# Ankylosing Spondylitis

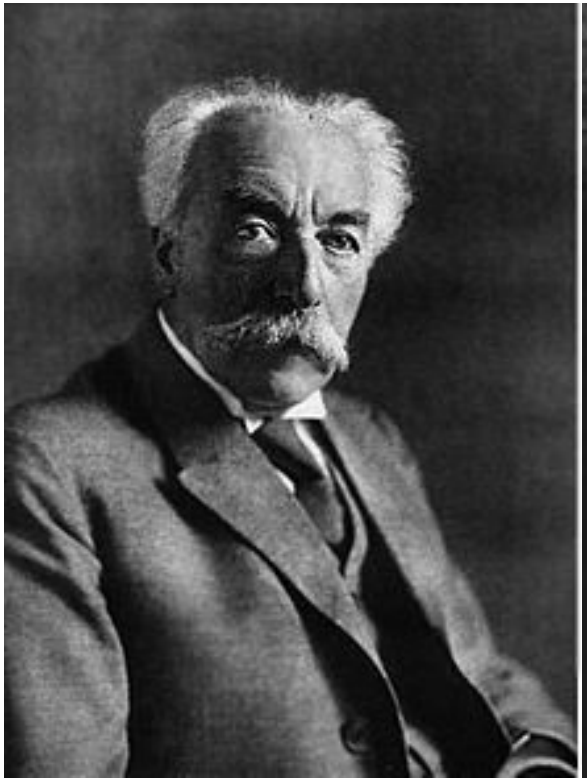
Gleb Slobodin MD

2017

# Спондилоартриты

# Discovery
# 1890s

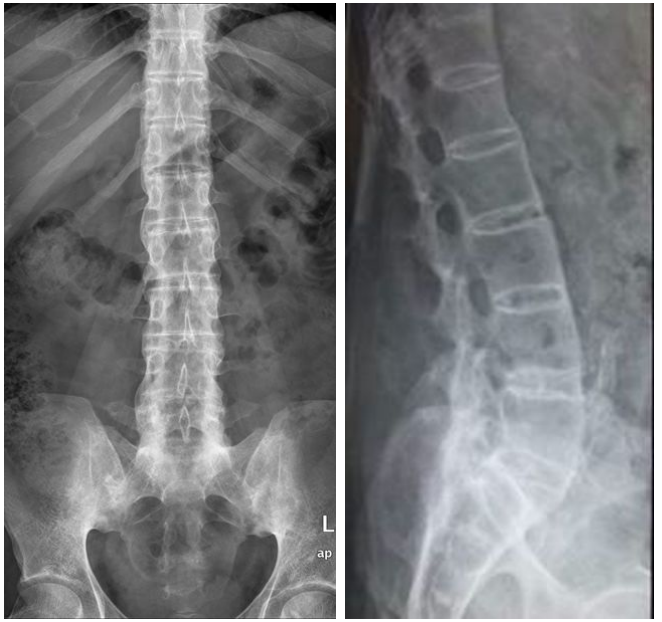
Bechterew W. (1893). "Steifigkeit der Wirbelsaule und ihre Verkrummung als besondere ."Erkrankungsform Neurol Centralbl 12: 426–434



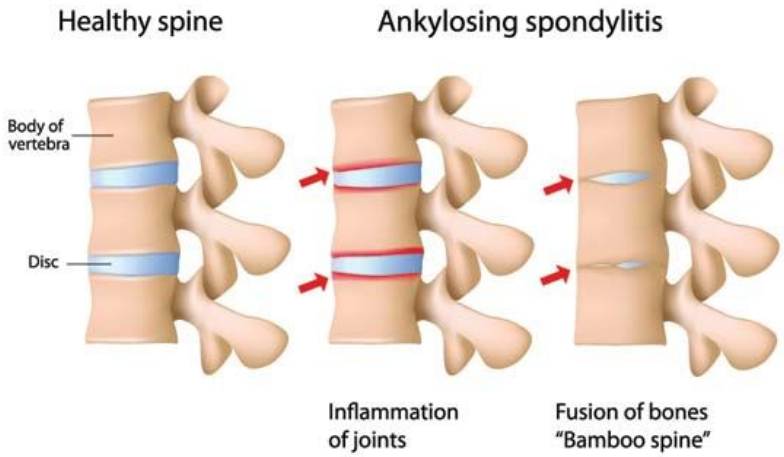
Strumpell A. (1897). "Bemerkung uber die chronische ankylosirende Entzundung der Wirbelsaule und der Huftgelenke". Dtsch Z Nervenheilkd 11 (3–4): 338–342

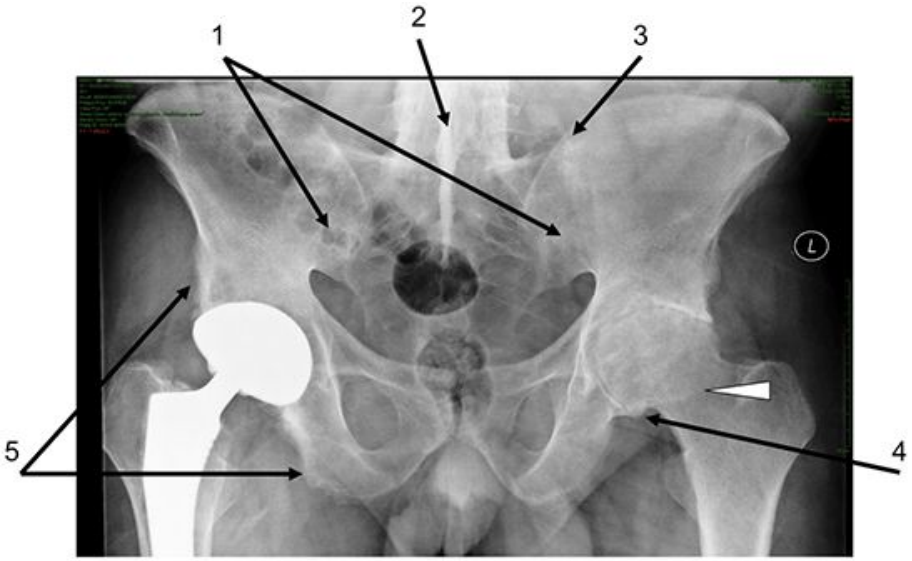
Marie P. (1898). "Sur la spondylose .rhizomelique". Rev Med 18: 285–315

# Description
# 20th century


# Bone formation in AS




# Критерии воспалительной боли в спине (Calin)

Анкилозирующий спондилит n = 42; «механическая» боль в нижней части спины n = 21

- возраст начала < 40 лет
- длительность боли в спине > 3 месяцев
- постепенное начало
- утренняя скованность
- улучшение после выполнения физических упражнений

Чувствительность: 95%; Специфичность: 76%

**Боль в спине считается воспалительной при наличии 4 из 5 критериев.**

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

# Spine

# BASMI

| | Mild<br>0 | Moderate<br>1 | Severe<br>2 |
|---|---|---|---|
| Cervical rotation (Mean of L & R) | > 70 degrees | 20 –70 degrees | < 20 degrees |
| Tragus to wall (Mean of L & R) | < 15cm | 15 – 30 cm | > 30 cm |
| Lumbar side flexion (Mean of L & R) | > 10cm | 5 – 10 cm | < 5 cm |
| Lumbar flexion (modified schobers) | > 4 cm | 2 – 4 cm | < 2 cm |
| Intermalleolar distance | > 100cm | 70 – 100 cm | < 70 cm |

# Модифицированные Нью-Йоркские критерии для анкилозирующего спондилита (1984)

**1. Клинические критерии:**

а.Боль в нижней части спины и скованность продолжительностью более 3 месяцев, которые уменьшаются при выполнении физических упражнений, но не в покое.

б. Ограничение подвижности поясничного отдела позвоночника в сагиттальной и фронтальной плоскостях.

в. Ограничение экскурсии грудной клетки по сравнению с нормальными показателями, соответствующими возрасту и полу.

**2. Рентгенологические критерии:**

Двусторонний сакроилиит $\geq$ 2 стадии или односторонний 3-4 стадии

**Диагноз анкилозирующего спондилита является определенным, если рентгенологический критерий сочетается с, как минимум, 1 клиническим критерием.**

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

ASAS

# Sacroiliac joints

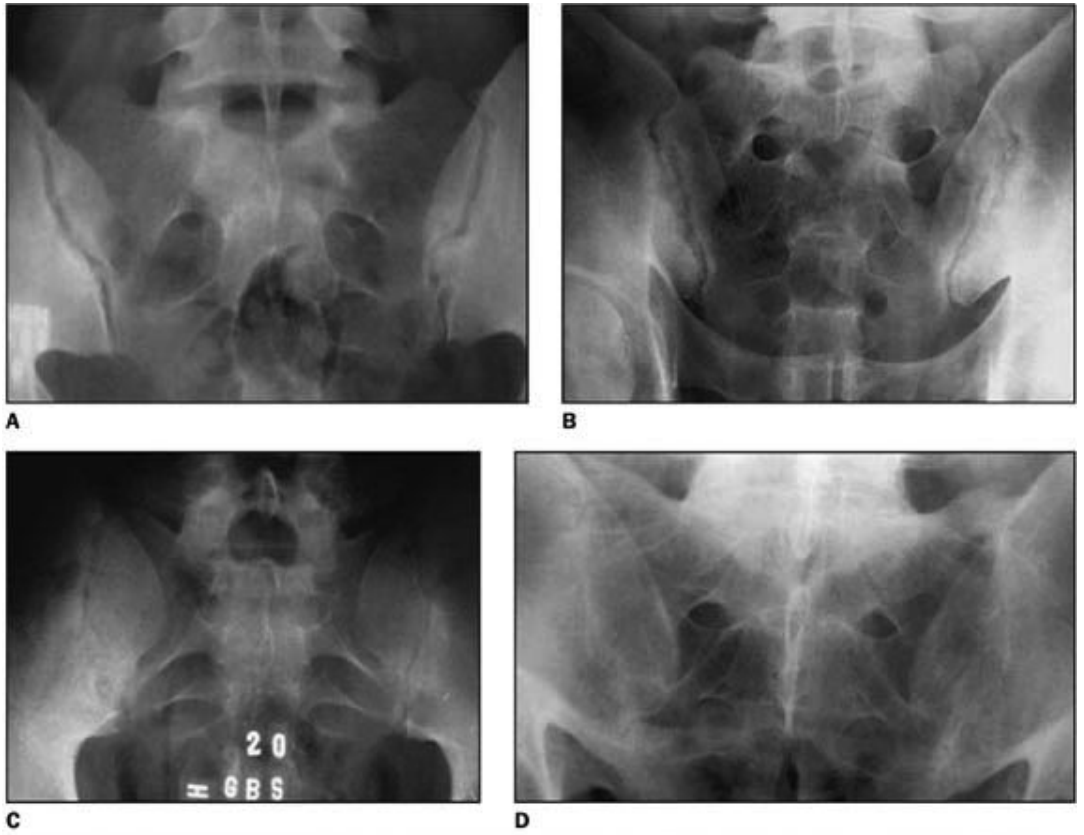
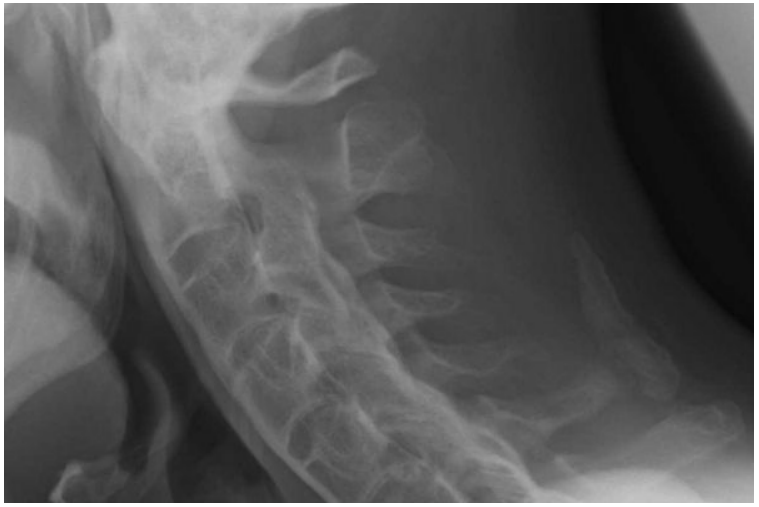




**Figure 4.** Radiographic classification in the evaluation of sacroiliac joints. Grade 0 – normal (**A**); grade I – suspicious; grade II – mild irregularity and sclerosis of articular surfaces, with preserved joint space (**B**); grade III – joint space narrowing, besides intense irregularity and subchondral sclerosis (**C**); grade IV – bilateral ankylosis (**D**).

# Spine



Please tick the box which represents your answer.
All questions refer to **last week**. (i.e. ☒ )

## Fatigue

1. How would you describe the overall level of fatigue/tiredness you have experienced?

0 1 2 3 4 **X** 6 7 8 9 10

none very severe

## Spinal pain

2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

0 1 2 3 4 5 6 **X** 8 9 10

none very severe

## Peripheral arthritis

3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?

0 **X** 2 3 4 5 6 7 8 9 10

none very severe

## Enthesitis

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0 1 **X** 3 4 5 6 7 8 9 10

none very severe

## Intensity of morning stiffness

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

0 1 2 3 4 5 6 **X** 8 9 10

none very severe

## Duration of morning stiffness

6. How long does your morning stiffness last from the time you wake up?

0 1 2 3 4 **X** 6 7 8 9 10

0 hr 1 hr 2 or more hrs

Courtesy of Joachim Sieper

# Bath AS Disease Activity Index (BASDAI)

On a Numeric Rating Scale
of 0 to 10 where
0 = none &
10 = very severe

**Total of first 4 Q = 5+7+1+2 = 15**

**Mean of these 2 Qs = (7+5)/2 = 6**

**BASDAI = (15 + 6) / 5**

**= 21/5 = 4.2**

Garrett S, et al. *J Rheumatol*. 1994;21:2286-2291.

## Ankylosing Spondylitis Disease Activity Score (ASDAS) II

# Calculation of the ASDAS

### $ASDAS_{CRP}$

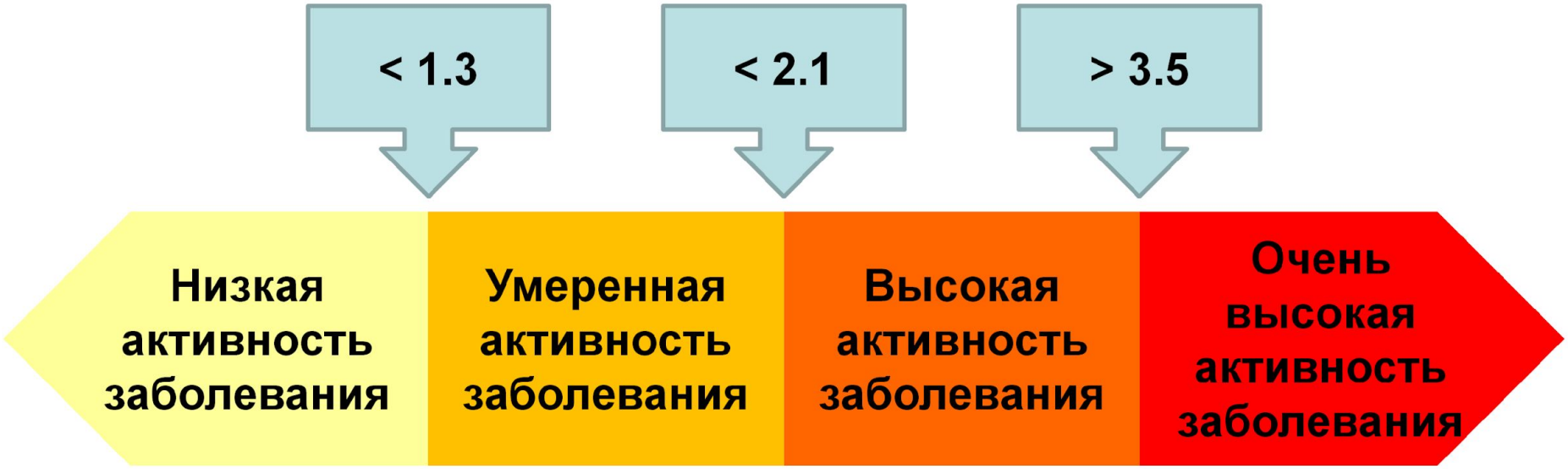
$$0.121 \times \text{Total Back Pain} + 0.110 \times \text{Patient Global} + 0.073 \times \text{Peripheral Pain/Swelling} + 0.058 \times \text{Duration of Morning Stiffness} + 0.579 \times \text{Ln(CRP+1)}$$

### $ASDAS_{ESR}$

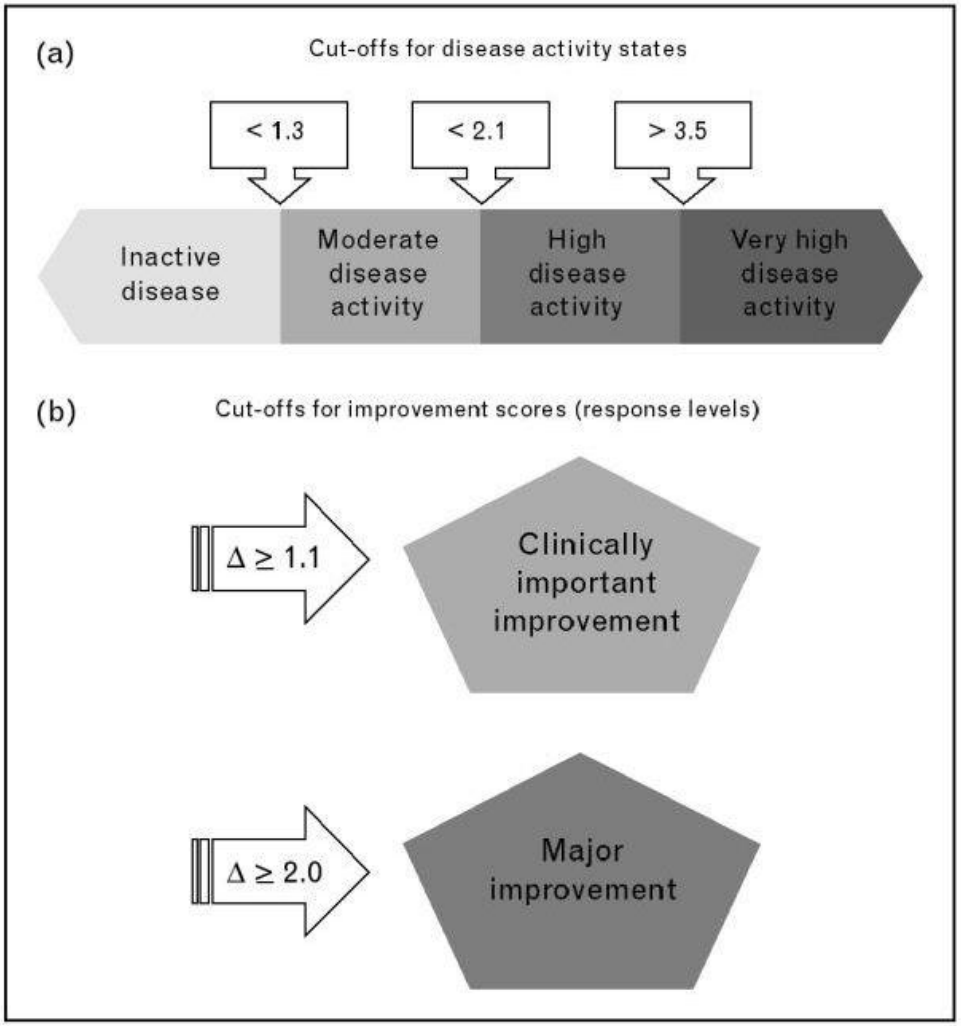
$$0.113 \times \text{Patient Global} + 0.293 \times \sqrt{ESR} + 0.086 \times \text{Peripheral Pain/Swelling} + 0.069 \times \text{Duration of Morning Stiffness} + 0.079 \times \text{Total back pain}$$

**$ASDAS_{CRP}$ is the preferred ASDAS but the $ASDAS_{ESR}$ can be used in case CRP is not available.** CRP in mg/l; all patient assessments on a 10 cm scale.

# Ключевые значения ASDAS для оценки активности заболевания

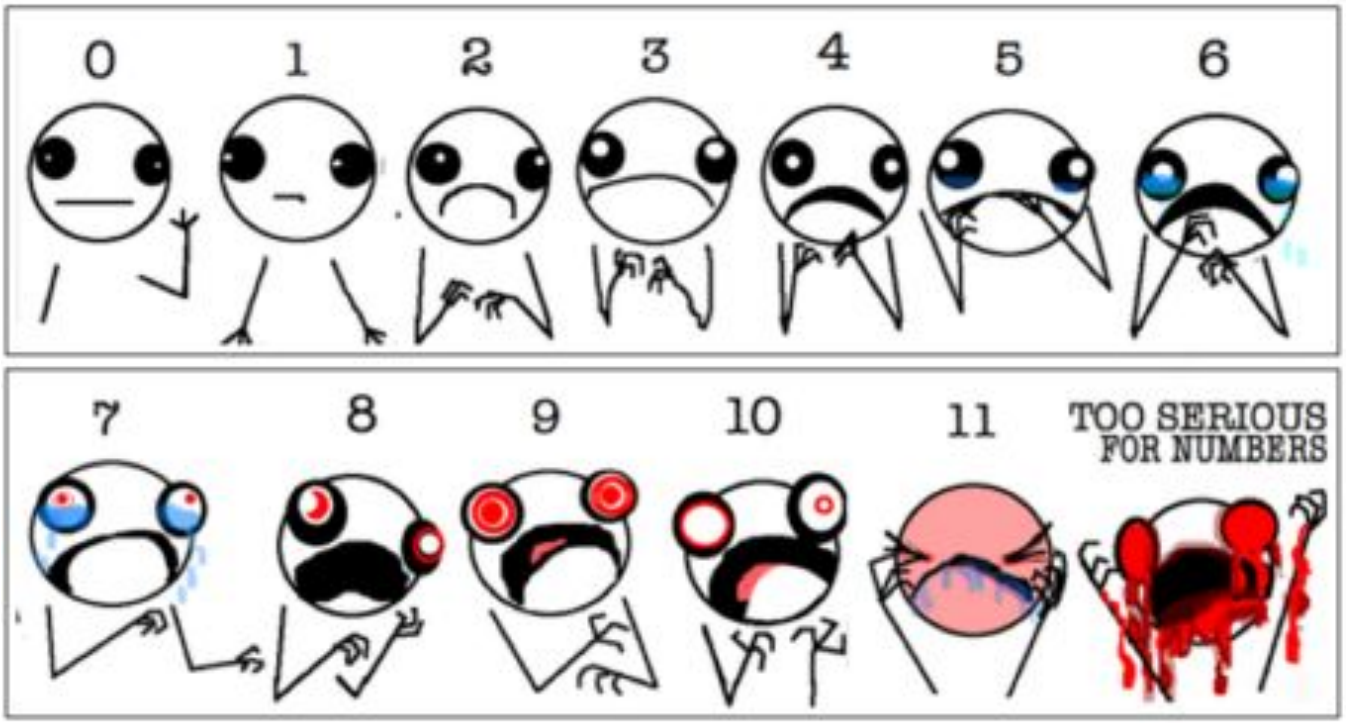



Machado P et al. Ann Rheum Dis 2011;70:47-53 (с разрешения)




(a) Cut-offs for disease activity states. (b) Cut-offs for improvement scores (response levels). Reproduced with permission from Fig. 1 of [11••].

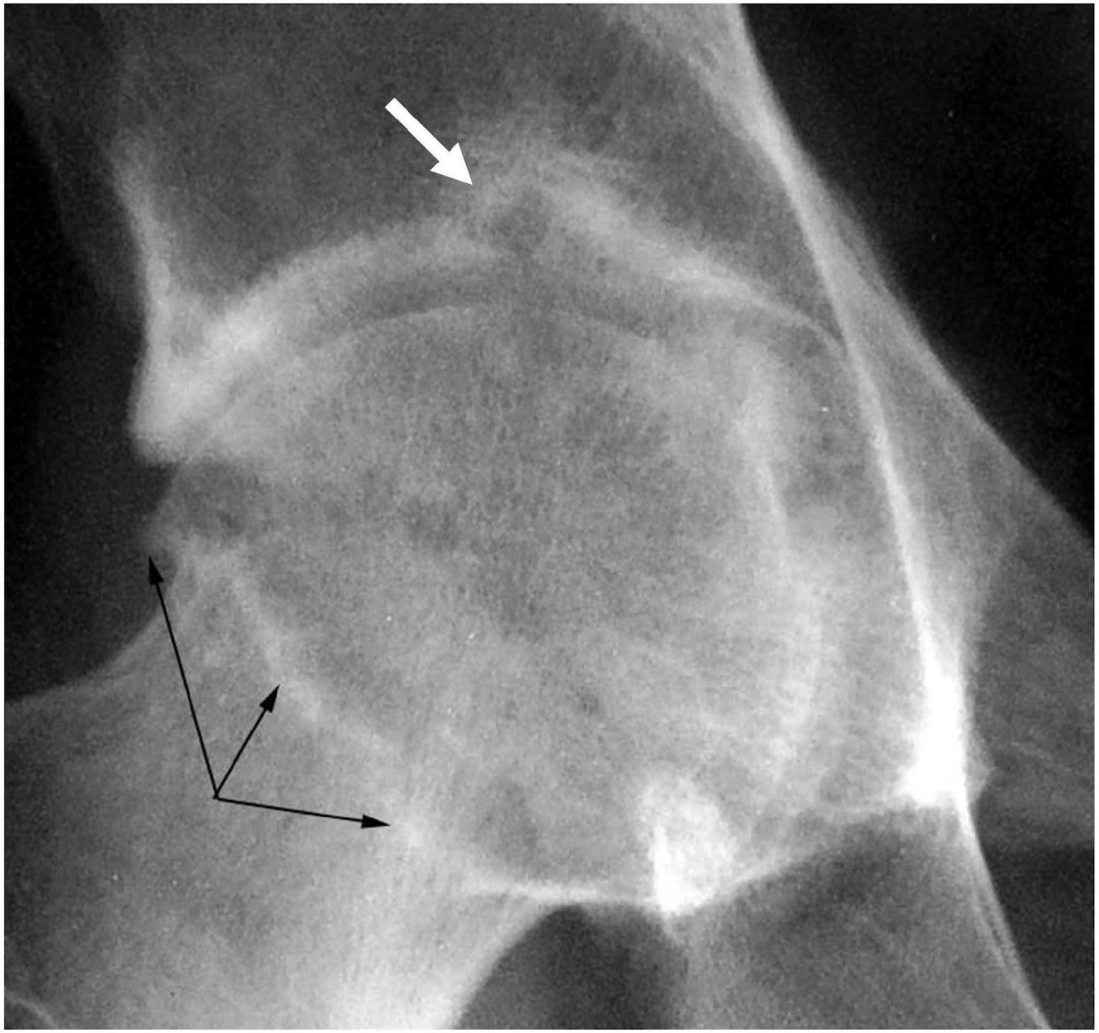
# Patient’s symptoms




**,One half comes from inflammation**
**the second half comes from structural changes**

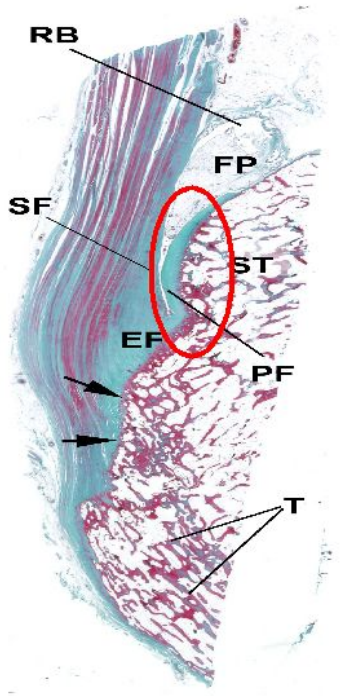
# Arthritis

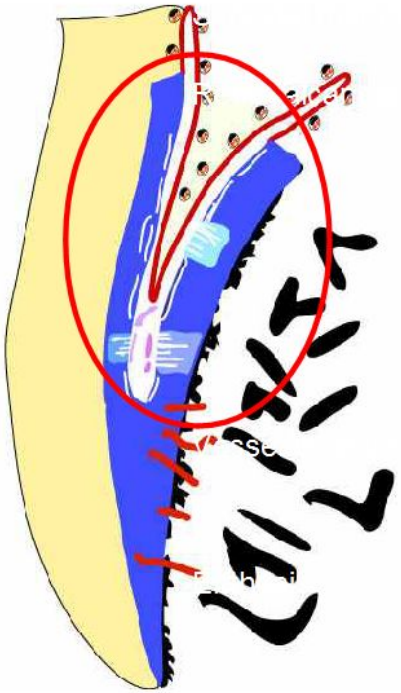
# Hip Arthritis in Ankylosing Spondylitis



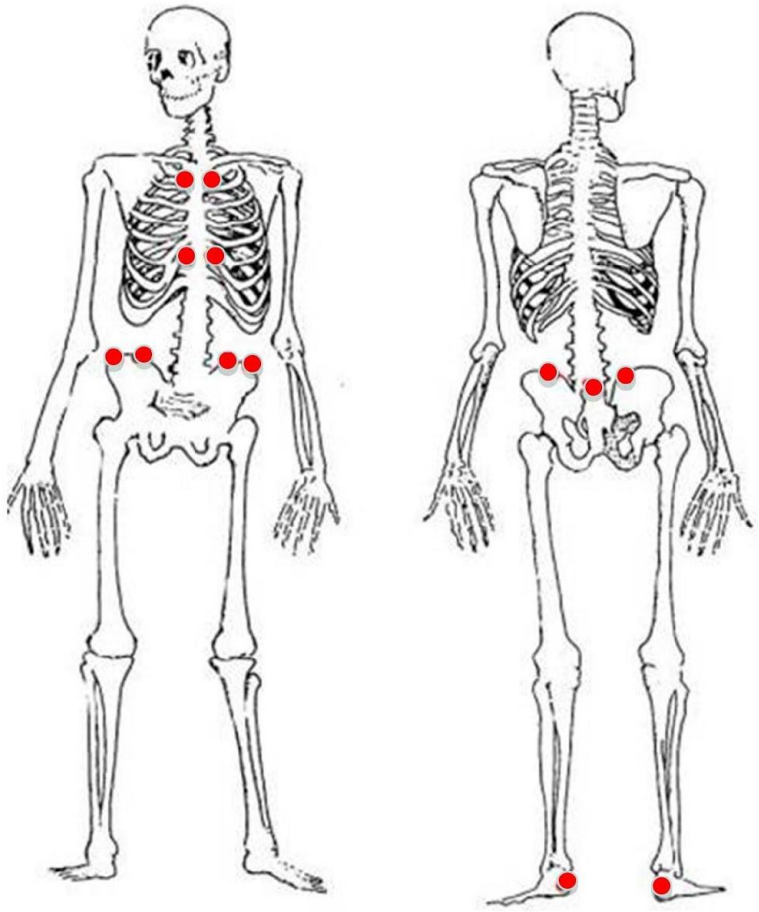
- concentric „necklace-like“ osteoproliferation with osteophytes at the femoral head (black arrows)
- erosion (white arrow)

# Enthesopathy




# MASES:
# Maastricht Ankylosing Spondylitis Enthesitis Score



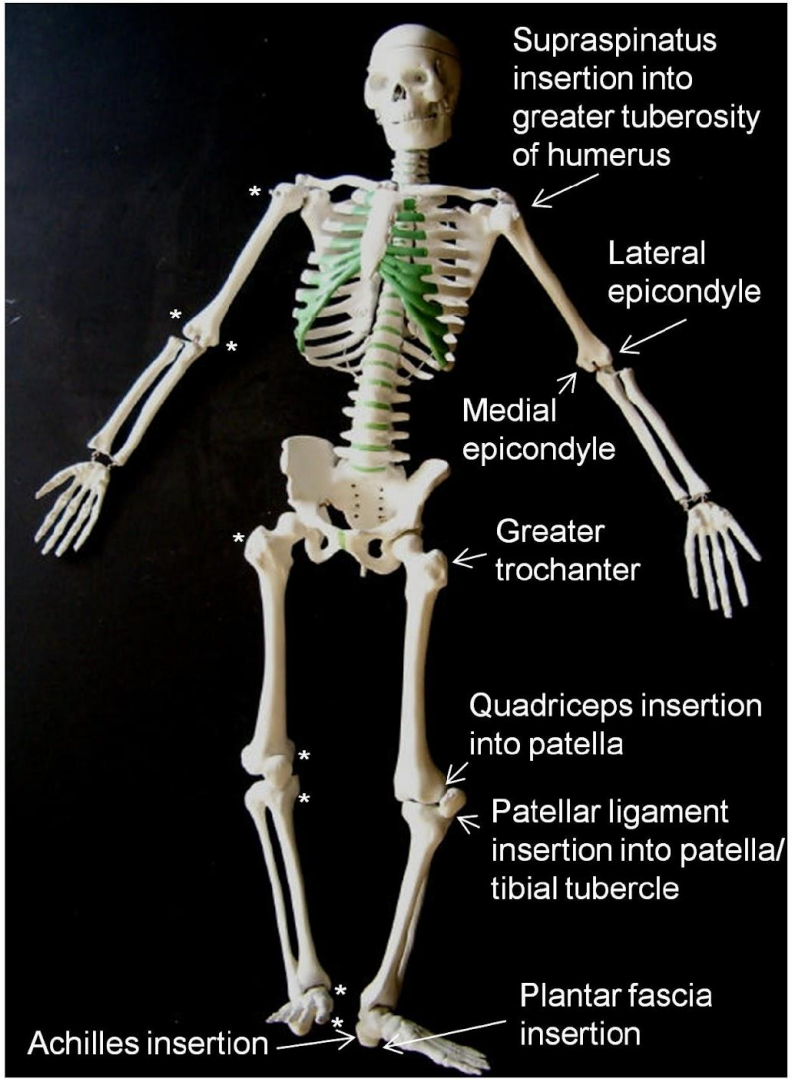
- 13 sites
- Easy to locate
- No grading
- Score from 0 to 13

Costochondral 1 ri/le
Costochondral 7 ri/le
Spina iliaca anterior superior ri/le
Crista iliaca ri/le
Spina iliaca posterior ri/le
Proc. spin L5
Achilles tendon prox. insertion ri/le

Adapted from Heuft et al. Ann Rheum Dis 2003;62:127-32 (with permission)

ASAS

# Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index

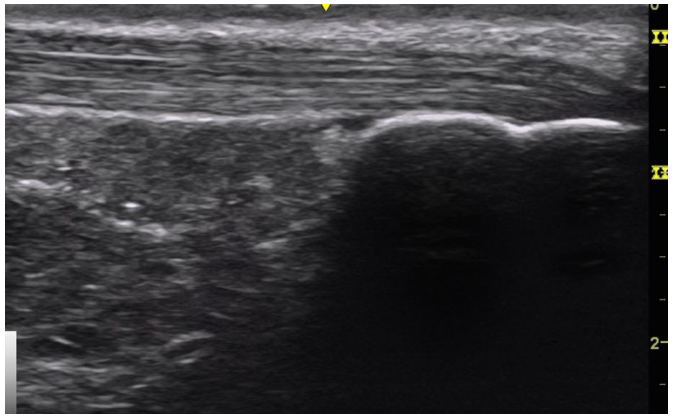


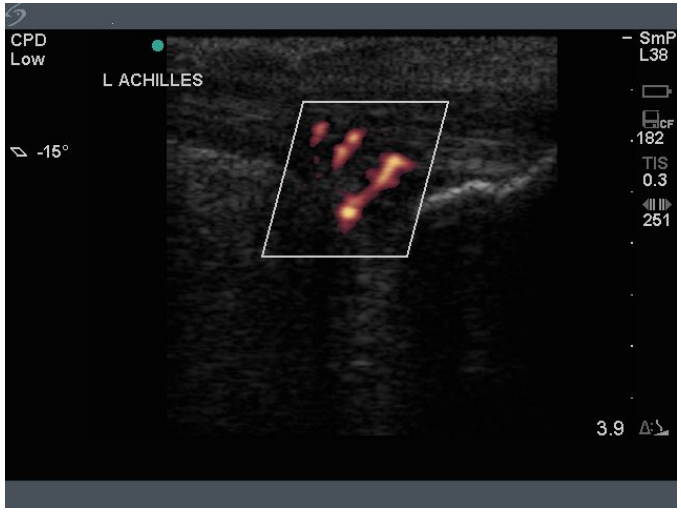

- 16 sites
- Easy to locate
- No grading
- Score from 0 to 16

* Entheses at the contralateral side

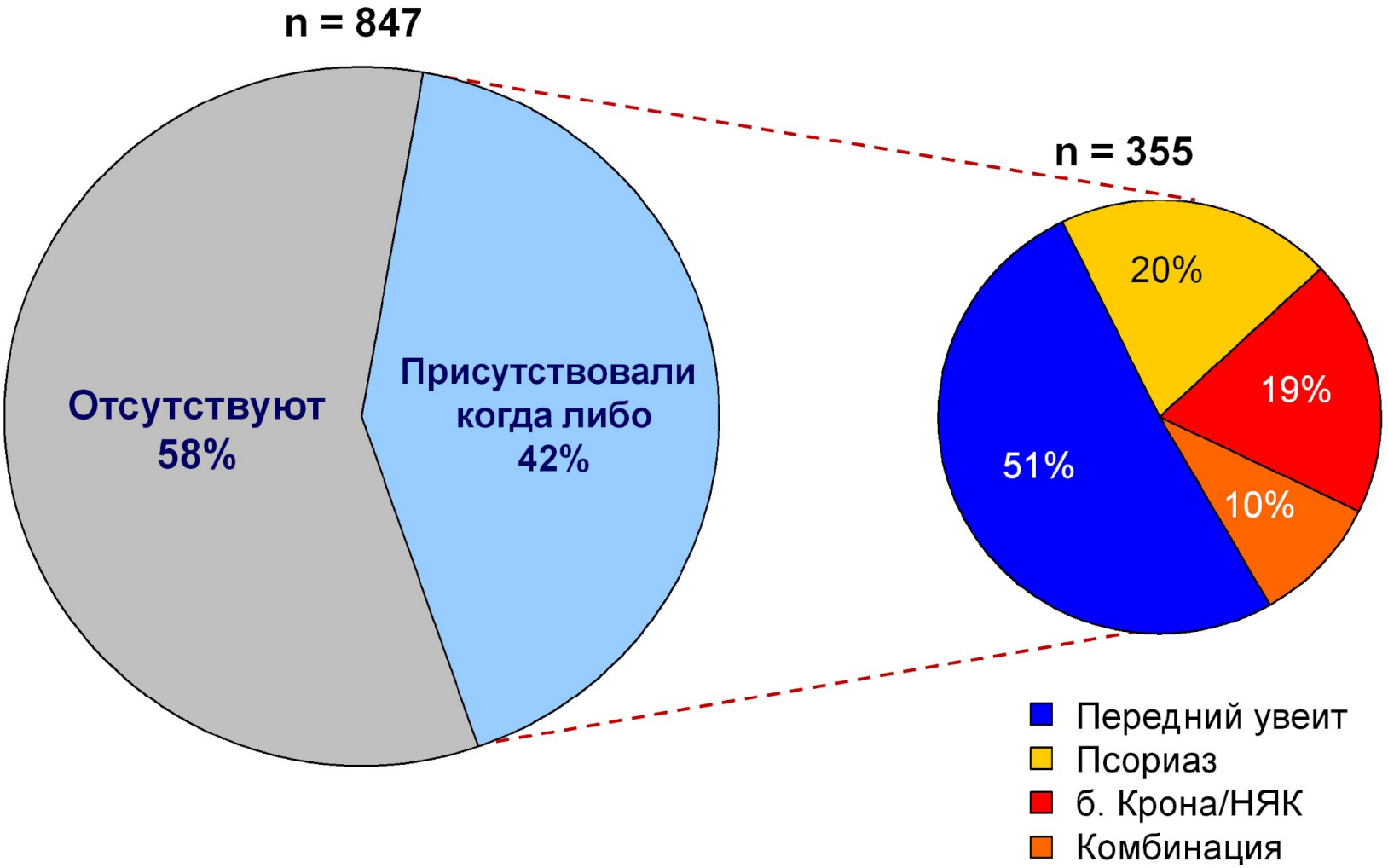
Maksymowych WP et al. Ann Rheum Dis 2009;68:948-953

# Enthesopathy





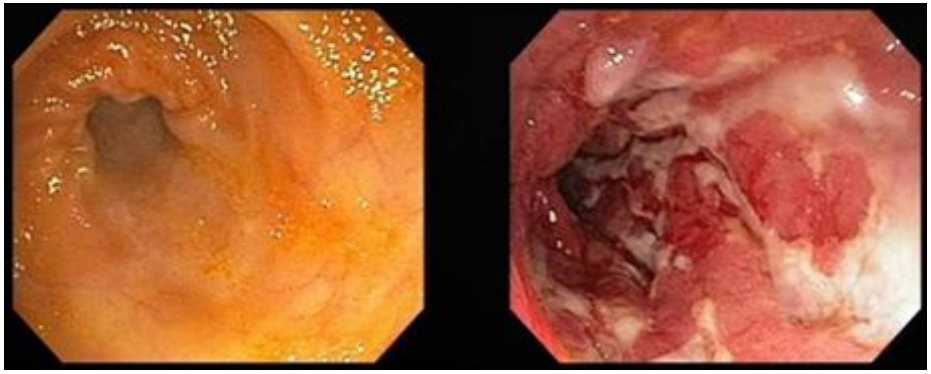

# Внесуставные проявления анкилозирующего спондилита

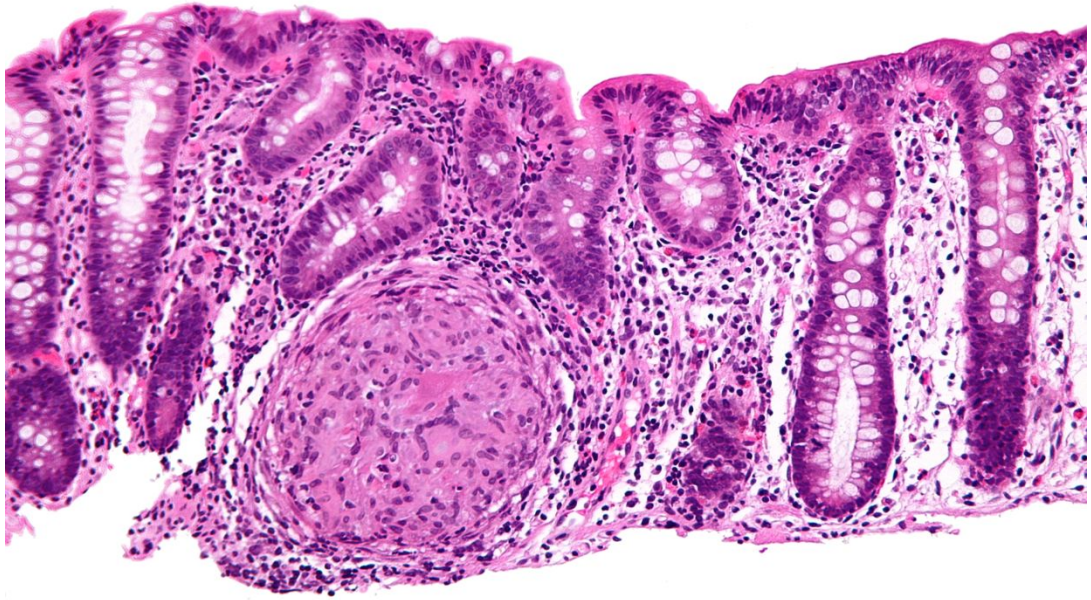



Vander Cruyssen B et al. Ann Rheum Dis 2007;66:1072-7

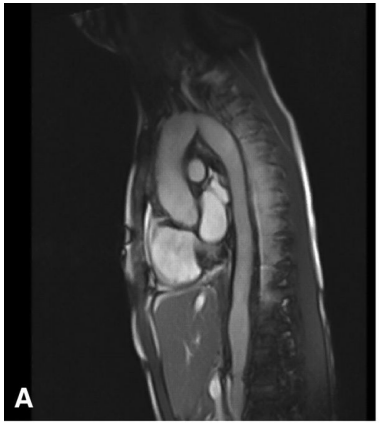
# Uveitis

# Diarrhea

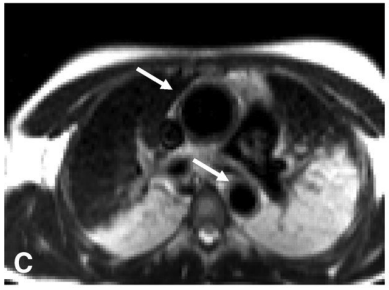


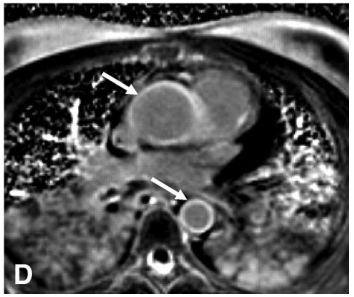


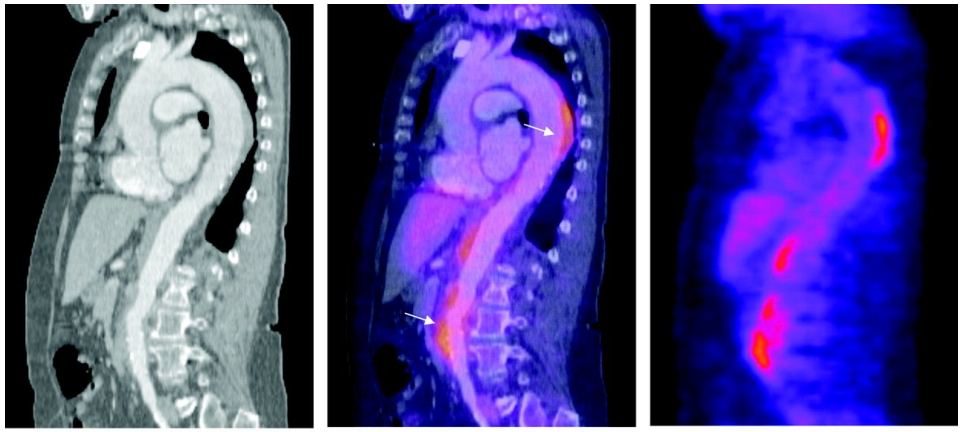
# Aortitis





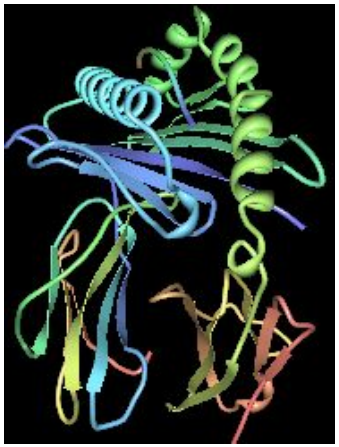


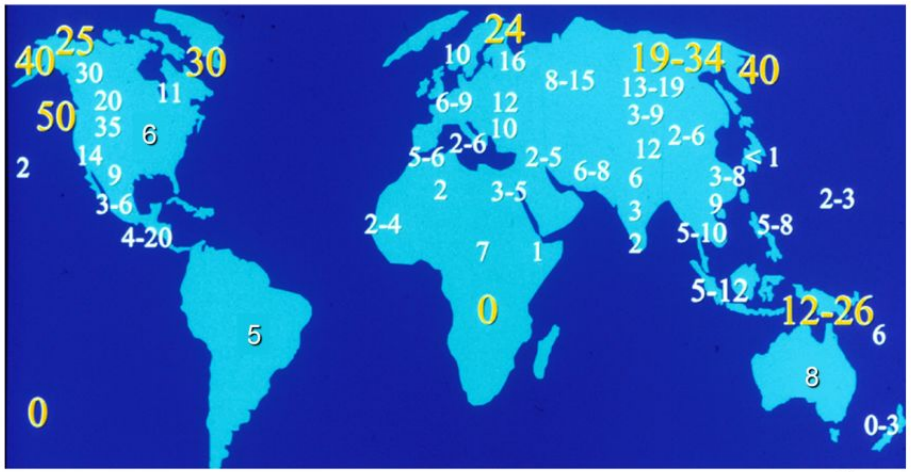



A B C

# HLA B27
# 1970s




**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

HLA B27 + in 90% of Caucasian AS pt
Only 5% of HLA B27+ persons will have AS
HLA B27 represents only about 25% of ‘genetic risk’ for AS

# Иммунопатология у HLA-B27 трансгенных крыс

## Проявления болезни

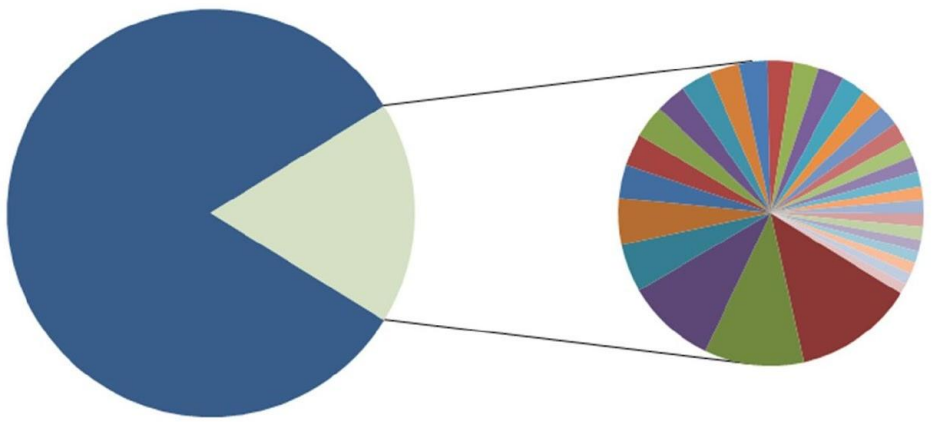
- Периферический артрит
- Поражение позвоночника
- Воспалительное заболевание кишечника
- Эпидидимо-орхит
- Поражение кожи

## Определяются

- Количеством копий гена HLA-B27
- Количеством копий гена человеческого β2 микроглобулина
- Линией и полом
- Кишечной флорой
- Гемопоэтическими клетками


Tran TM et al. Arthritis Rheum 2006;54:1317-27 (с разрешения)

# What known genes are involved in AS?

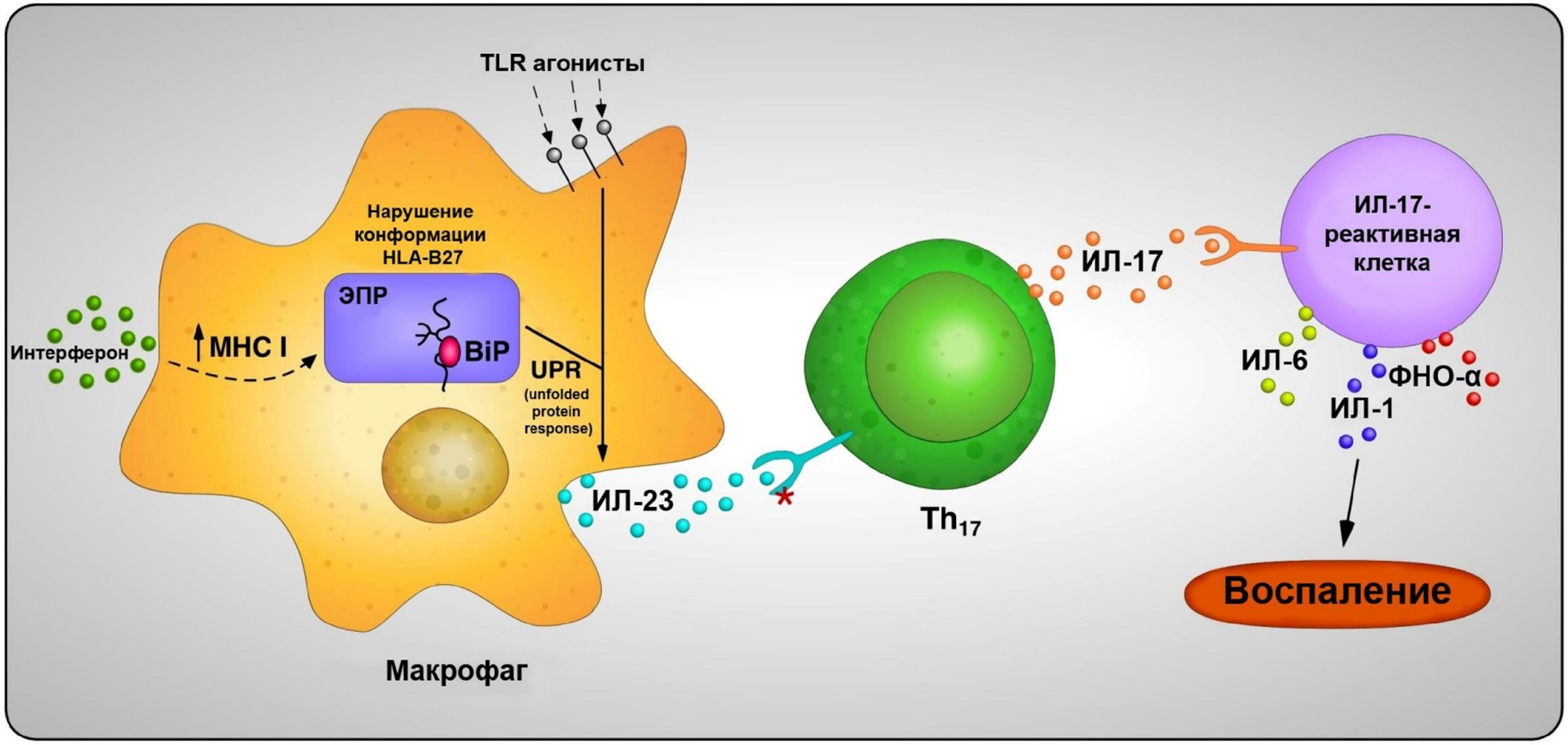


- HLA-B*27
- ERAP1
- IL23R
- chr2p15
- HLA-A*02
- KIF21B
- IL6R
- LTBR-TNFRSF1A
- ERAP2
- chr21q22
- RUNX3
- NKX2-3
- NOS2
- IL12B
- FCGR2A
- TYK2
- NPEPPS-TBKBP1-TBX21
- IL1R2-IL1R1
- BACH2
- GPR65
- CARD9
- IL27-SULT1A1
- EOMES
- UBE2E3
- GPR35
- SH2B3
- ZMIZ1
- IL7R
- GPR37
- ICOSLG
- UBE2L3
- PTGER4

Cortes A et al. Nat Genet 2013;45:730-8

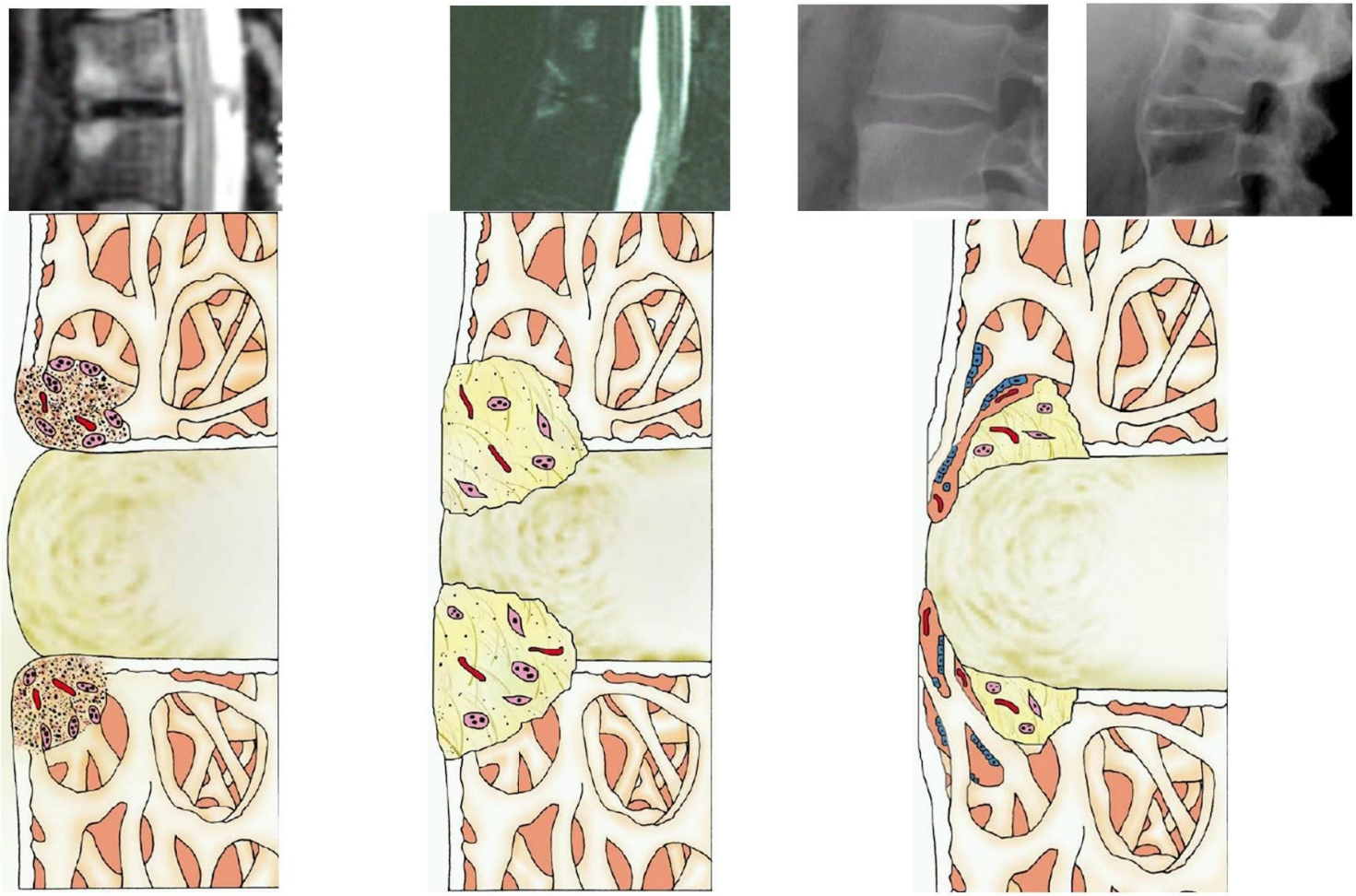
# Нарушение конформации HLA-B27 и система интерлейкин-23/интерлейкин-17

## Возможные последствия нарушения конформации HLA-B27




Layh-Schmitt G and Colbert RA. Curr Opin Rheum 2008; 20:392-397 (с разрешения)

# Proposed Sequence of Structural Damage in Ankylosing Spondylitis



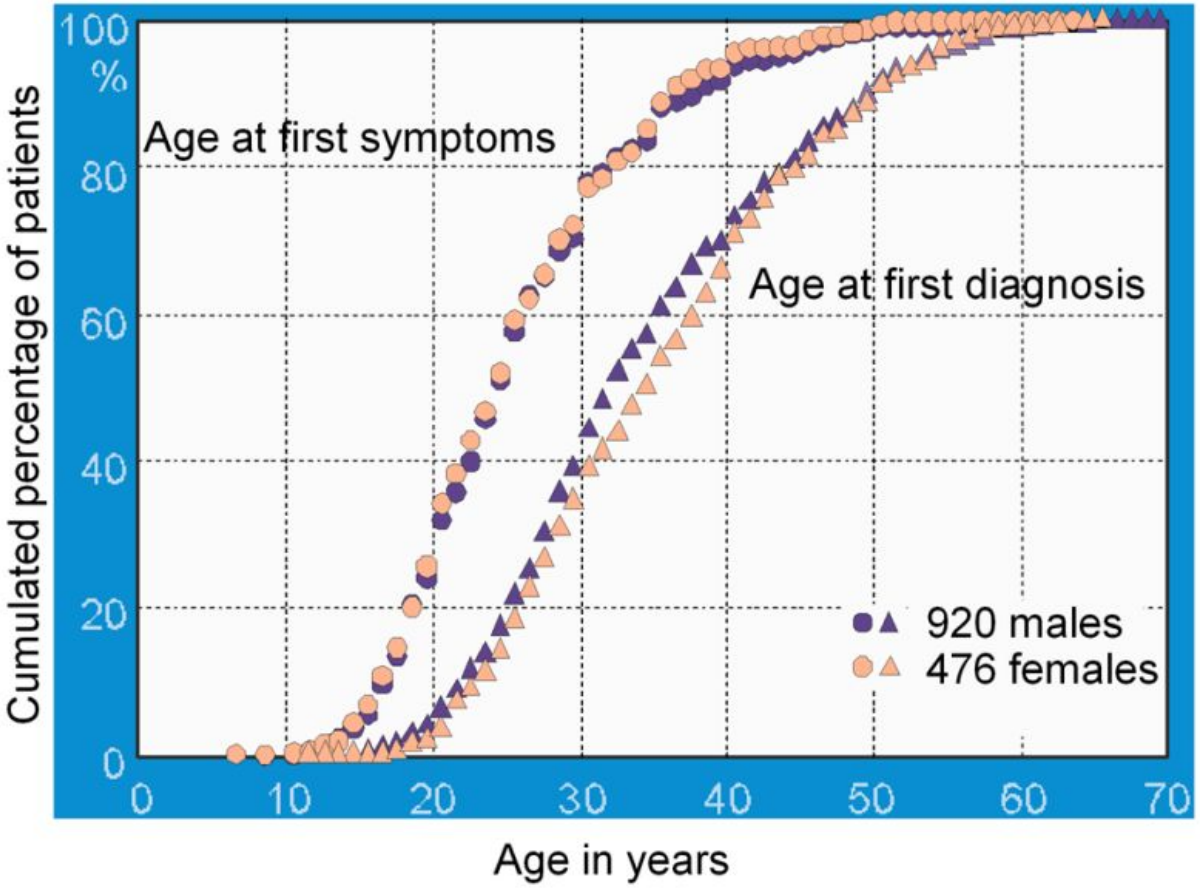
Inflammation

Erosive damage
Repair

New bone formation

Appel H & Sieper J et al. Curr Rheumatol Rep. 2008;10:356-63 (with permission)

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

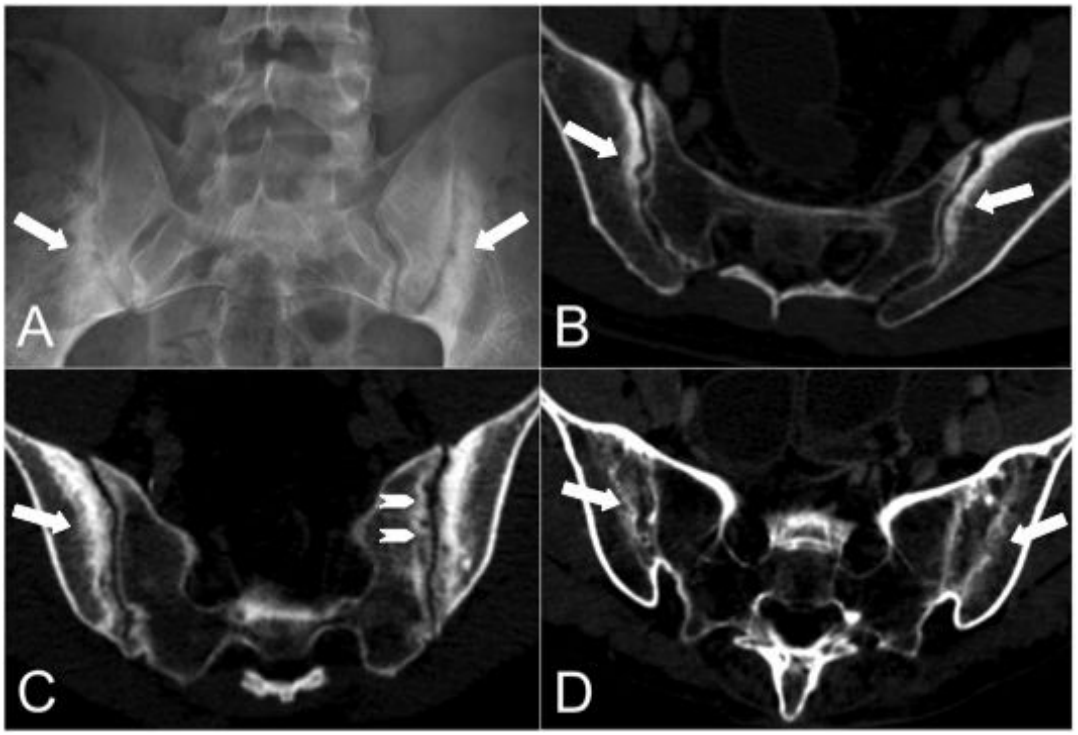



**Average delay in diagnosis: 9 years**

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

# Non X-ray imaging

## Computed tomography




Better comparing to X-rays

But not validated and radiation-related

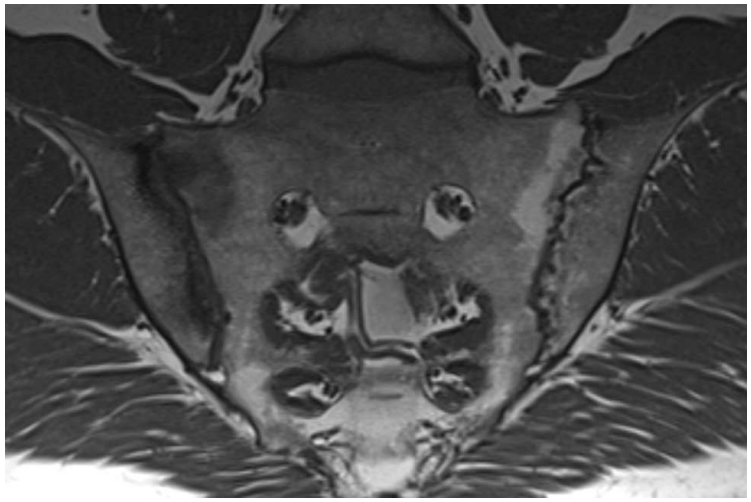
# Non X-ray imaging of SIJ

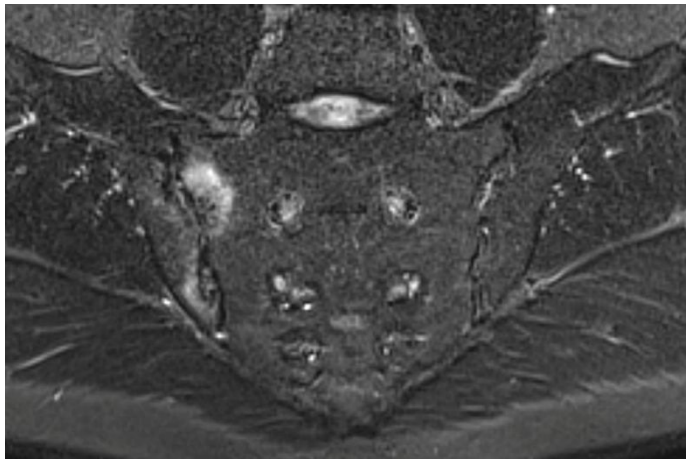
- Bone scan


Sensitivity is about 50%
Specificity is about 50%

# Non X-ray imaging of SIJ

MRI •

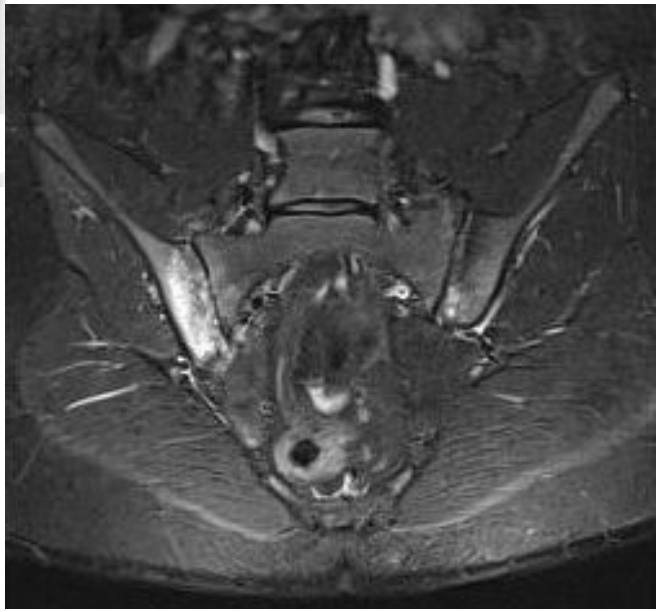




yo F with right LBP 22

# Non X-ray imaging of SIJ

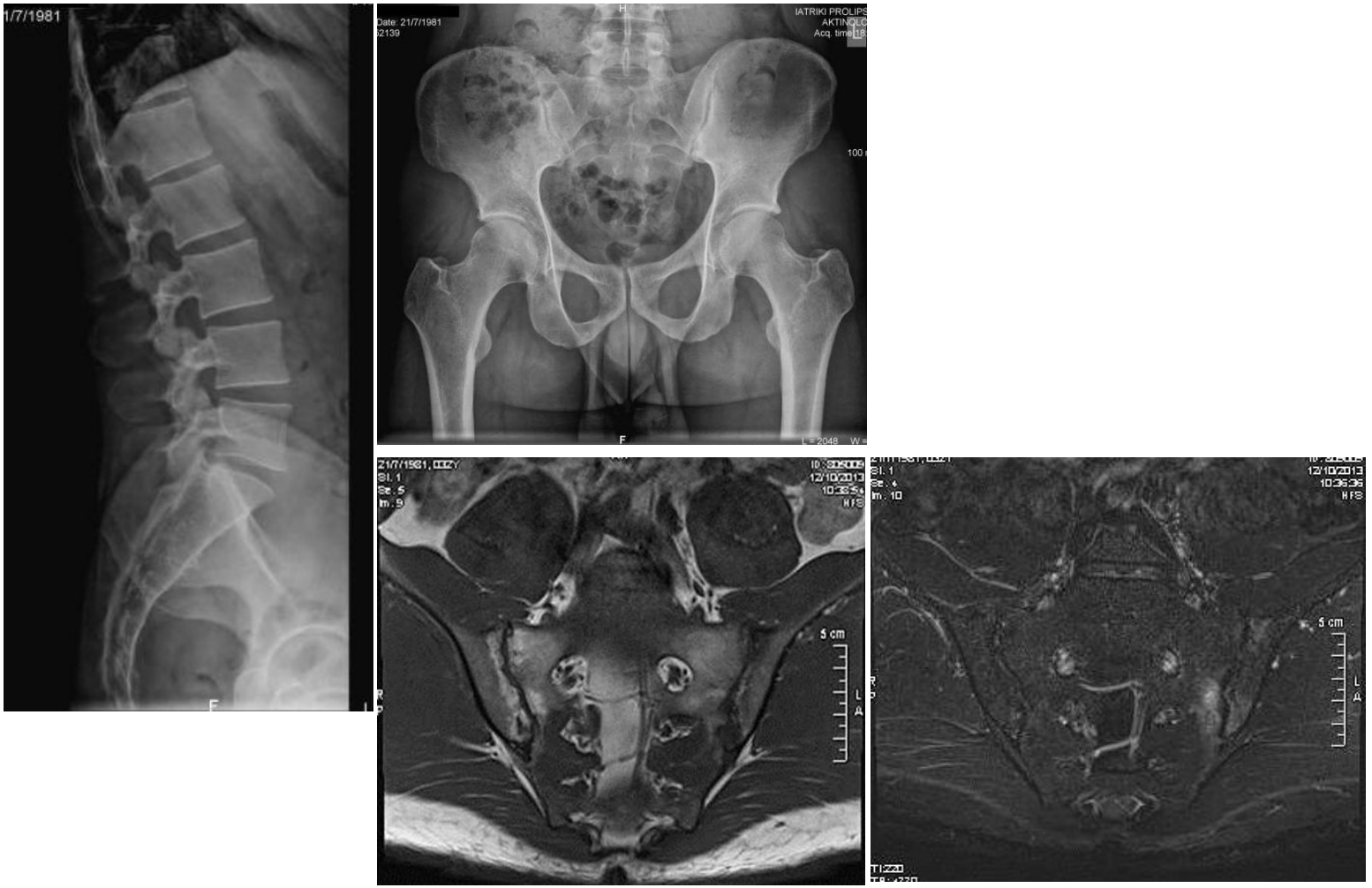
MRI •

yo M with 6 months  LBP 16

# Non X-ray imaging of SIJ

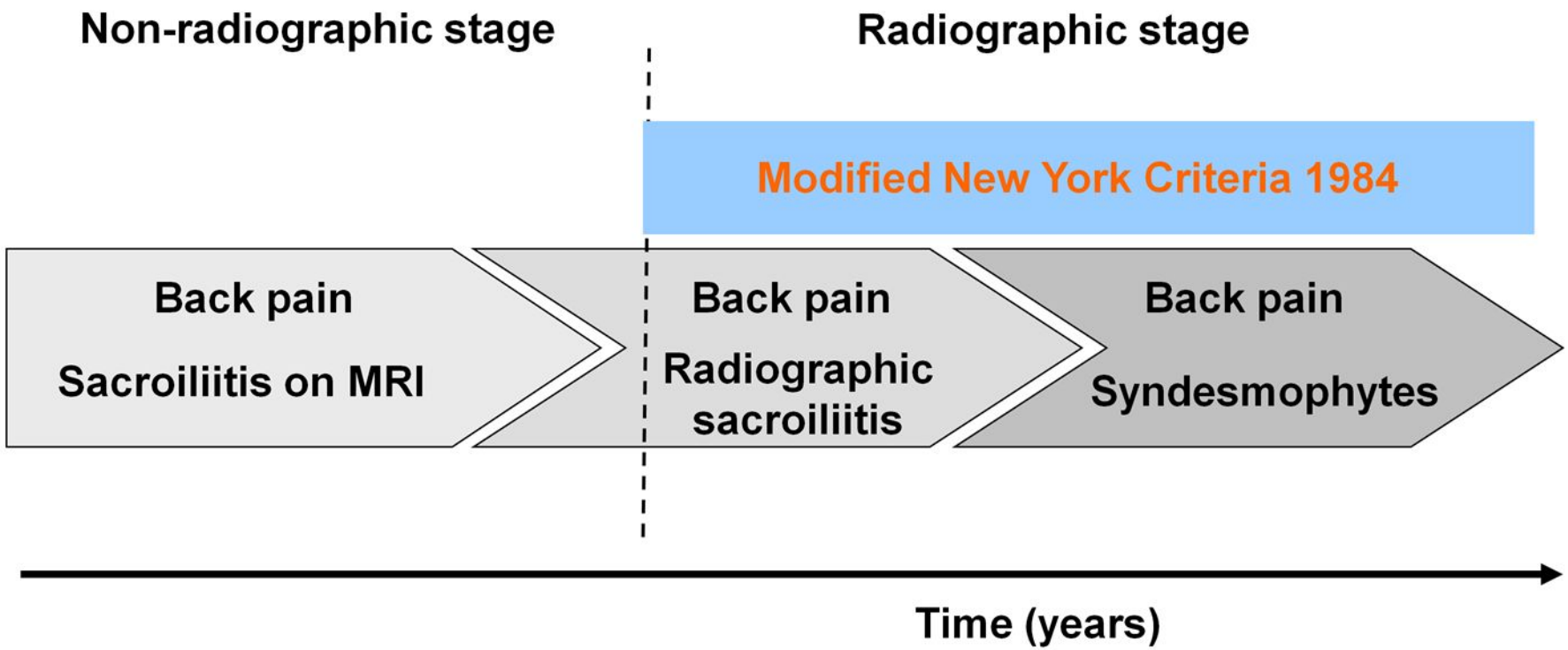
MRI •




yo M with Psoriasis & LBP 33

# Spine - MRI

# Axial Spondyloarthritis




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

# Классификационные критерии ASAS для аксиального спондилоартрита (СпА)

**Пациент с болью в спине продолжительностью ≥3 мес. и возрастом начала <45 лет**

**Сакроилиит по данным МРТ или рентгенографии***

**плюс**

**≥1 признак СпА#**

**или**

**HLA-B27**

**плюс**

**≥2 других признака СпА#**

**Признаки СпА:**

- воспалительная боль в спине
- артрит
- энтезит (пяточный)
- увеит
- дактилит
- псориаз
- болезнь Крона/ язвенный колит
- хороший ответ на НПВП
- семейный анамнез СпА
- HLA-B27
- повышенный уровень С-РБ

***Сакроилиит:**

- **активное воспаление по данным МРТ, характерное для сакроилиита при СпА**
- **достоверный сакроилиит при рентгенографии по модифицированным Нью-Йоркским критериям**

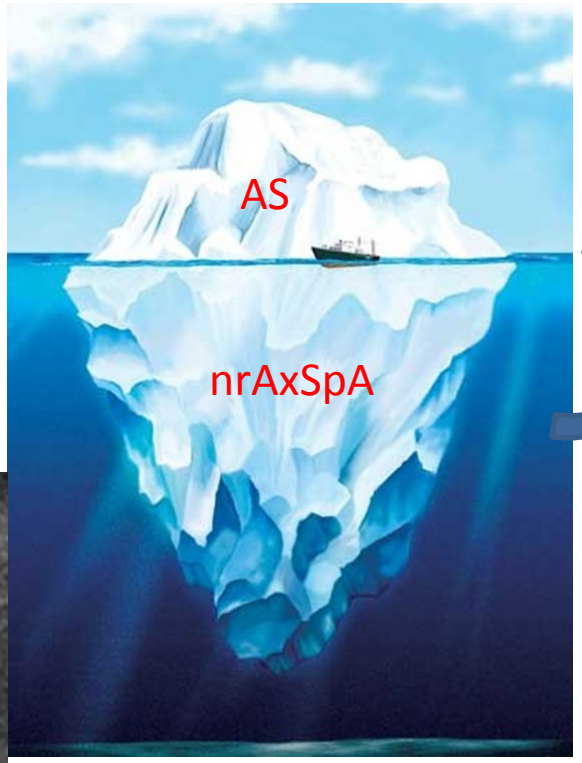
649 пациентов с болью в спине;
Критерии в целом:
Чувствительность: 82,9%,
Специфичность: 84,4%
При наличии сакроилиита:
Чувствительность: 66,2%,
Специфичность: 97,3%

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

# Prevalence of Axial SpA

**in US (NHANES study)**

chronic back pain in 20% of population
IBP in 7% of population; > in younger adults
AxSpA (including AS) in 1.4%
AS in 0.5%

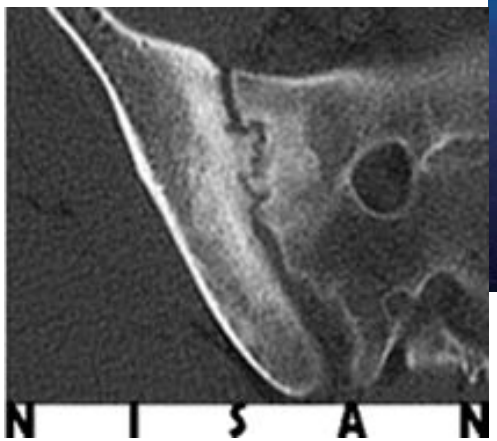



**12% in years 2**

NISAN cohort (2010):

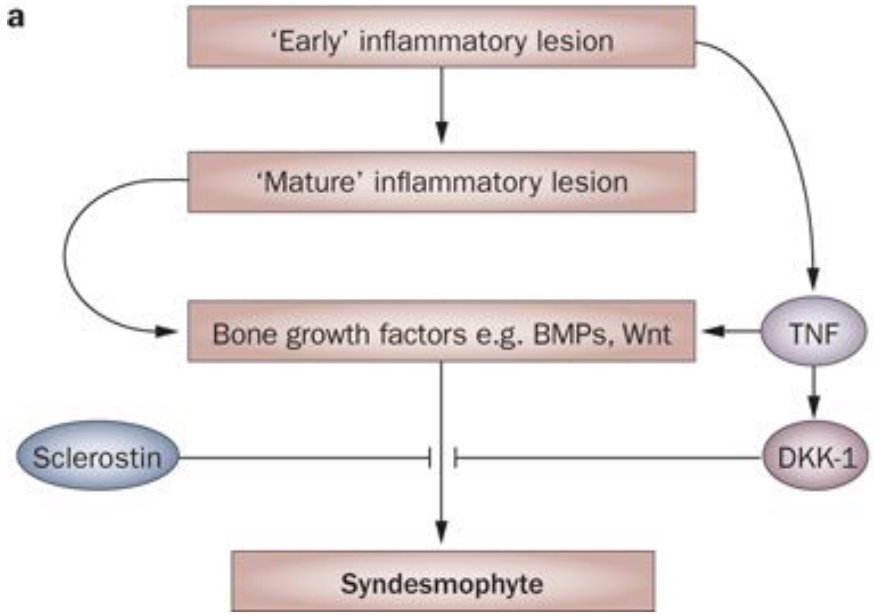
151 SpA patients:

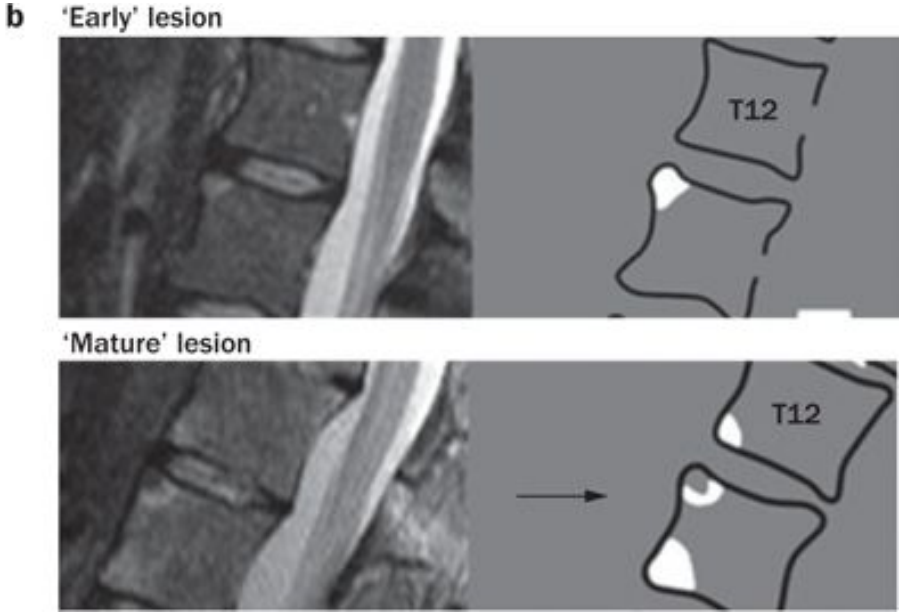
55 patients with AS
96 patients with nrAxSpA



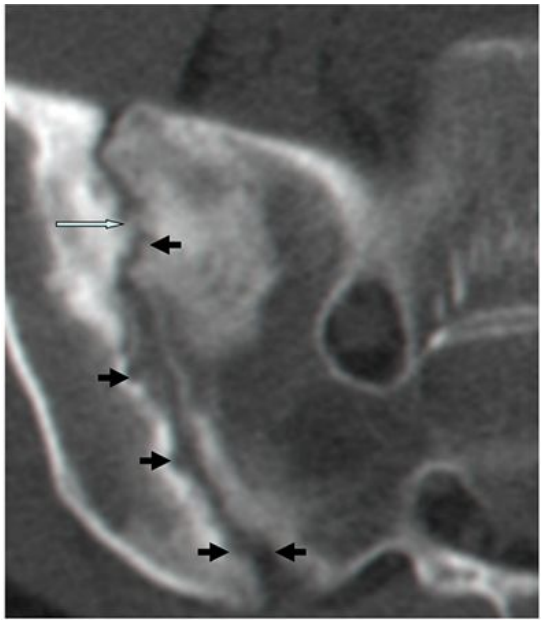

**MALES=FEMALES (AxSpA); M:F=2:1 (AS)**

# Disease progression



# Disease progression



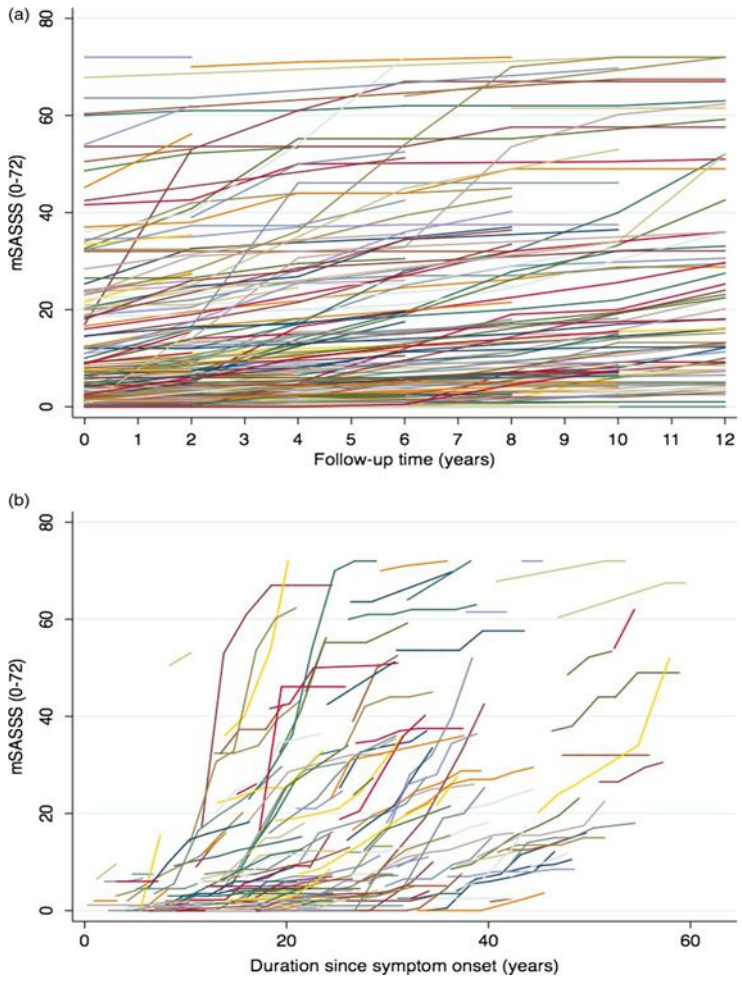
in males <

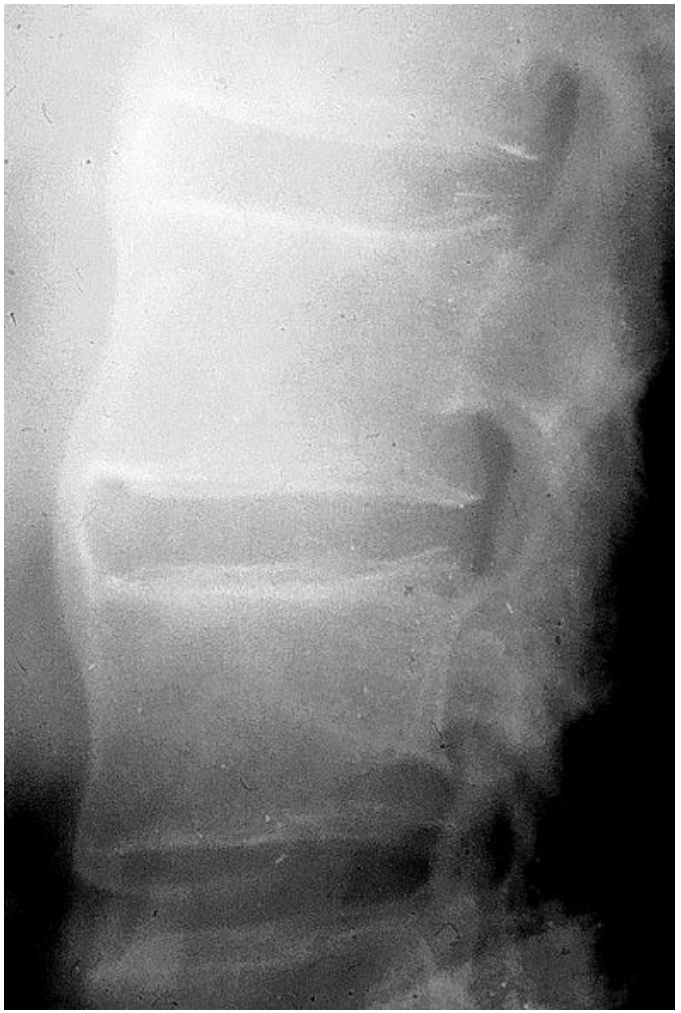
in smokers <

in those with high CRP <

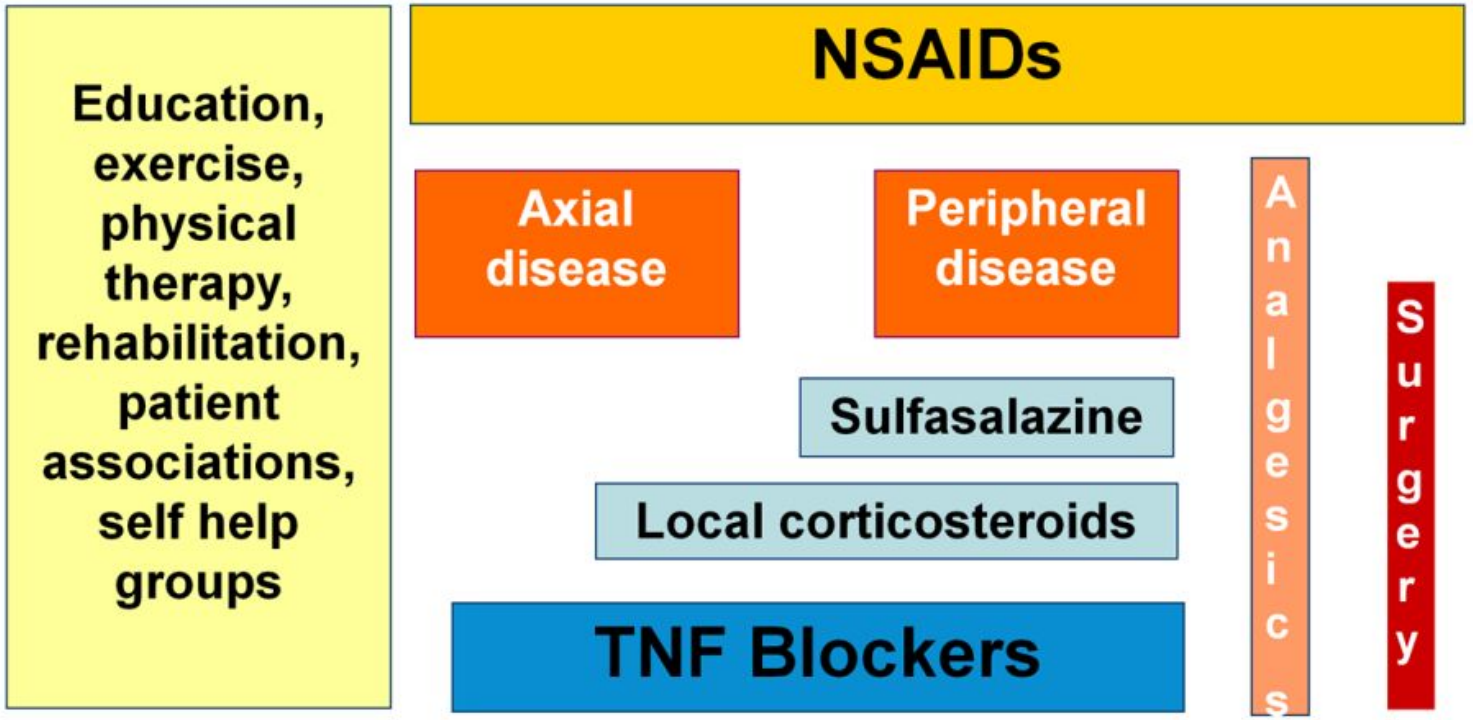
in those with syndesmophytes at baseline <<<

# Disease progression



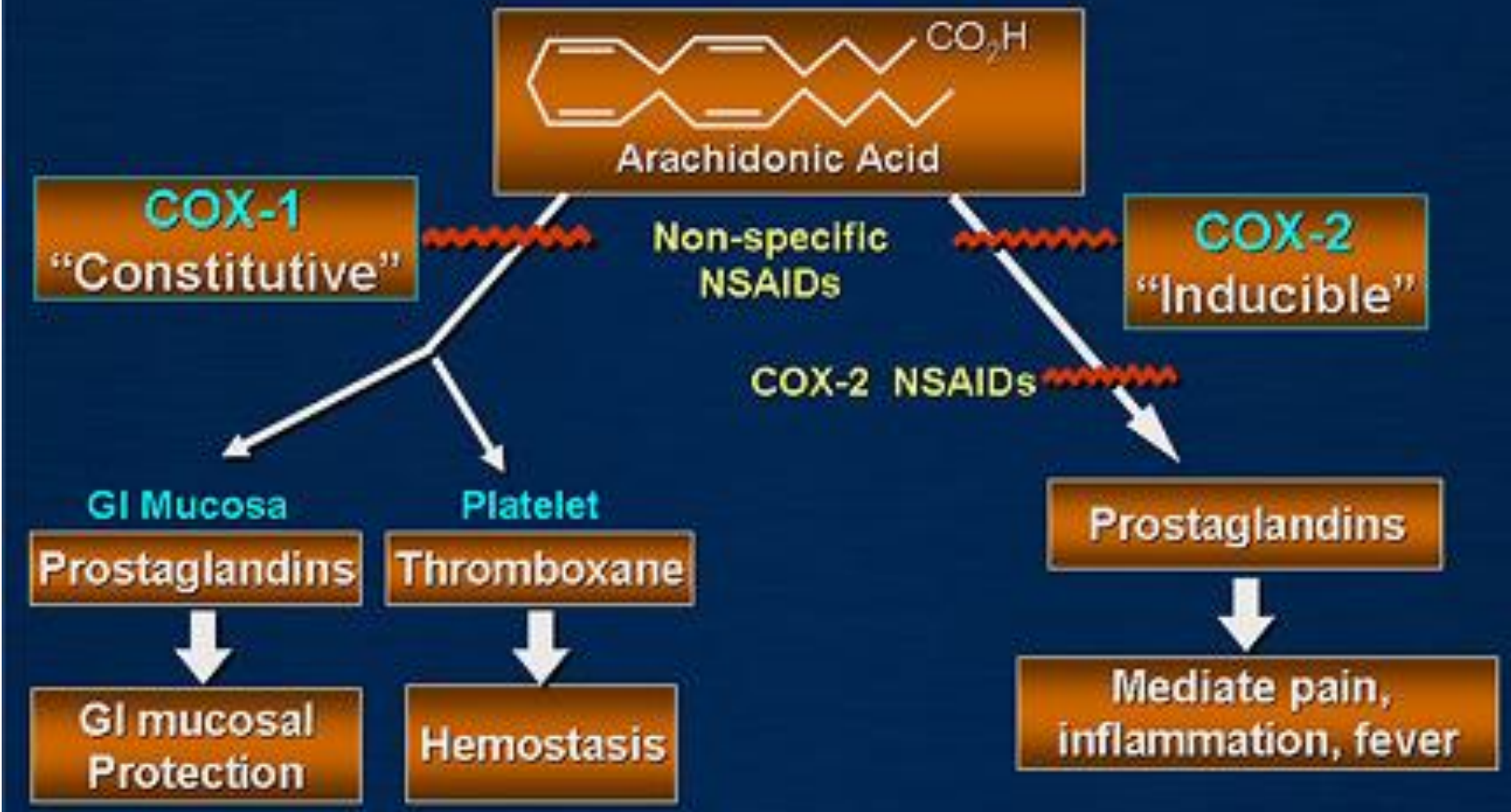
# ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis




Zochling J et al. Ann Rheum Dis 2006;65:442-52 (with permission)

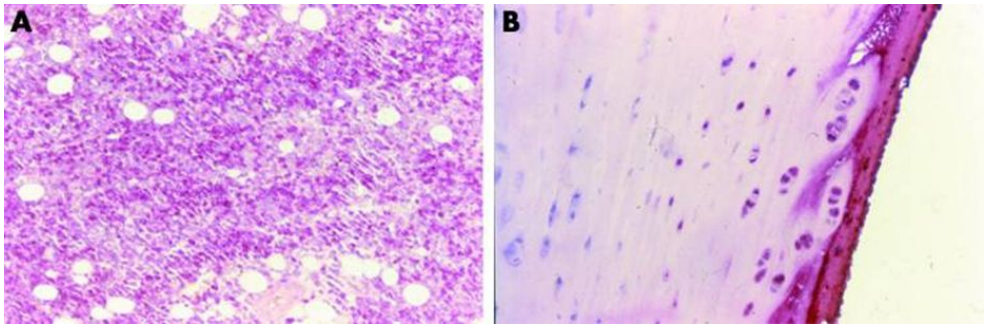
ASAS

# Mechanism of Action of NSAIDs



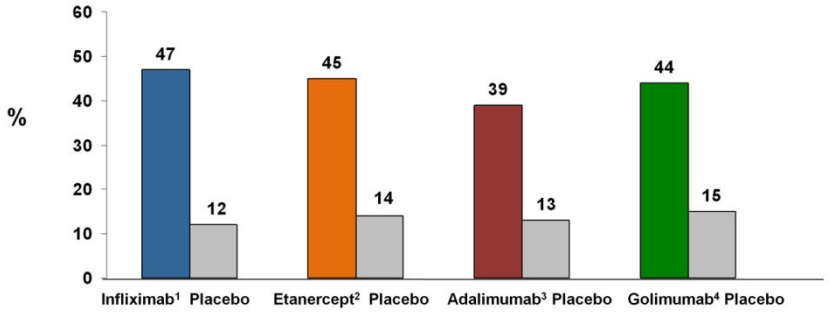

Vane JR, Botting RM. *Inflamm Res.* 1995;44(1):1-10.

# TNF – iTNF
# 1990s-2000s




## ASAS 40 Response after 24 Weeks of Treatment of AS Patients with TNFα Blocking Agents*

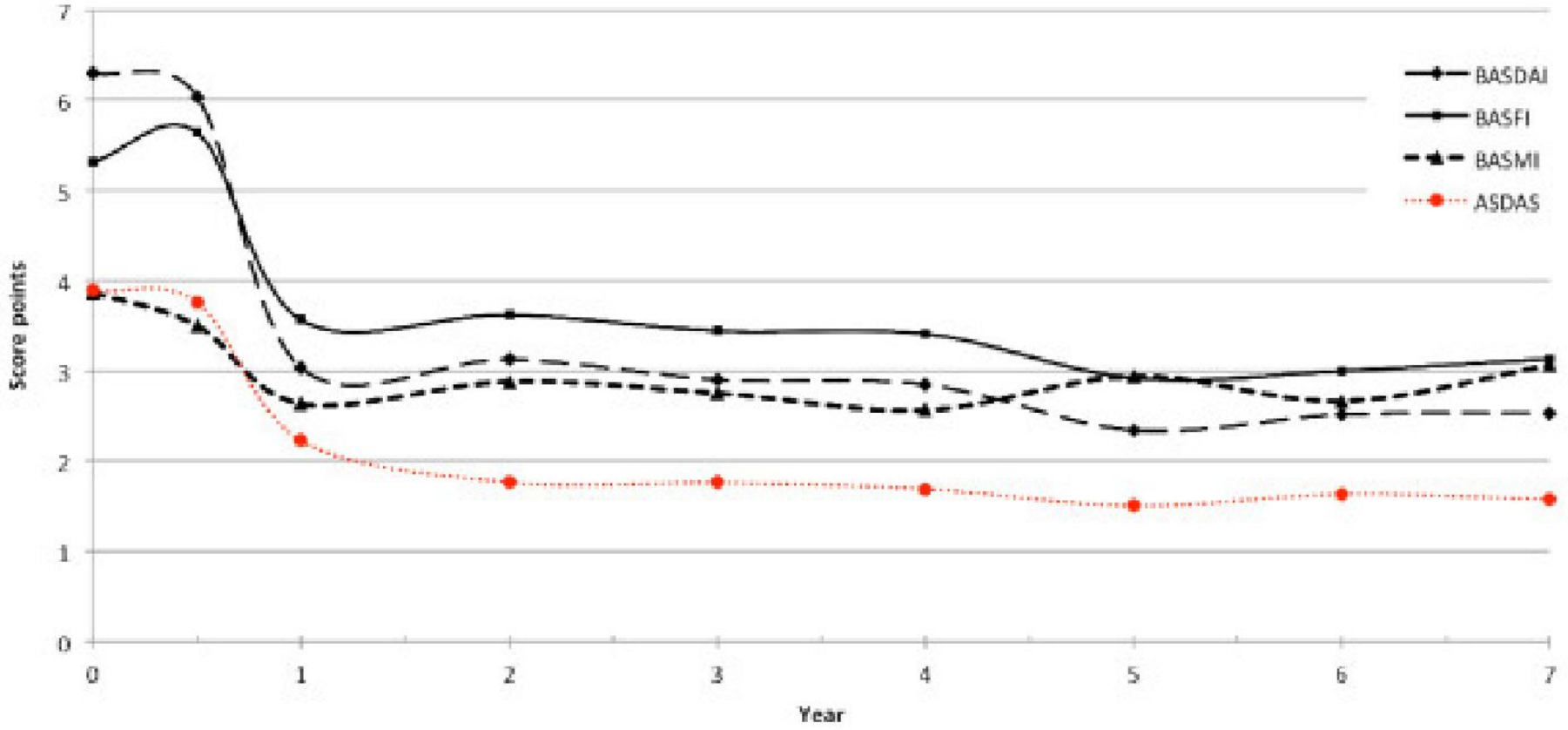
*Different studies, no head to head comparison



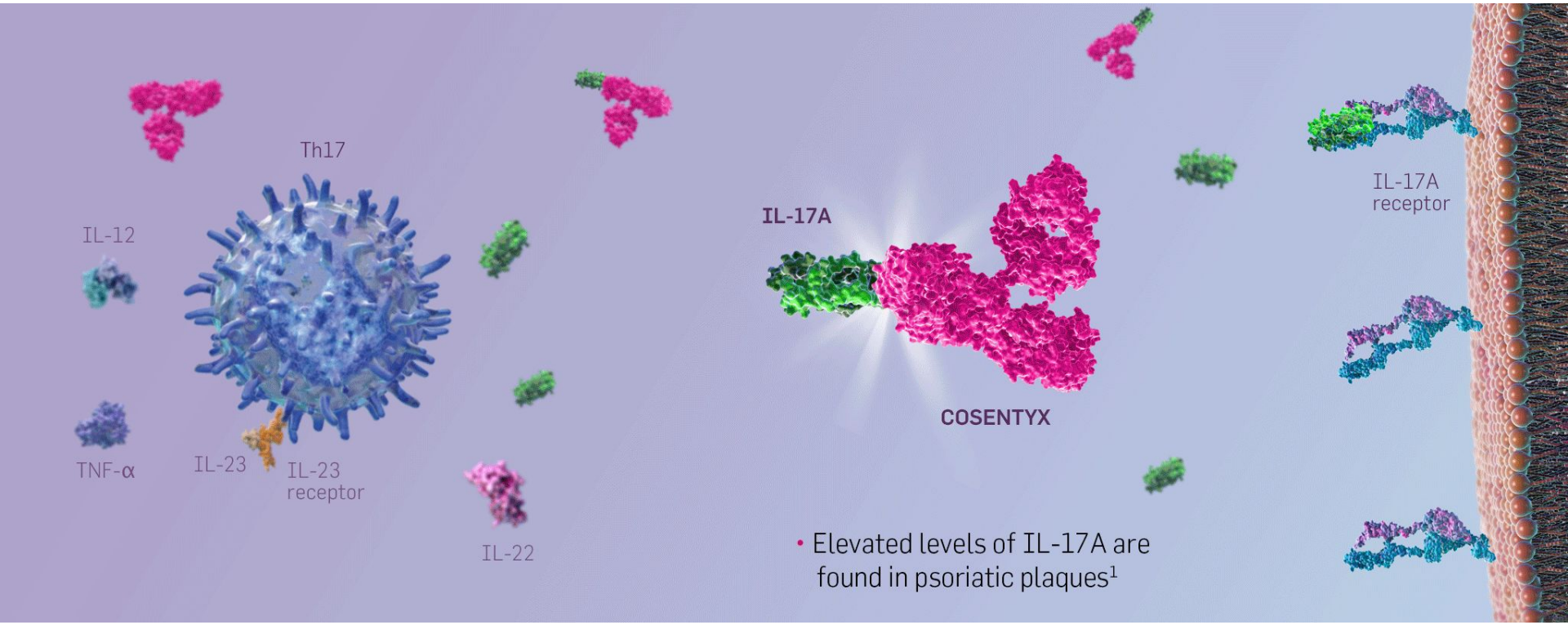

1. van der Heijde D et al. Arthritis Rheum 2005;52:582-91
2. Davis JC et al Ann Rheum Dis 2005;64:1557-62
3. van der Heijde D et al. Arthritis Rheum 2006;54:2136-46
4. Inman RD et al. Arthritis Rheum 2008;58:3402-12

ASAS

# Efficacy of TNFi in AS



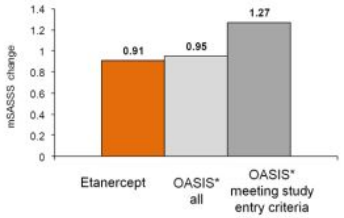
# Other biologics: anti IL-17



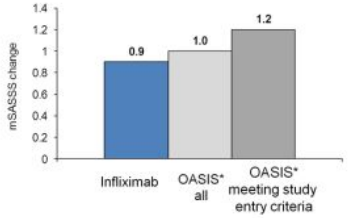
# Anti-TNF & NSAIDS

## Anti-TNFα-Therapy over 2 Years Does not Inhibit Radiographic Progression in AS

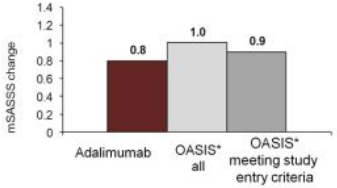
### Etanercept[1]




### Infliximab[2]




### Adalimumab[3]



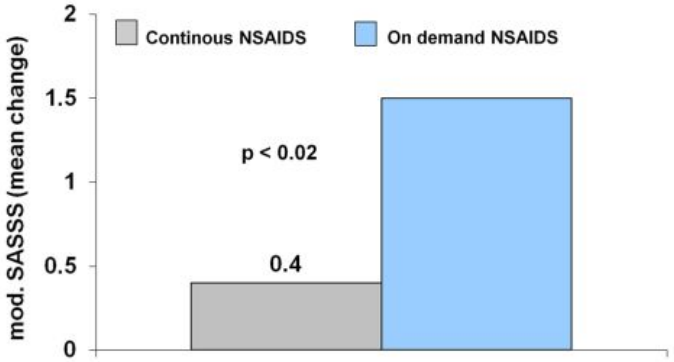

*OASIS=historical AS control group without anti-TNF therapy over 2 years
All comparisons p-value NS.


1. van der Heijde D et al. Arthritis Rheum 2008;58:1324-31
2. van der Heijde D et al. Arthritis Rheum 2008;58:3063-70
3. van der Heijde D et al. Arthritis Res Ther 2009;11:R127


ASAS

## NSAID Therapy in Ankylosing Spondylitis: Radiographic Progression

**Less Radiographic Progression (mSASSS*) after 2 Years of Continuous vs. On Demand Use of NSAIDs (n = 150)**




* scored with blinded time sequence

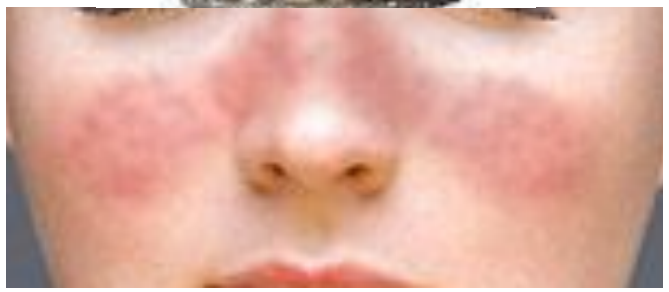
Wanders A et al. Arthritis Rheum 2005;52:1756-65

ASAS

# A ROYAL FAMILY

## of rheumatic diseases





# Q1

A female with daily inflammatory low back pain during the last two years presents for evaluation. You do not find anything wrong on her examination. Your next step will be to order everything but

HLA B27 .1

X-ray of her pelvis .2

MRI of her pelvis .3

C-reactive protein .4

# Q2

HLA B27 is negative, and CRP is normal. Pelvis X-rays are normal as well. Your next step will be

MRI of sacroiliac joints .1

Technetium bone scan .2

Computed tomography of the whole spine .3

Follow up after 6 months .4

# Q3

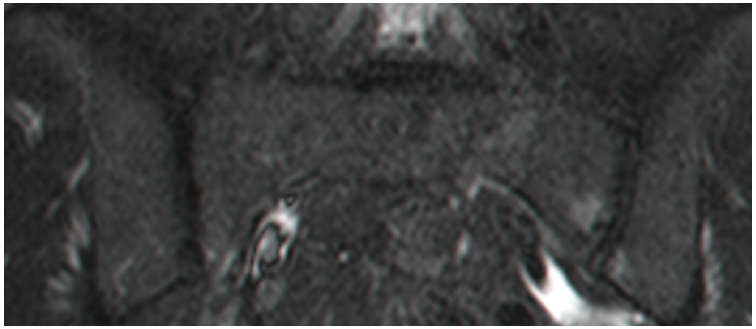
The MRI shows

Enthesitis .1

Bone marrow edema .2

Capsulitis .3

Erosion .4



# Q4

MRI of sacroiliac joints is reported as abnormal, with bone marrow edema around SIJ on both sides. The diagnosis is

Non specific low back pain .1

Ankylosing spondylitis .2

Undifferentiated spondyloarthritis .3

Non-radiographic axial spondyloarthritis .4

# Q5

Non-radiographic axial spondyloarthritis is

An early phase of ankylosing spondylitis .1

A variant of osteitis condensanse ilii .2

A new name for DISH .3

A variant of reactive arthritis .4

# Q6

Recommended treatment will be

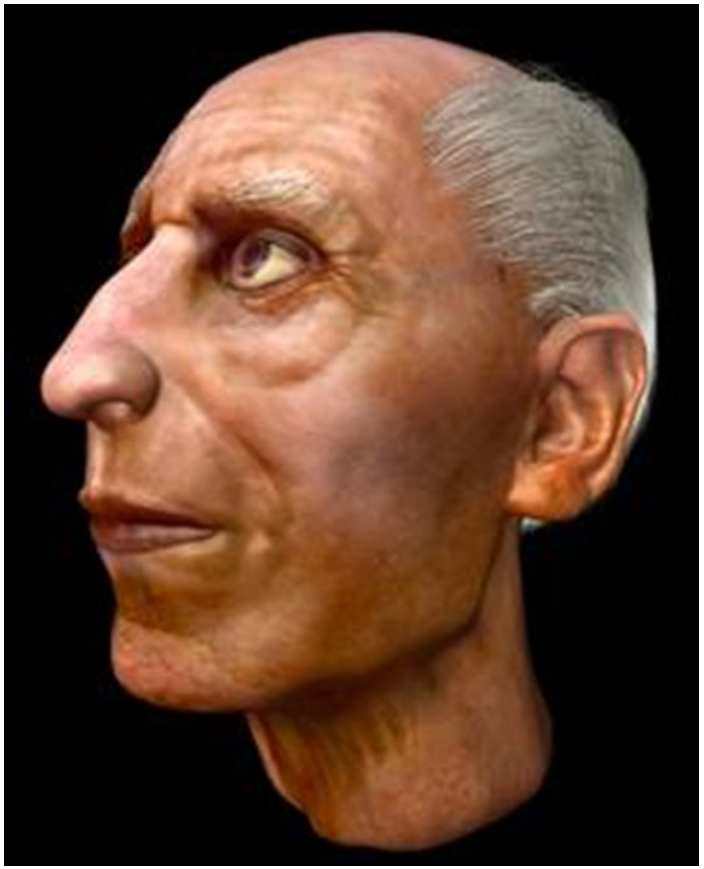
NSAIDs .1

Physical therapy .2

TNF-alpha blockade .3

Surgery .4

# The great
# A case from 1200s BC



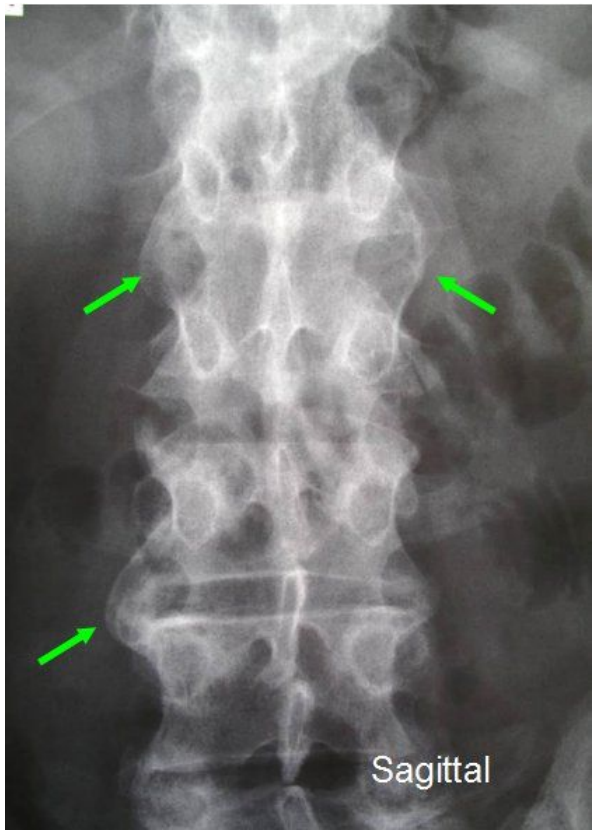
# The great
# A case from 1200s BC

**Fig. 8.** The mummy of Ramses II in his sarcophagus [7].

# DISH vs AS


# Psoriatic arthropathy

# Psoriatic arthropathy



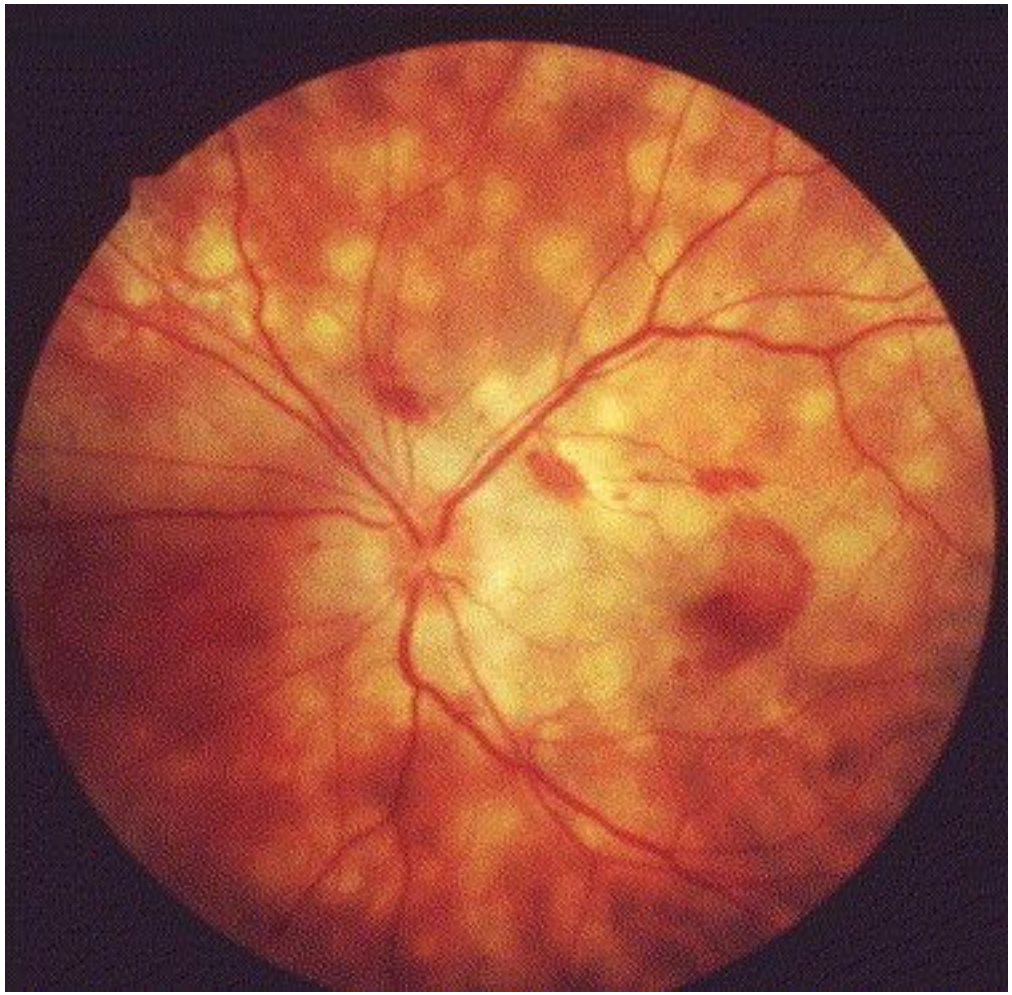

## Types of Psoriatic Arthritis:

1. Symmetric psoriatic arthritis
2. Asymmetric psoriatic arthritis
3. Distal interphalangeal predominant (DIP)
4. Spondylitis
5. Arthritis mutilans

# Psoriasis


# Enthesopathy


# Uveitis

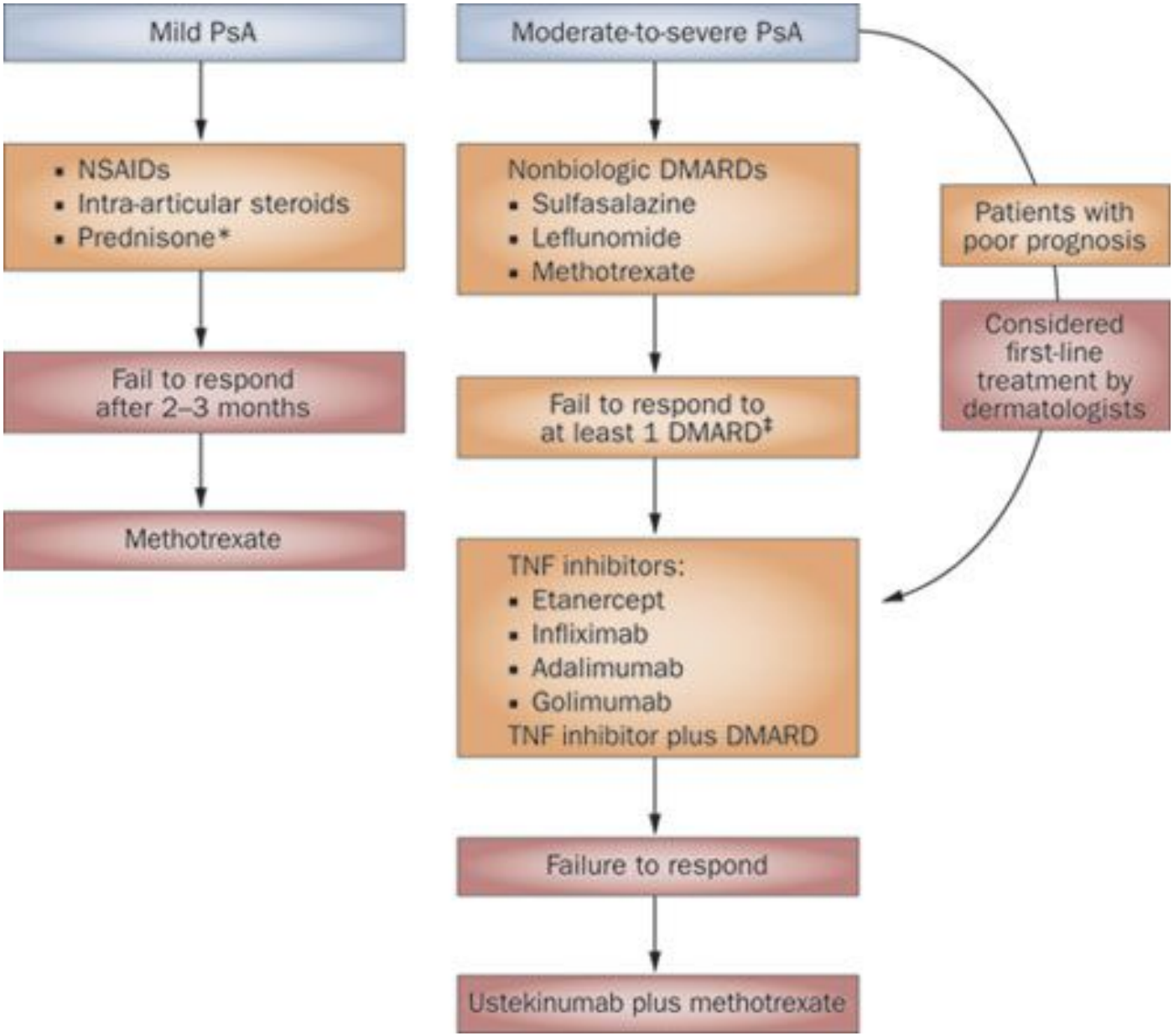


# CASPAR CRITERIA FOR THE CLASSIFICATION OF PSA

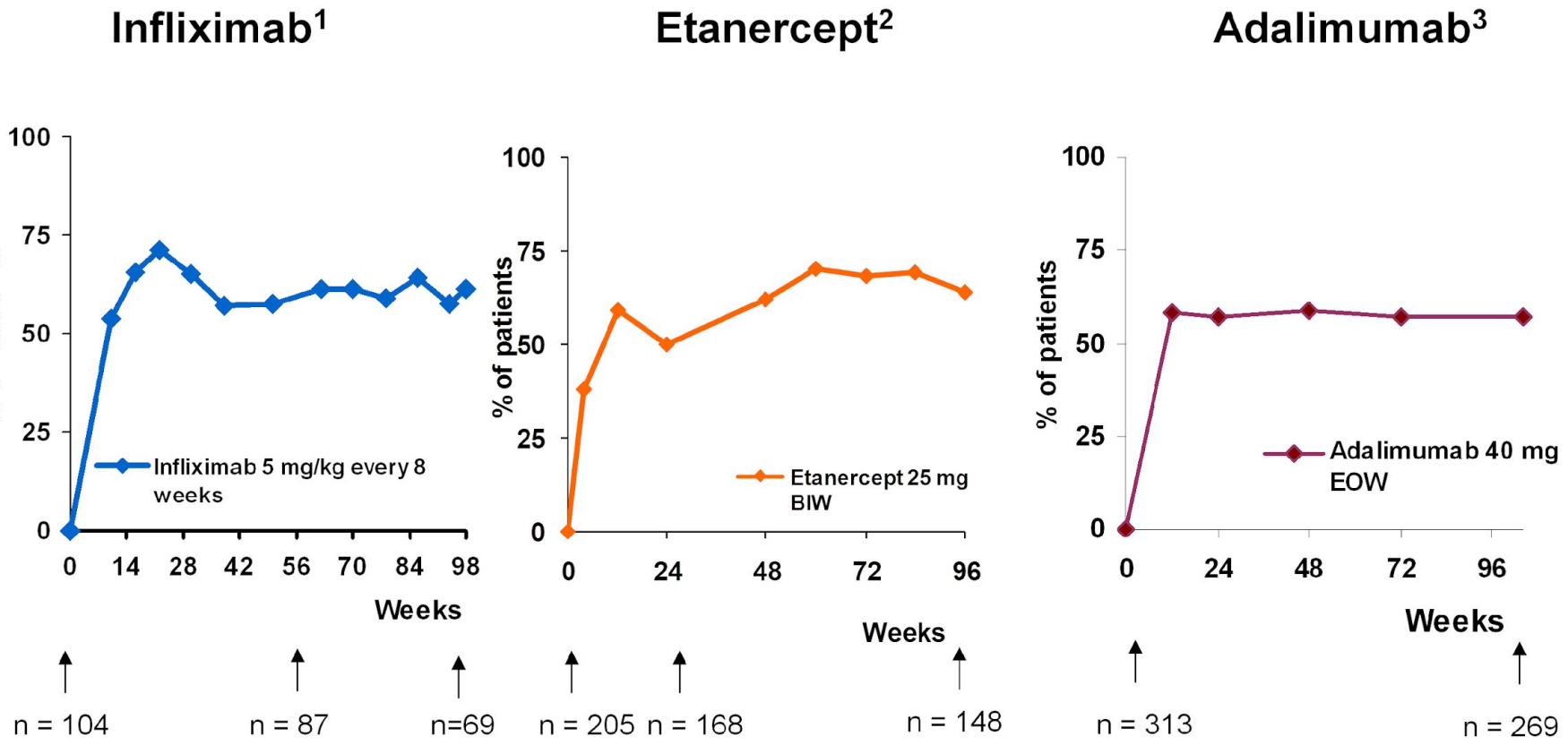
- Inflammatory articular disease (joint, spine, or entheseal)
- With ≥3 points from following categories:
  - Psoriasis: current (2), history (1), family history (1)
  - Nail dystrophy (1)
  - Negative rheumatoid factor (1)
  - Dactylitis: current (1), history (1) recorded by a rheumatologist
  - Radiographs: (hand/foot) evidence of juxta-articular new bone formation
- Specificity 98.7%, Sensitivity 91.4%

Taylor et al. Arthritis & Rheum 2006;54: 2665-73

# Treatment


Mild PsA
• NSAIDs
• Intra-articular steroids
• Prednisone*
Fail to respond after 2–3 months
Methotrexate
Moderate-to-severe PsA
Nonbiologic DMARDs
• Sulfasalazine
• Leflunomide
• Methotrexate
Fail to respond to at least 1 DMARD‡
TNF inhibitors:
• Etanercept
• Infliximab
• Adalimumab
• Golimumab
TNF inhibitor plus DMARD
Failure to respond
Ustekinumab plus methotrexate
Patients with poor prognosis
Considered first-line treatment by dermatologists

# Long Term Efficacy of TNF-Antagonists for the Treatment of Psoriatric Arthritis (ACR 20)

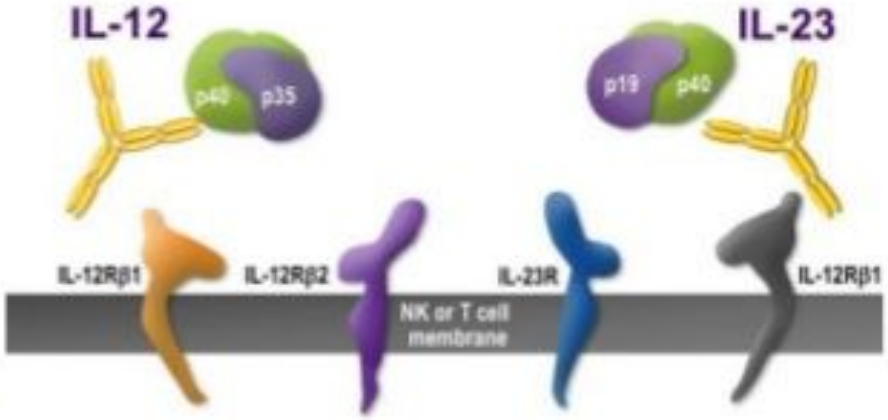




1. Antoni CE et al. J Rheumatol 2008;35:869-76
2. Mease P et al. J Rheumatol 2006;33:712-21
3. Mease PJ et al. Ann Rheum Dis 2009;68:702-9

# Interleukin 12/23 Inhibitor

- Binds to p40 protein found in IL-12 and IL-23 to inhibit inflammation that triggers psoriasis and psoriatic arthritis
- Current treatment:
  - Stelara (Ustekinumab) - Janssen

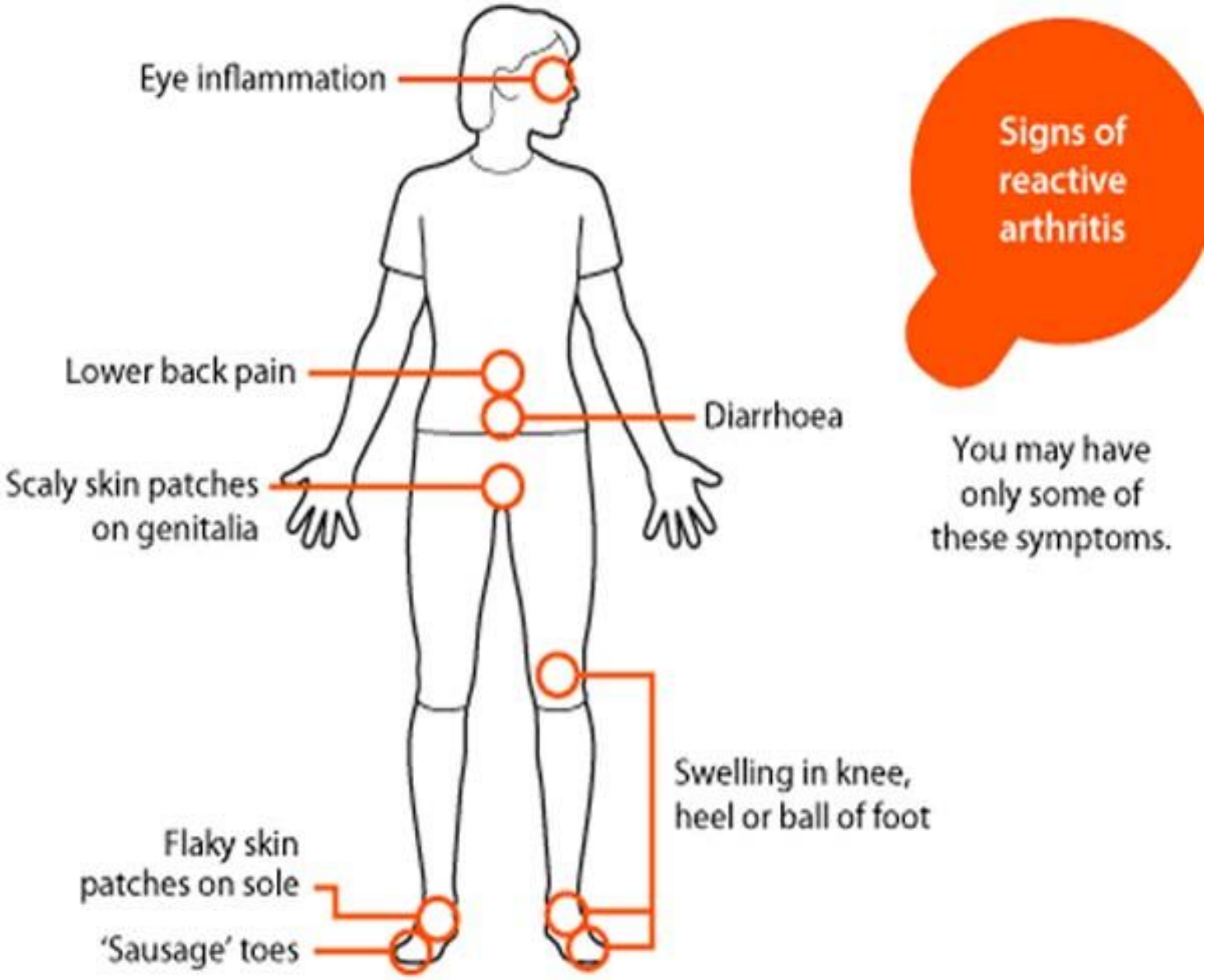


# Reactive arthritis

Table 2

## Common Pathogenic Causes of Reactive Arthritis[1]

- *Chlamydia trachomatis*
- *Yersinia*
- *Shigella*
- *Salmonella*
- *Campylobacter*


Eye inflammation
Lower back pain
Diarrhoea
Scaly skin patches on genitalia
Swelling in knee, heel or ball of foot
Flaky skin patches on sole
'Sausage' toes
Signs of reactive arthritis
You may have only some of these symptoms.

# Keratoderma Blenorrhagicum