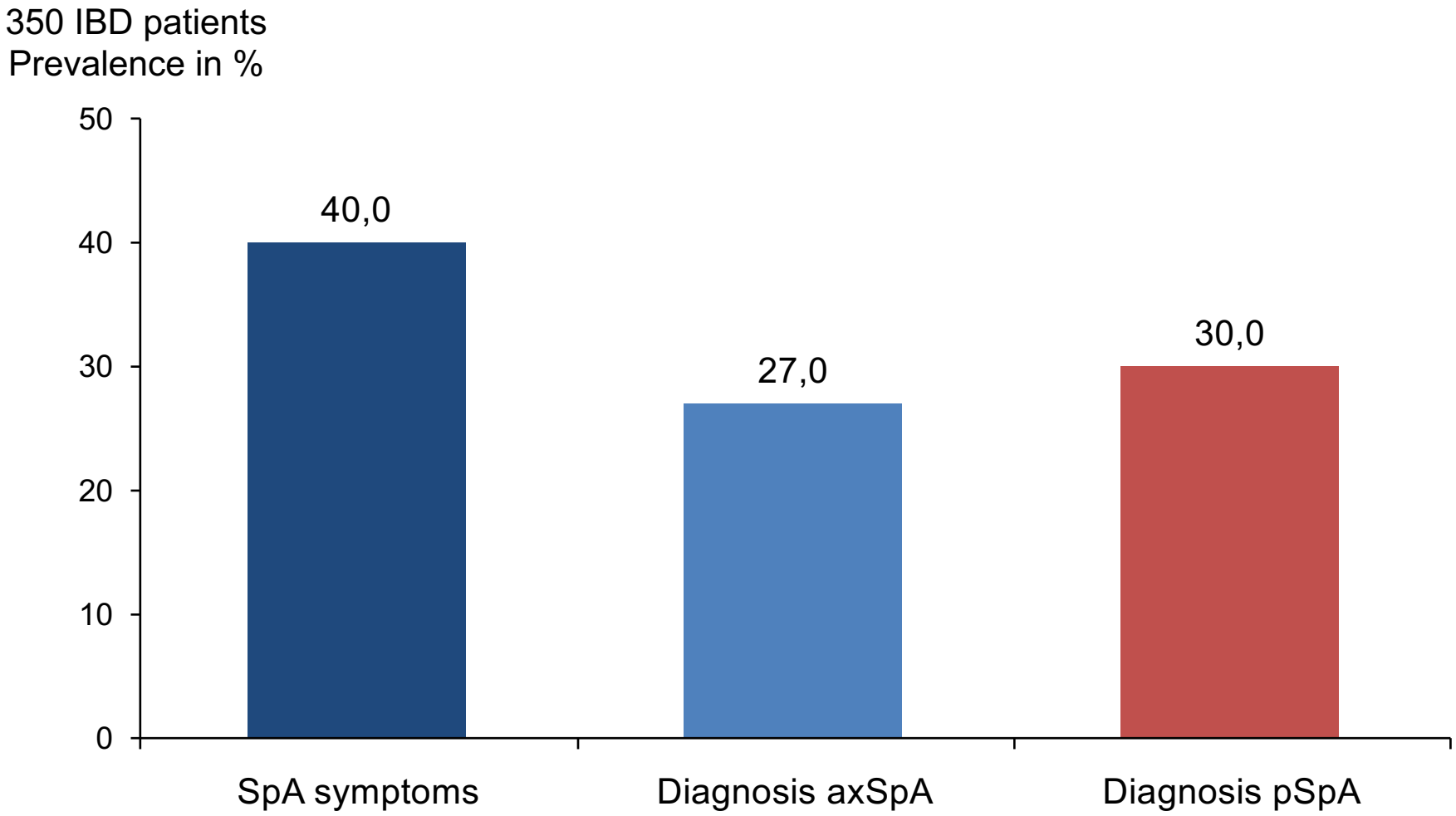
7% of AS patients suffer from IBD symptoms...

Meta-analysis of 156 publications



Stolwijk C et al. Ann Rheum Dis. 2013

... and 27% of IBD patients can be diagnosed with SpA



Stolwijk et al. Can J Gastroenterol 2013

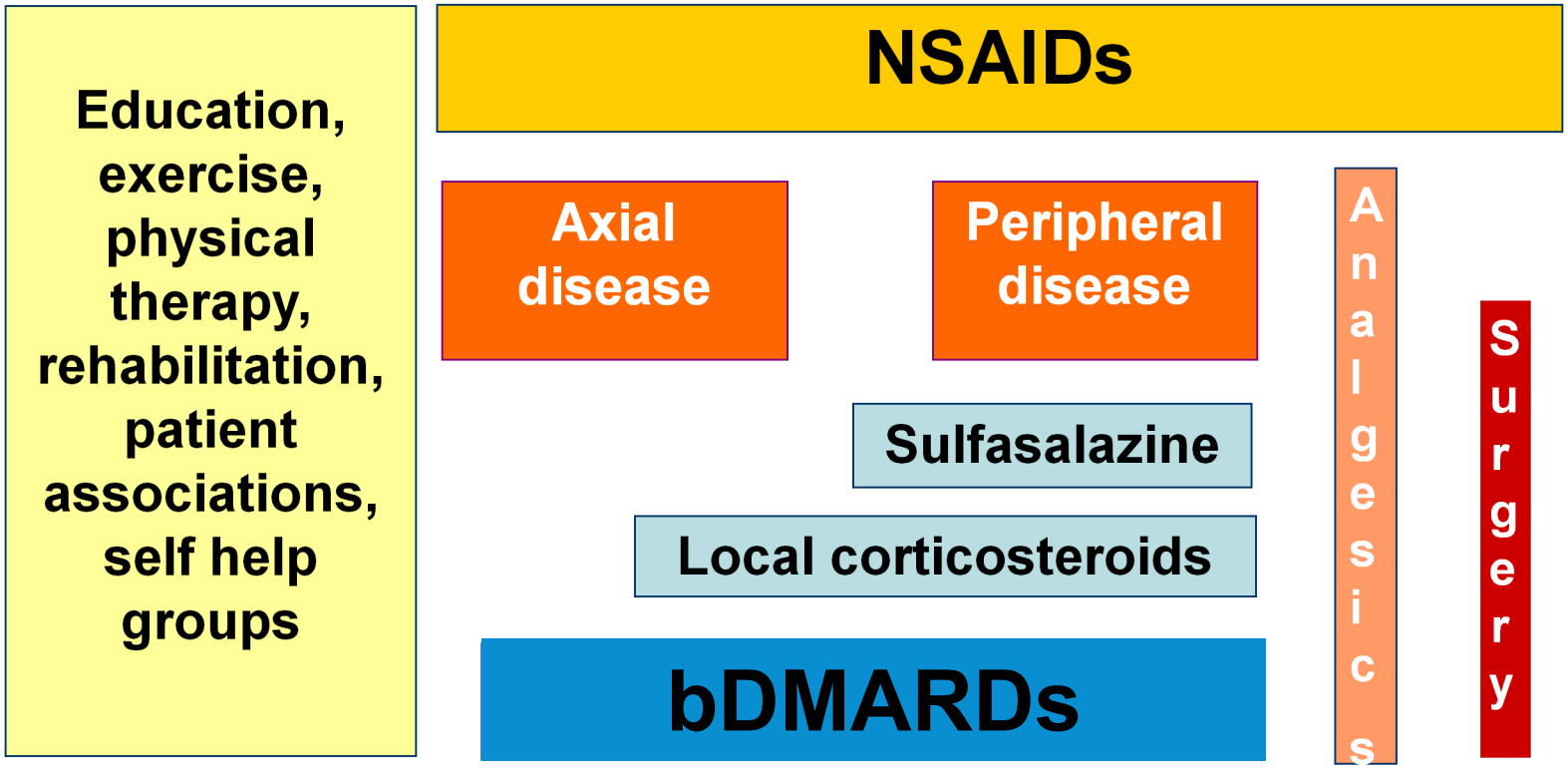
Question: Are there risk factors for thinking about bowel involvement in patients with axSpA?

Risk factors for bowel involvement in axSpA

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
Constant	0.97		0.981
Nagelkerke R^2	0.52		
TPR and TNR	81.8% and 78.3%		
ROC-AUC	0.88		

van Praet E et al, Ann Rheum Dis 2013

ASAS/ELAR Recommendations for the Management of axial Spondyloarthritis

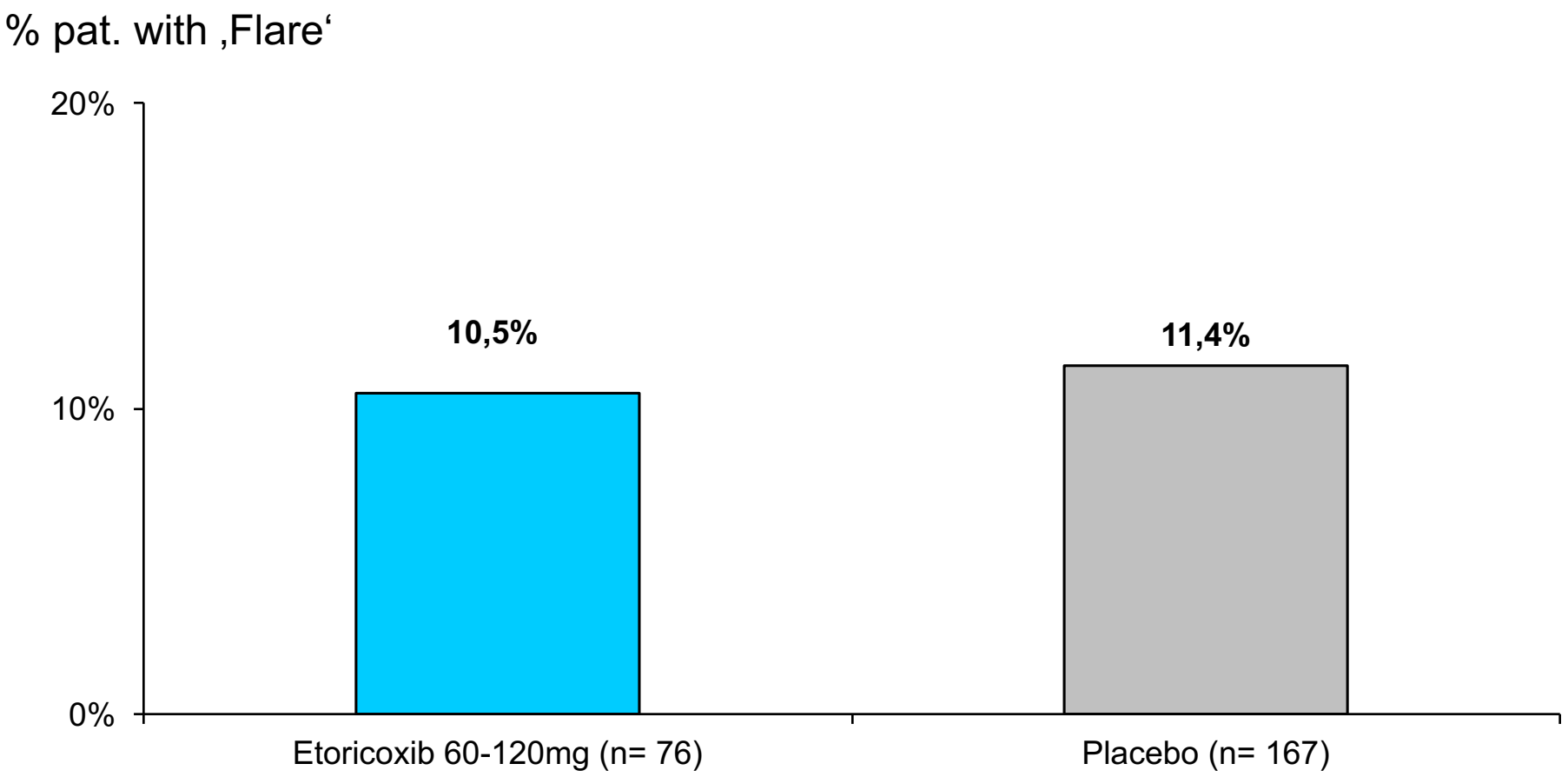


Zochling J et al, Ann Rheum Dis 2006
Braun J et al, Ann Rheum Dis 2011 & 2016

Question: **Is this therapeutic algorithm also applicable in patients with extra-spinal manifestations?**

NSIADs/COX-II inhibitors: safe in patients with IBD and rheumatic diseases?

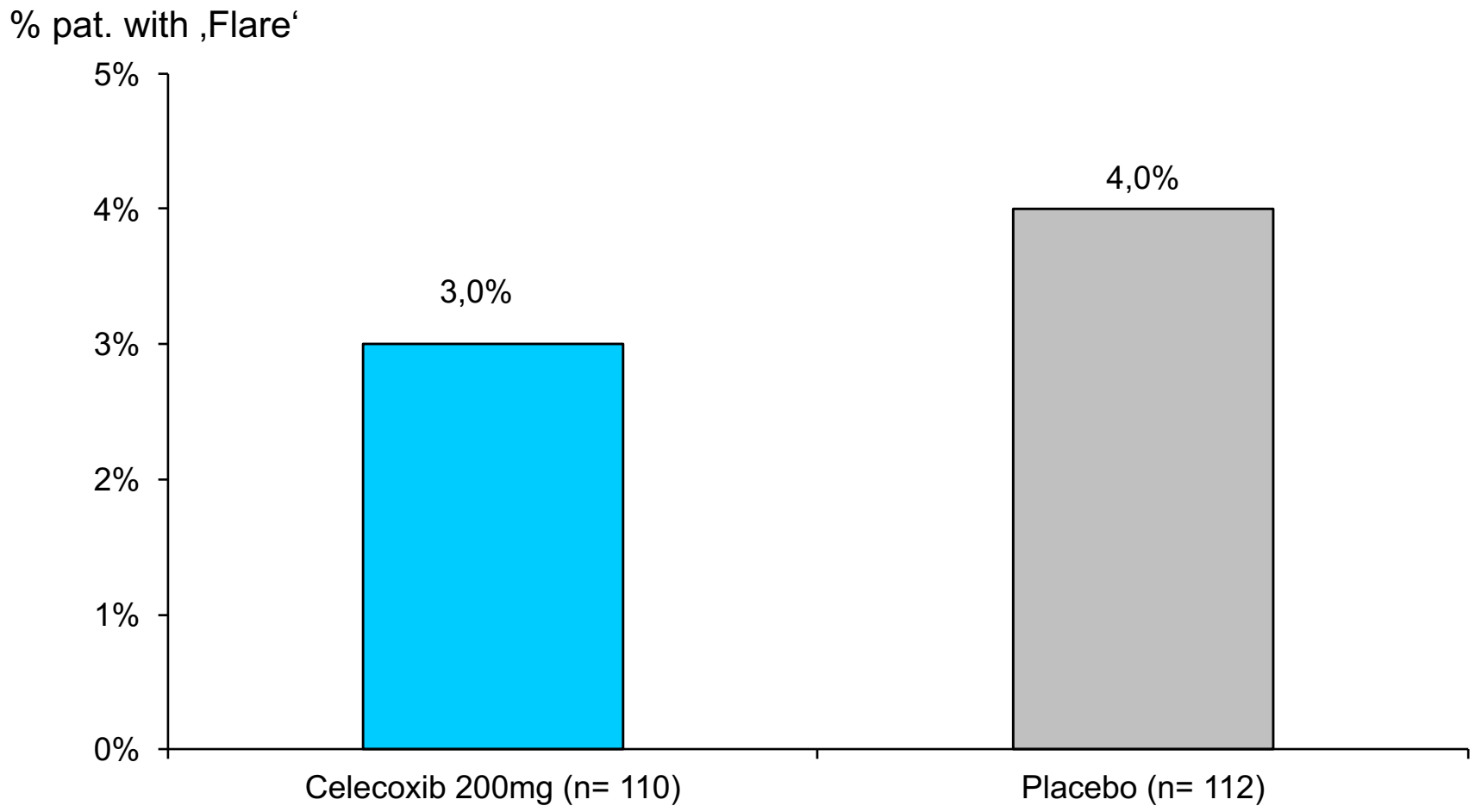
- DBPC-study with **Etoricoxib 60-120mg/day** over 3 months in patients with IBD and rheumatic manifestations



Miedany et al, Am J Gastroenterol 2006

NSIADs/COX-II inhibitors: safe in patients with IBD and rheumatic diseases?

- DBPC-study with **Celecoxib 200 mg/day** over 14 days in patients with UC
- NSAID intake due to joint symptoms, UC not active
- Remission and Flare: first clinical and then confirmed via endoscopy



Sandborn et al, Clin Gastroenterol Hepatol 2006

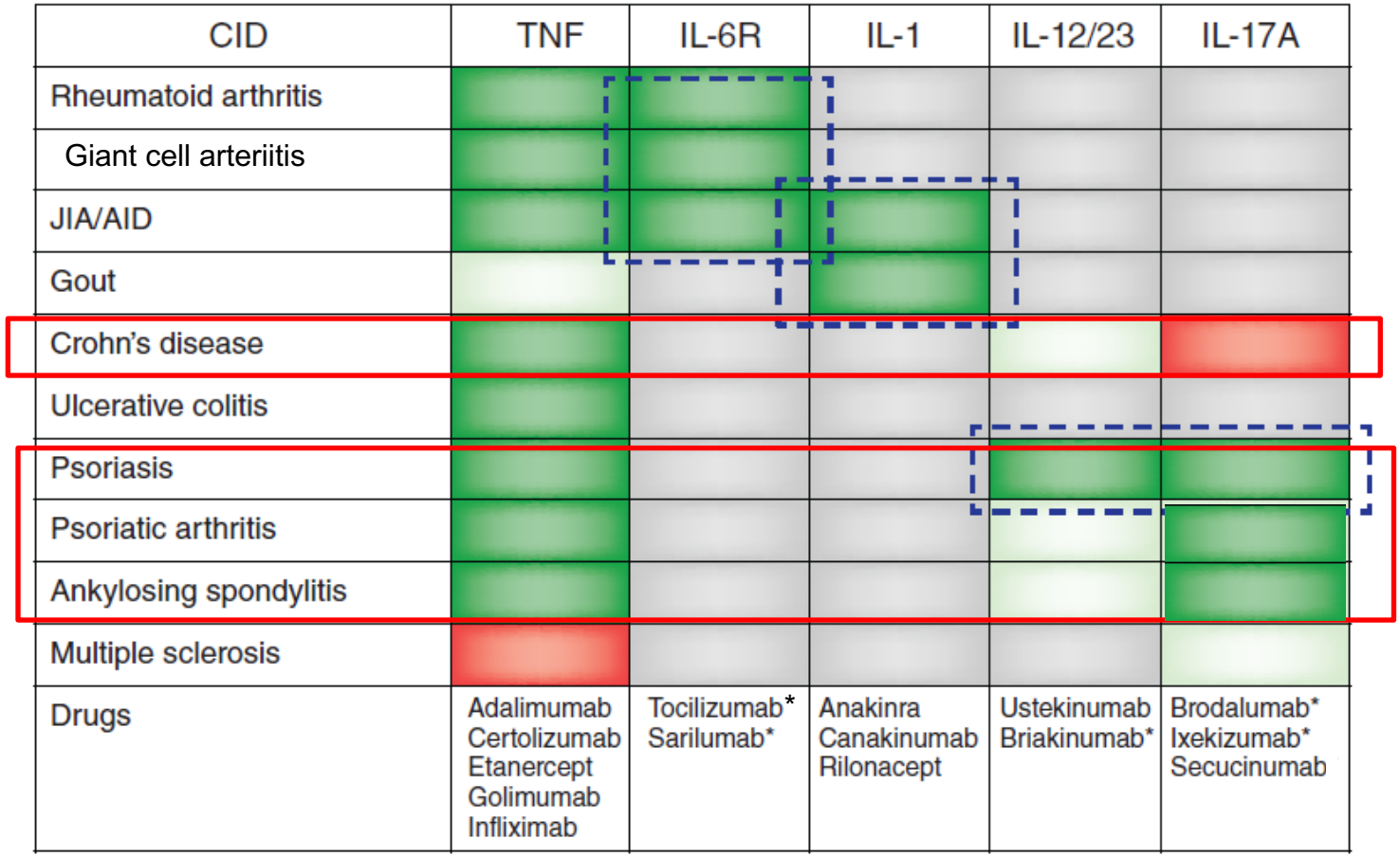
Sulfasalazine in axSpA – what is the evidence?

NOR-DMARD registry, 3-month Follow-up

	All patients *n* = 139	Swollen joints at baseline *n* = 64	No swollen joints at baseline *n* = 75	*P*-value	Adjusted *P*-value[a]
Δ Patient global	−9.8 (24.7)	13.4 (23.4)	−4.3 (25.1)	0.04	0.12
Δ Physician global	−10.3 (21.1)	−10.3 (22.0)	−9.0 (19.0)	0.72	0.49
Δ MHAQ	−0.11 (0.36)	−0.15 (0.38)	−0.07 (0.32)	0.19	0.57
Δ SF-6D	0.05 (0.11)	0.05 (0.11)	0.04 (0.11)	0.31	0.92
Δ CRP	−4.5 (19.5)	−7.1 (24.7)	−1.3 (9.7)	0.11	0.90
Δ Swollen joints (0–32)	−0.6 (3.2)	−1.4 (2.9)	0.3 (0.7)	NA	NA
	n = 79[b]	*n* = 37[b]	*n* = 42[b]		
ASDAS M.I., %	6.7	7.7	5.6	1.0[c]	0.84
ASDAS C.I.I., %	17.8	23.1	11.1	0.44[c]	0.43
BASDAI50 response, %	27.4	28.6	22.2	0.54	0.19
BASDAI response, %	35.6	40.0	27.8	0.28	0.21
ASAS20 response, %	21.4	25.7	15.2	0.28	0.52
ASAS40 response, %	12.9	17.1	9.1	0.48[c]	0.65
Δ ASDAS	−0.4 (1.0)	−0.6 (1.0)	−0.1 (0.8)	0.10	0.38
Δ BASDAI	−0.9 (1.9)	−1.4 (1.9)	−0.3 (1.7)	0.02	0.008
Δ BASDAI back pain score (Q2)	−0.9 (0.8)	−1.3 (2.1)	−0.5 (2.6)	0.25	0.58
Δ BASDAI peripheral pain score (Q3)	−0.9 (0.5)	−1.6 (2.6)	0.1 (2.3)	0.007	0.006
Δ BASFI	−0.6 (1.8)	−0.7 (2.0)	−0.6 (1.8)	0.76	0.32

Fagerli K et al, Rheumatology 2015

Inflammatory cytokines in chronic inflammatory diseases



Schett G. et al. Nature Medicine 2013

TNF-Inhibitors in IBD and SpA

Indication	Infli-ximab	Adalimumab	Golimumab	Certolizumab	Etanercept
CD	☺	☺	✖	✖	✖
UC	☺	☺	☺	✖	✖
axSpA	☺ (AS)	☺	☺	☺	☺
PsA	☺	☺	☺	☺	☺

☺ Approved

✖ Not effective, no studies or not (yet) approved

CD = Crohn´s disease, UC = ulcerative colitis

Biologics in IBD

Indication	Infliximab	Adalimumab	Golimumab	Vedolizumab
CD – severe	☺	☺	✗	☺
CD – Mod +/- AZA naive	☺	☺	✗	☺
CD, fistulizing	☺	✗	✗	✗
CD Children	☺	☺	✗	✗
UC Adults	☺	☺	☺	☺
UC Children	☺	✗	✗	✗

☺ Effective and approved for the indications

✗ Not effective, no studies or not (yet) approved

CD = Crohn´s disease, UC = ulcerative colitis

IL-17A inhibition and IBD: still more data needed

- 10 Phase 2 and Phase 3 studies in moderate to severe PsO
- 2 Phase 3 studies in active PsA
- 2 Phase 3 studies in active AS

Entire treatment period, n (EAIR per 100 pt-years) [95% CI]				
Short-term period, n (%)				
	PsO Studies		PsA Studies	AS Studies
	Any SEC[a] (n=3430)	ETN (n=323)	Any SEC[a] (n=974)	Any SEC[a] (n=591)
Mean exposure, days	290.1	331.9	542.4	670.0
Crohn's disease	3 (0.11) [0.02-0.32]	0 [0-1.26]	1 (0.07) [0.00-0.39]	8* (0.77) [0.33-1.51]
-Exacerbations[b]	3	0	0	3
Ulcerative colitis	4 (0.15) [0.04-0.38]	1 (0.34) [0.01-1.90]	2 (0.14) [0.02-0.50]	3 (0.29) [0.06-0.84]
-Exacerbations[b]	2	0	1	1

*Final diagnosis was not confirmed in 2 cases
[a]Includes pts switched from placebo (PBO)
[b]Exacerbations count to the overall incidence rate
EAIR = Exposure adjusted treatment rate

Schreiber S et al, EULAR 2016

IL-17A inhibition and IBD: still more data needed

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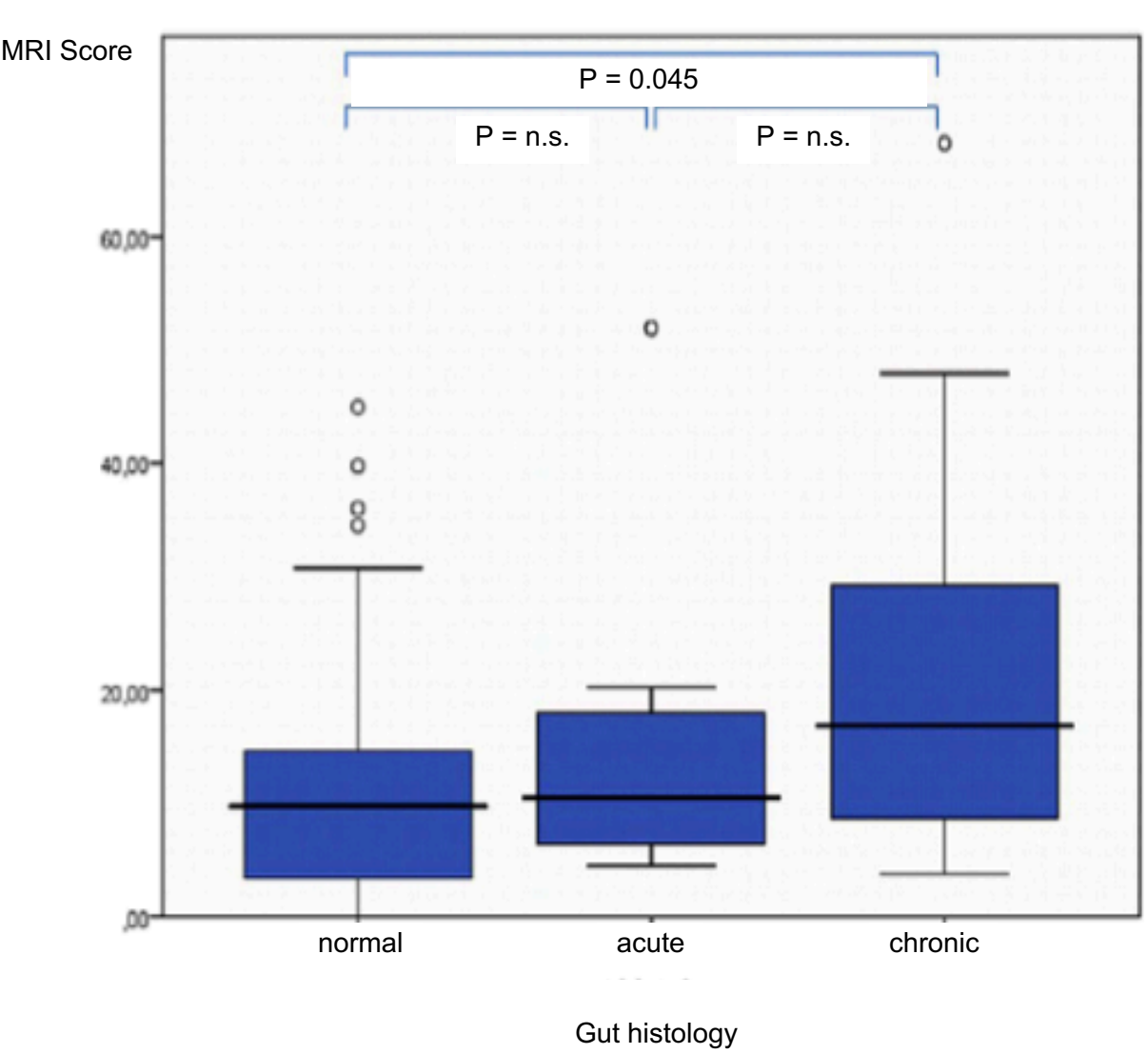
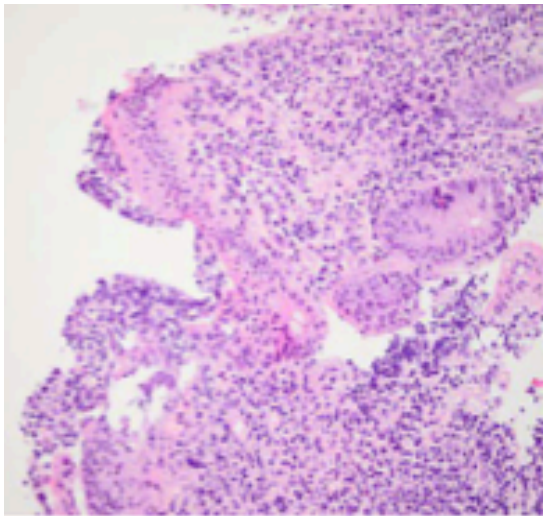
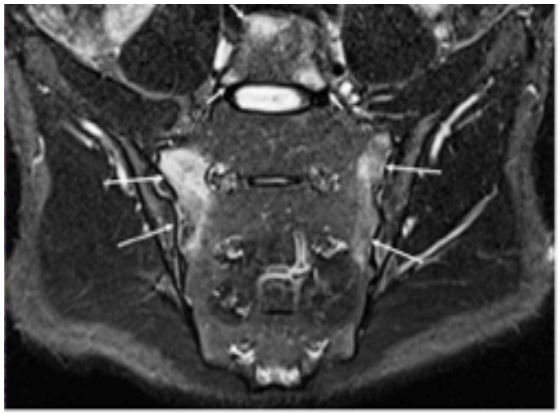
Schreiber S et al, EULAR 2016

Question: **Is there a correlation between IBD and objective axSpA findings?**

Bowel inflammation:
Predictor for inflammatory activity on MRI in axSpA







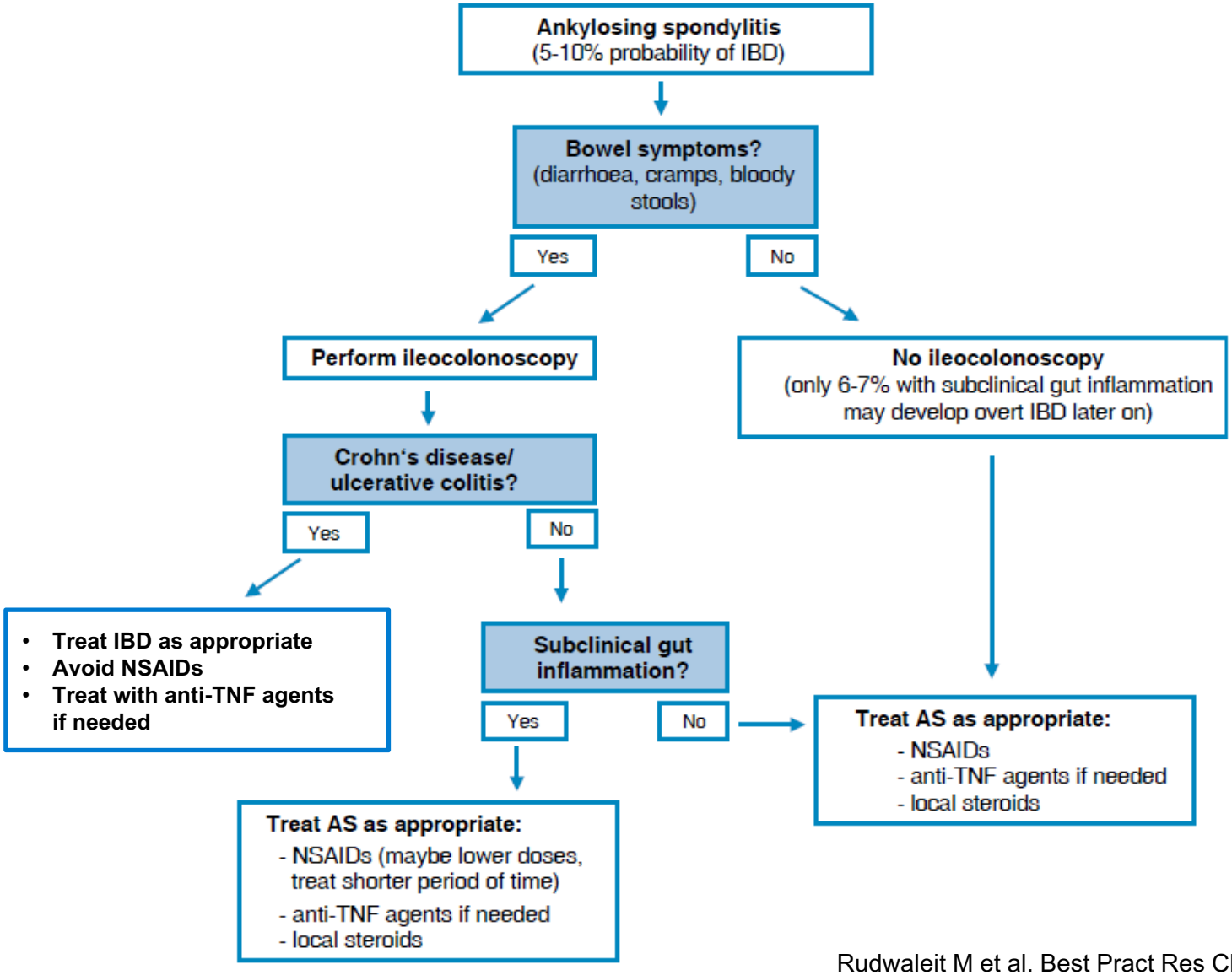
Van Praet L et al, Ann Rheum Dis 2013

Bowel inflammation: Predictor for erosive changes on MRI in axSpA

Peluso R et al, J Rheumatol 2012

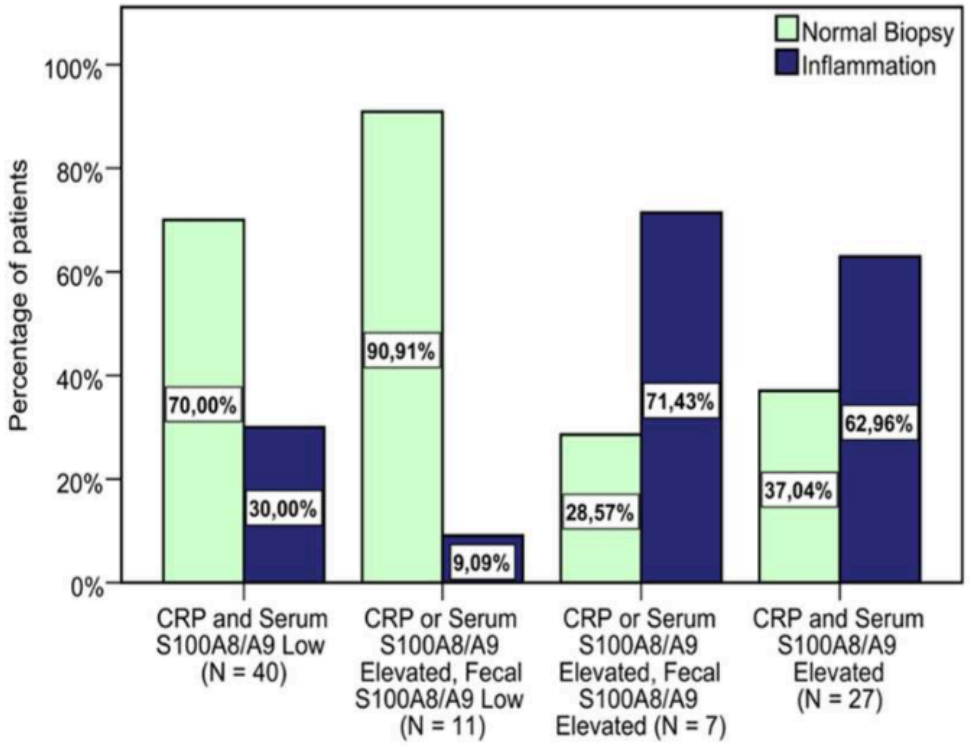
SpA und IBD–
How to approach?

Possible approach in patients with axSpA and suspicion of IBD



Rudwaleit M et al. Best Pract Res Clin Rheumatol. 2006

Increased calprotectin levels are highly suspective for IBD in patients with axSpA



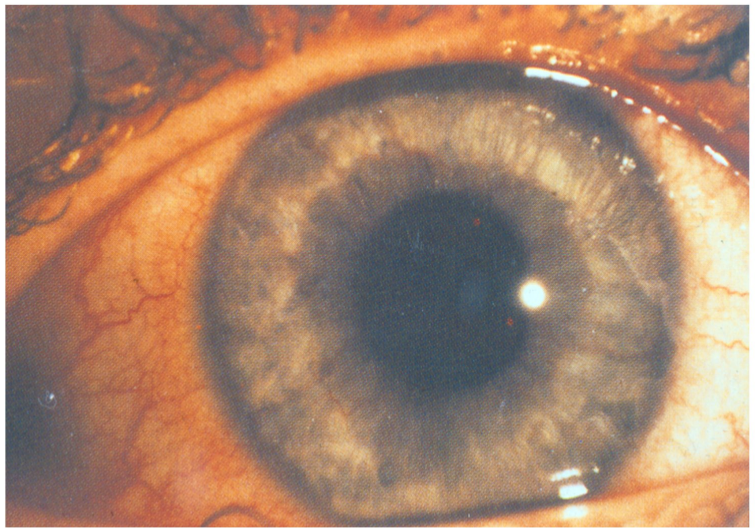
CRP and serum S100A8/S100A9 both elevated	⇨ Consider ileocolonoscopy	
Either serum S100A8/S100A9 or CRP elevated	↗ Fecal calprotectin < 85µg/g	⇨ No further action
	↘ Fecal calprotectin > 85µg/g	⇨ Consider ileocolonoscopy
CRP and serum S100A8/S100A9 both low	⇨ No further action	

Cypers H et al, Ann Rheum Dis 2015

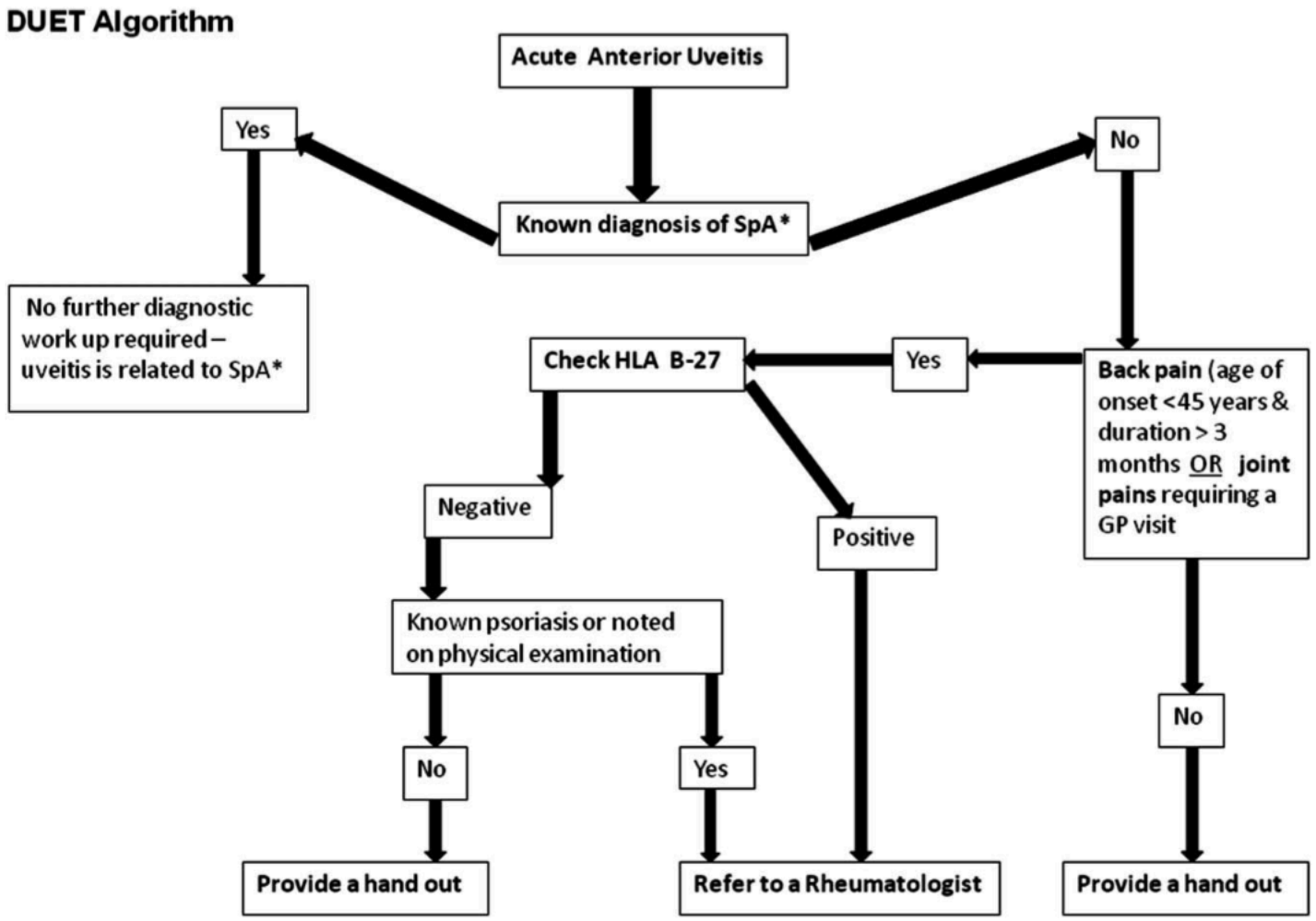
Focus on anterior uveitis

Eye: Acute Anterior Uveitis in Spondyloarthritis

- Acute onset
- Unilateral
- Anterior
- Spontaneous remission
- Recurrent
- Related to HLA B27



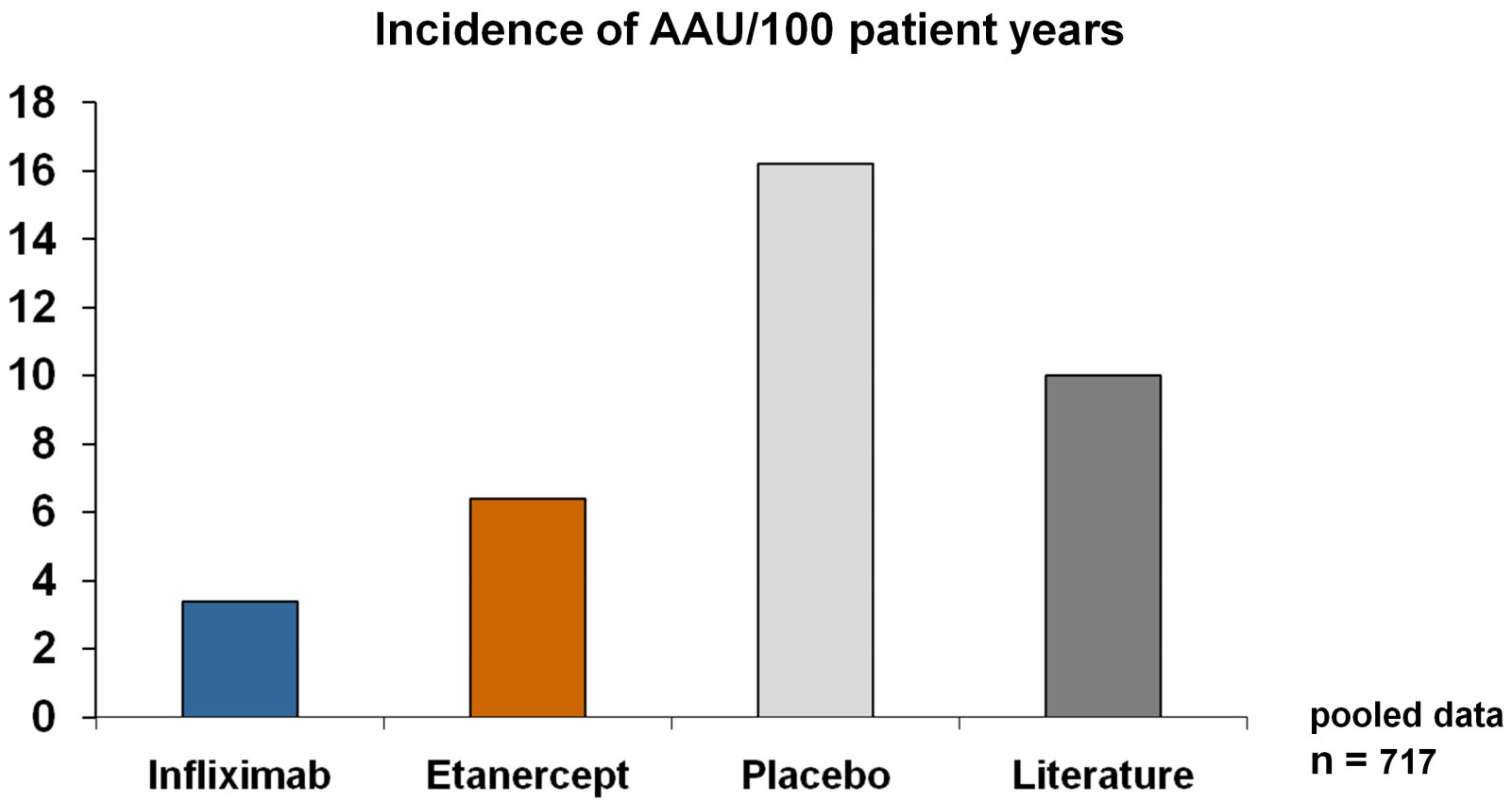
DUET-Algorithm: 40% of patients with idiopathic AAU received the diagnosis of SpA from a rheumatologist



Sensitivity: 96%
Specificity: 97%

Haroon N et al, Ann Rheum Dis 2015

Decreased Incidence of Acute Anterior Uveitis (AAU) in Patients on Anti-TNFα-Therapy



Braun J et al. Arthritis Rheum 2005;52:2447-51

Decreased Incidence of Acute Anterior Uveitis (AAU) in Patients on Anti-TNFα-Therapy

Incidence of uveitis flares in axSpA patients treated with CZP or PBO to Week 24						
	CZP			PBO		
	All Patients (n=218)	History of Uveitis (n=38)	No History of Uveitis (n=180)	All Patients (n=107)	History of Uveitis (n=31)	No History of Uveitis (n=76)
IR per 100 patient-years*	2.0	11.9	0.0	10.6	42.1	0.0
Patients (Exposure, patient-years)	2 (97.6)	2 (16.8)	0 (80.7)	4 (37.7)	4 (9.5)	0 (28.2)

Incidence of uveitis flares in axSpA patients treated with CZP to Week 48†			
	All Patients (n=315)	History of Uveitis (n=63)	No History of Uveitis (n=252)
IR per 100 patient-years*	3.8	17.8	0.5
Patients (Exposure, patient-years)	9 (238.1)	8 (44.9)	1 (193.2)

- The incidence of uveitis flares in CZP-treated patients (IR=3.8/100 patient-years) was comparable to rates observed for other anti-TNFs in AS patients including adalimumab (IR=6.9/100 PY) and etanercept (IR=6.7/100 PY)

Adapted from Rudwaleit M et al. Ann Rheum Dis. 2014;73(Suppl 2):721-722. Abstract SAT0355.

*Incidence rates (IR) are reported per 100 patient-years with censoring at the time of event; † for Week 48 analyses all patients exposed to CZP were considered; no analyses of statistical significance were carried out on these data

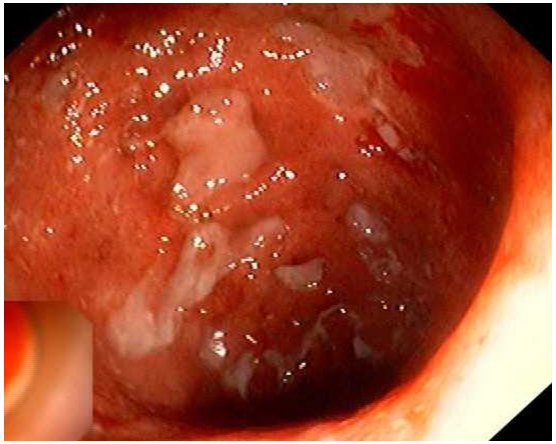
Decreased Incidence of Acute Anterior Uveitis (AAU) in Patients on Anti-TNFα-Therapy

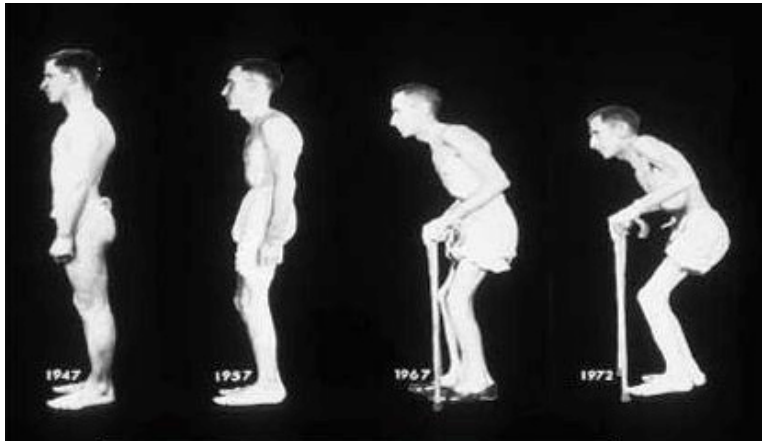
Pt no.	Biologics employed before GOL	Immunosuppressive treatment at last visit	Systemic steroids (at beginning of GOL and at last visit) (prednisolone mg/day)	drops (at beginning of GOL and at last visit) (1% prednisolone acetate drops/ daily frequency)	Follow-up GOL (months)	Response to GOL	Recurrences (month)	Activity of uveitis at last visit
1	Etan, Infl, Adal, Ritux	GOL, MTX	25–none	4–0	25	Yes	8	No
2	Etan, Infl, Adal	GOL	5–5	2–0	28	Yes	No	No
3	Etan, Infl, Adal	GOL	25–15	3–0	26	Yes	No	No
4	Etan, Infl, Adal	GOL	20–10	2–0	25	Yes	7,12	No
5	Etan, Infl, Adal	GOL	None	2–0	28	Yes	No	No
6	Infl, Adal	GOL, MTX	None	6–3	22	Yes	15	Yes
7	Infl, Adal	GOL, MTX	25–none	5–0	27	Yes	10	No
8	Etan, Infl, Adal, Ritux	GOL, MTX	25–12.5	5–3	7	No	—	Discontinued
9	Infl, Adal	GOL	None	4–3	27	Yes	20	Yes
10	Infl	GOL, MTX	None	6–3	7	No	—	Discontinued
11	Etan, Infl, Adal, Abatacept	GOL, MTX	12.5–none	3–0	18	Yes	No	No
12	Etan, Infl, Adal	GOL, MTX	None	4–0	22	Yes	14	No
13	Etan, Infl, Adal, Abatacept	GOL	None	2–0	29	Yes	No	No
14	Etan, Infl, Adal	GOL, MTX	12.5– none	4–0	26	Yes	No	No
15	Etan, Infl, Adal	GOL, MTX	37.5–12.5	6–4	6	No	—	Discontinued
16	Etan, Infl, Adal, Abatacept	GOL	12.5–5	3–0	26	Yes	5	No
17	Infl	GOL, MTX	12.5–none	4–0	23	Yes	No	No

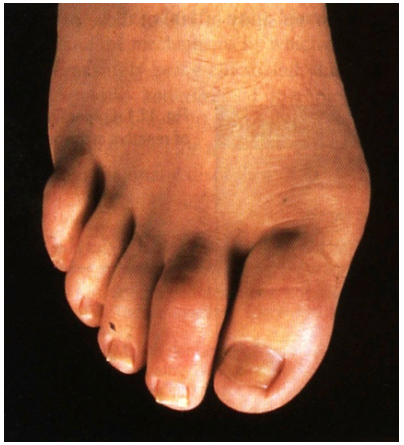
GOL, golimumab; MTX, methotrexate; Etan, etanercept; Infl, infliximab; Adal, adalimumab; Ritux: rituximab.

Miserocchi E et al. Ocular Imm & Infl, 2013

Update on extra-articular manifestations in axial Spondyloarthritis







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