RHEUMATOLOGY SPONDYLOARTHRITIS

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DISCLOSURES

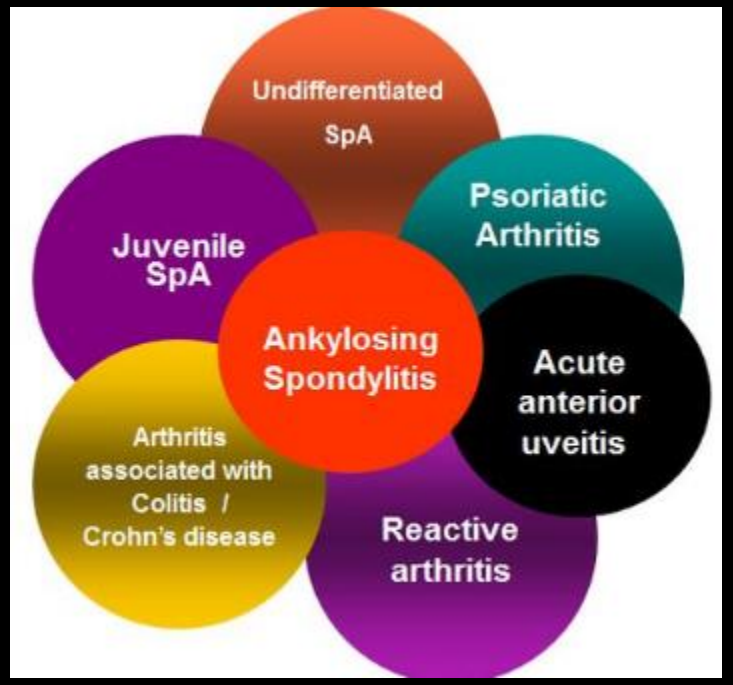
- NONE

SERONEGATIVE SPONDYLOARTHROPATHIES

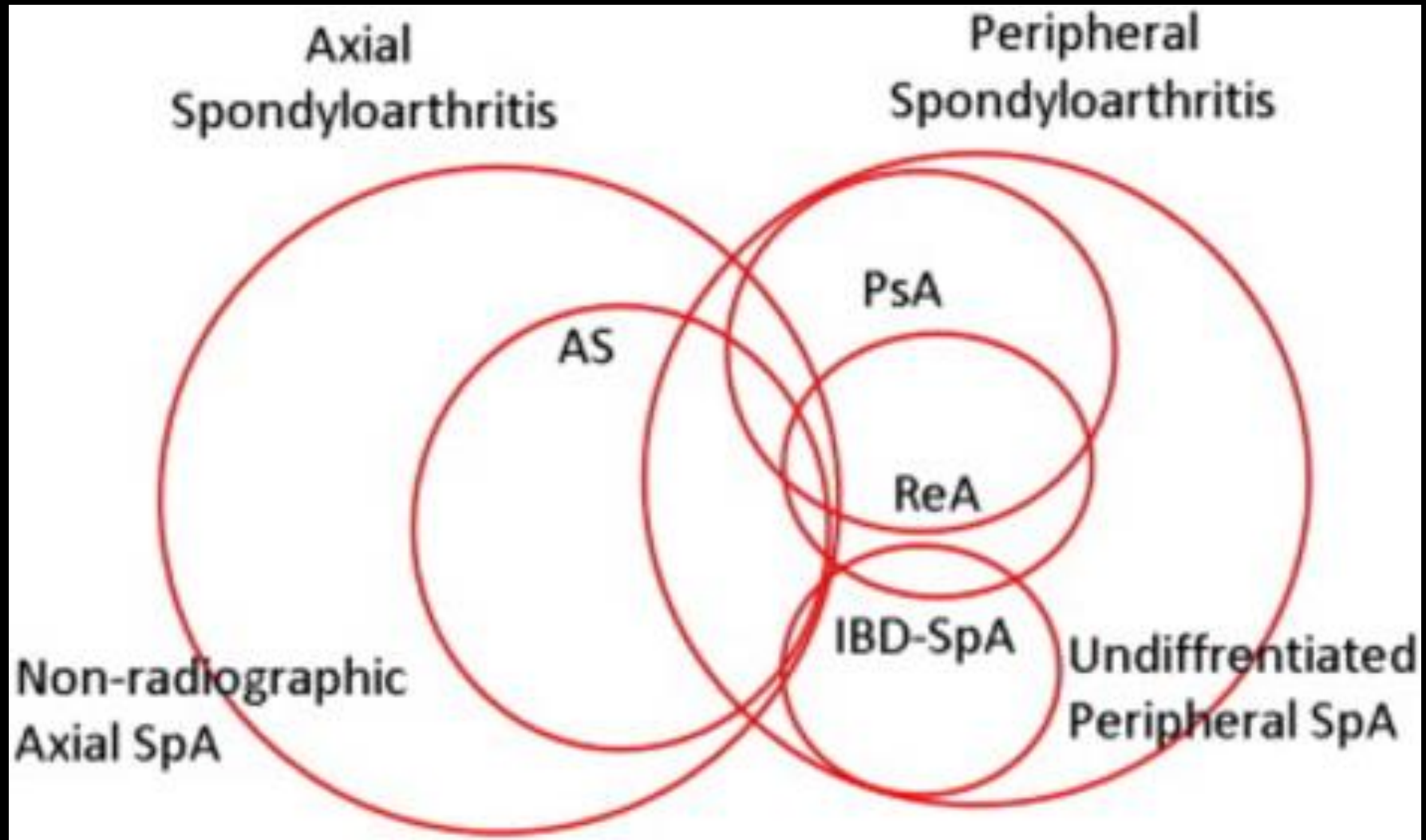
SLIDES PREPARED BY GENE JALBERT, DO
SENIOR RHEUMATOLOGY FELLOW

THE SPONDYLOARTHROPATHIES:

- Ankylosing Spondylitis (A.S.)
- Non-radiographic Axial spondyloarthropathies (nr-axSpA)
- Psoriatic Arthritis (PsA)
- Inflammatory Bowel Disease Associated (Enteropathic)
  - Crohn and Ulcerative Colitis
  - +/- Microscopic colitis
- Reactive Arthritis (ReA)
- Juvenile-Onset SpA
- Others: Bechet's dz, Celiac, Whipples, pouchitis.



THE FAMOUS VENN DIAGRAM:

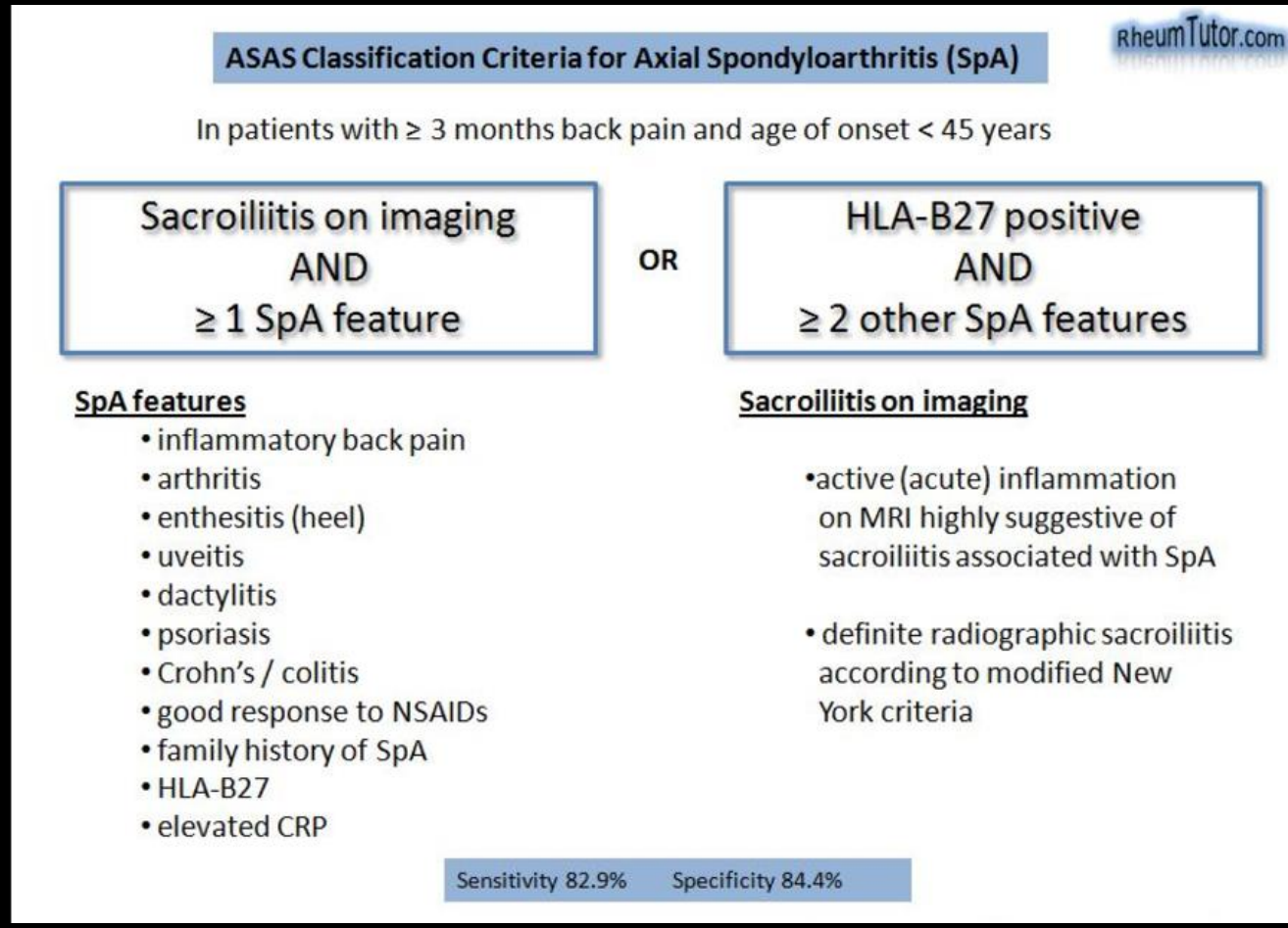


SPONDYLOARTHROPATHY:

- First case of Axial SpA was reported in 1691 however some believe Ramses II has A.S.
- **2.4 million adults** in the United States have Seronegative SpA
  - Compare with RA, which affects about 1.3 million Americans
- Prevalence variation for A.S.: Europe (0.12-1%), Asia (0.17%), Latin America (0.1%), Africa (0.07%), USA (0.34%).
- Pathophysiology in general:
  - Responsible Interleukins: IL-12, IL17, IL-22, and IL23.

SPONDYLOARTHROPATHY:

- Axial SpA:
  - Radiographic (Sacroiliitis seen on X-ray)
  - No Radiographic features → non-radiographic SpA (nr-SpA)
    - Nr-SpA was formally known as undifferentiated SpA
- Peripheral SpA:
  - Enthesitis, dactylitis and arthritis
  - Eventually evolves into a specific diagnosis → A.S., PsA, etc.
  - Can be a/w IBD, HLA-B27 positivity, uveitis



SHARED CLINICAL FEATURES:

- Axial joint disease (especially SI joints)
- Asymmetrical Oligoarthritis (2-4 joints).
- Dactylitis (Sausage Digits)
- Enthesitis
- Associations with infections
- Eye inflammation
- Bowel inflammation
- HLA-B27+ and family history associations
- Constellation of muco-cutaneous features

SHARED CLINICAL FEATURES:

- Inflammatory Back Pain:
  - Chronic back pain better with exercise but not with rest and pain at night
  - Insidious onset with more than 3 months in duration
  - Usual onset <45 years of age
  - Marked improvement w/ NSAIDs within 24-48 hours
  - Above features are not diagnostic
- Peripheral Arthritis:
  - Acute in onset
  - Seen in the knees and ankles more commonly
  - Asymmetrical, Oligoarticular

HLA-B27:

- The SpAs are a/w HLA-B27, an HLA class I gene (CD8+ T Cell Response).
- The prevalence of HLA-B27 in "healthy" population:
  - ~8% in healthy whites and ~3% in N. American Blacks.
  - + in up to 90% of those with A.S.
  - *+ in up to 80% of those with ReA in hospitalized (more severe) cases.*
  - + in 50% of those with Axial PsA.
  - 10x risk for developing arthritis in those with IBD.
- There are 59 associated subtypes of HLA-B27 (B*2705 is most common)
- Other genetic risk factors (see next slide):
  - Endoplasmic Reticulum Aminopeptidase (ERAP-1)
  - IL-23R = IL-23 Receptor

SACROILIITIS:

- Causes of sacroiliitis:
  - Inflammatory: SpAs, Infection (bacteria, fungal, mycobacterial).
  - Traumatic: Fracture, OA, OCI.
  - Generalized Disease: Gout, Hyperparathyroidism, Paget's Dz, Paraplegia, neoplastic mets.
- Involves the lower 2/3rd synovial-lined of the SI joints.
- In A.S. it is symmetric and bilateral.
- In PsA it is asymmetric and unilateral.
- Earliest radiographic change: Erosions of the iliac side of the SI joint where the cartilage is thinner.
- Early on: "pseudo-widening" of the SI joints, then leading the sclerosis and ankyloses or fusion of the joint (Grade 4).

SACROILIITIS:

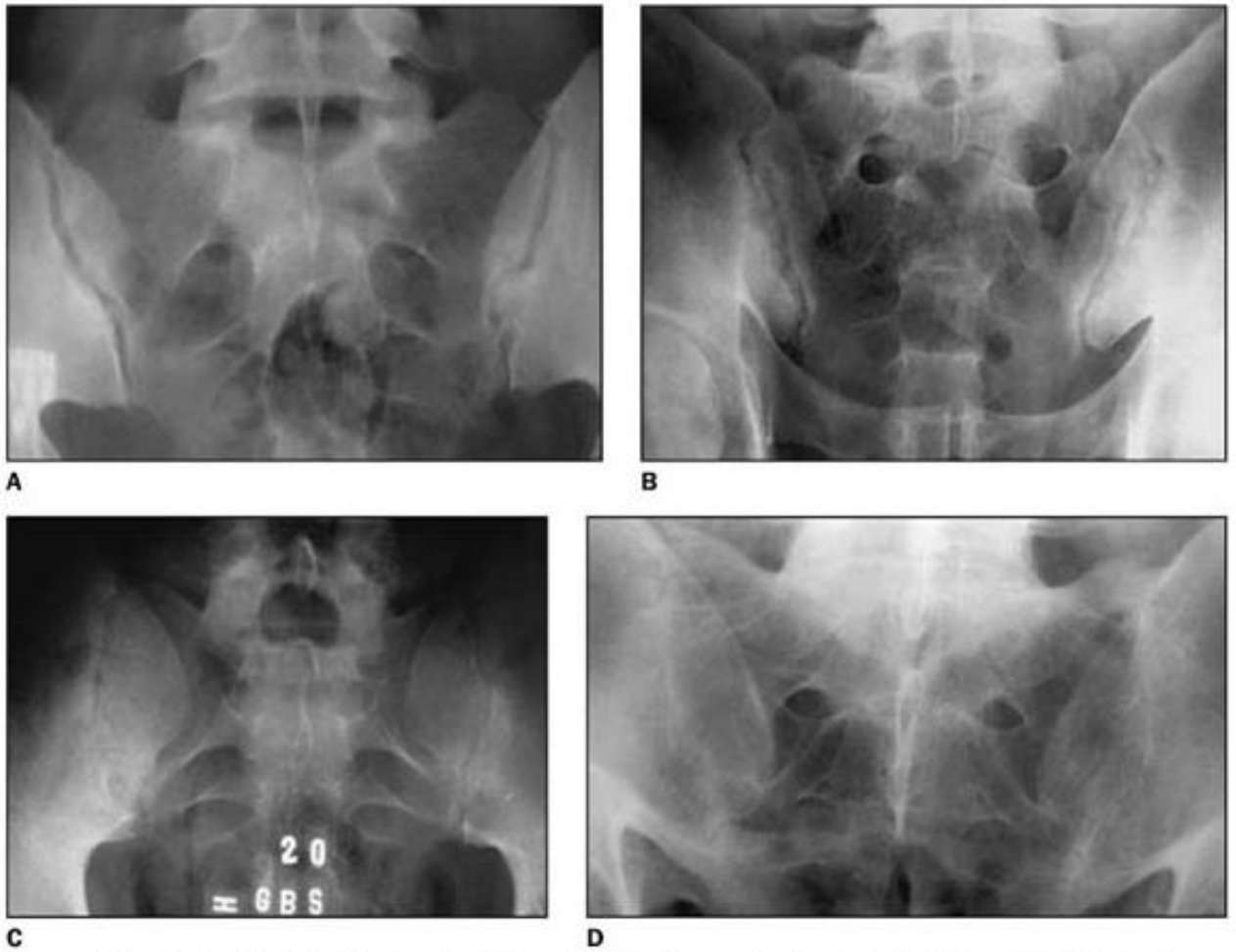
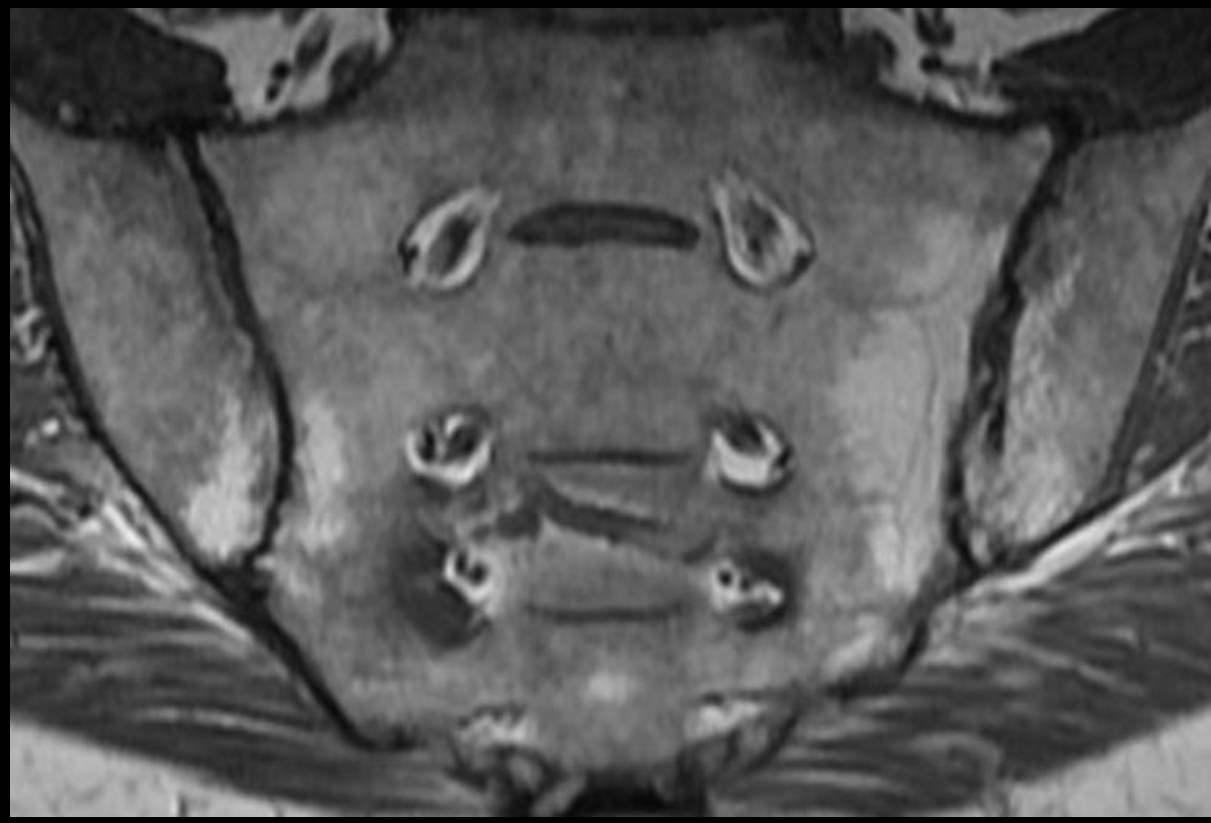
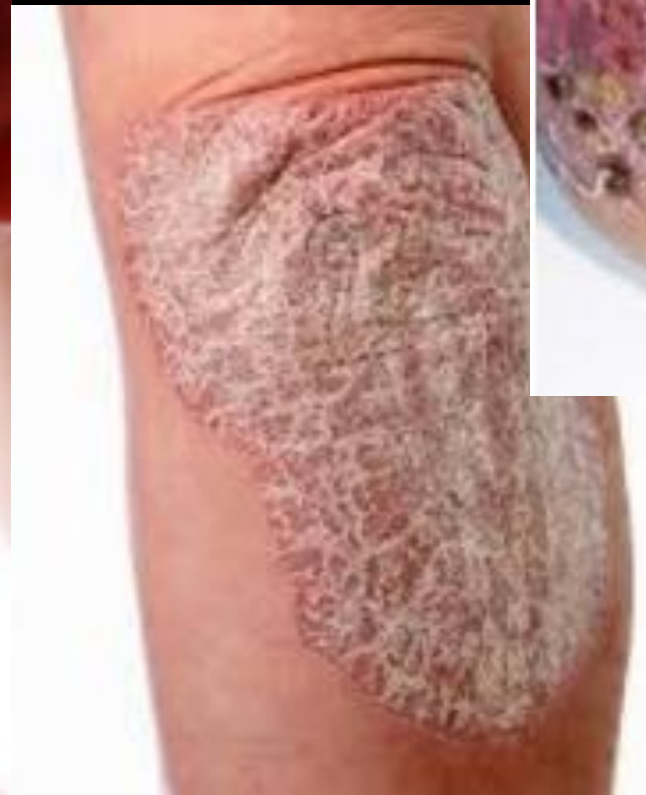
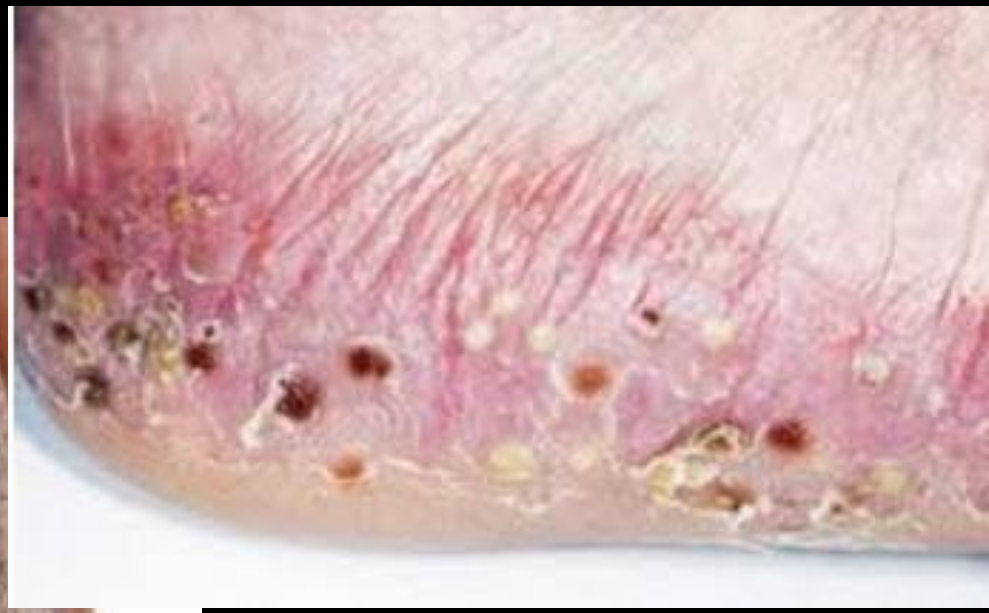


Figure 4. Radiographic classification in the evaluation of sacroiliac joints. Grade 0 – normal (**A**); grade I – suspicious; grade II – mild irregularity and sclerosis of articular surfaces, with preserved joint space (**B**); grade III – joint space narrowing, besides intense irregularity and subchondral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

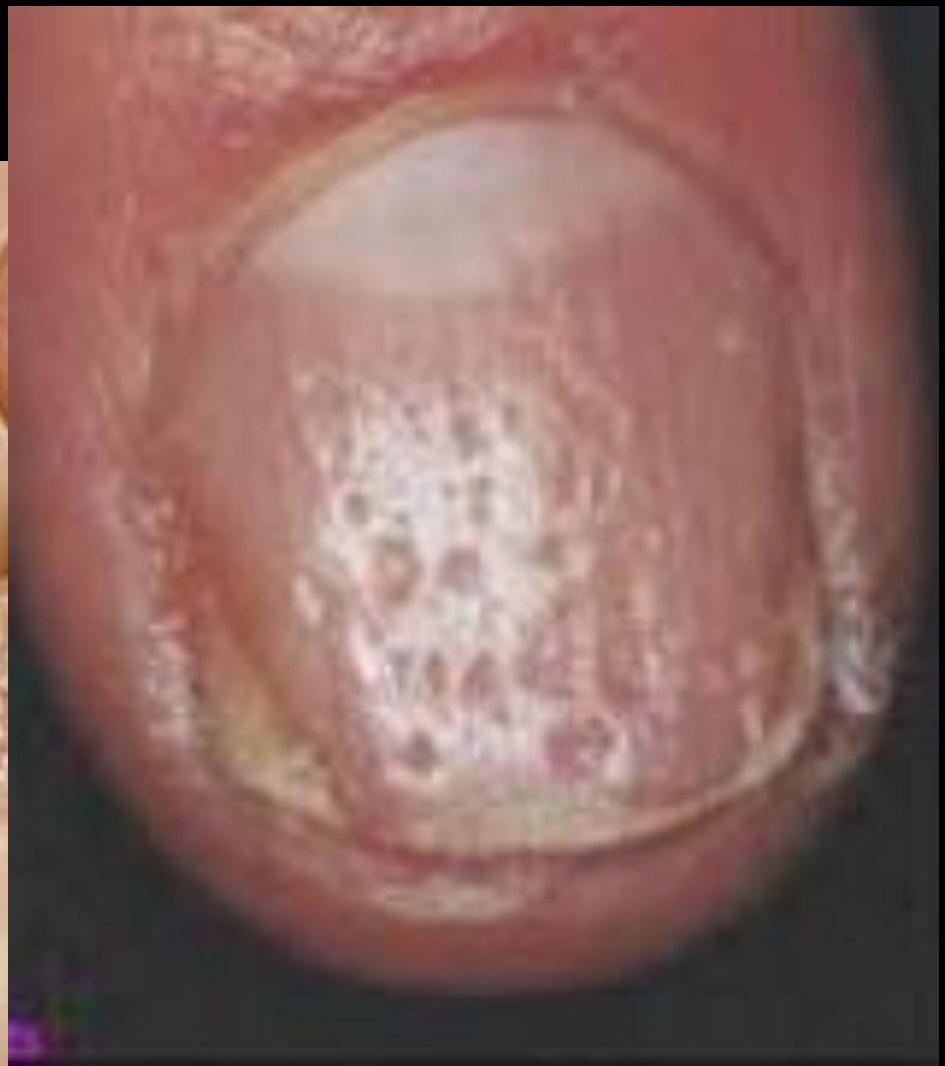


PSORIASIS:



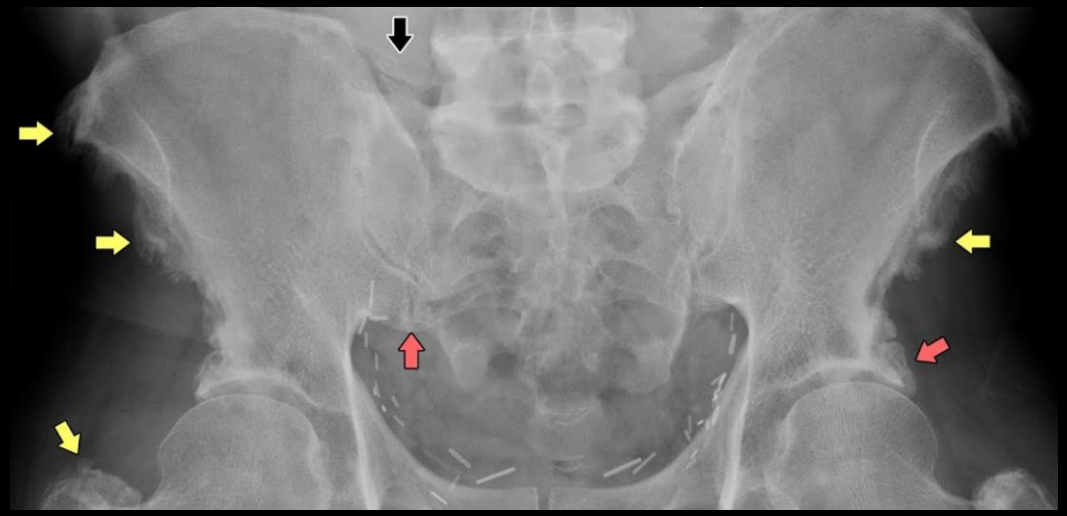


ONYCHOLYSIS/PITTING:



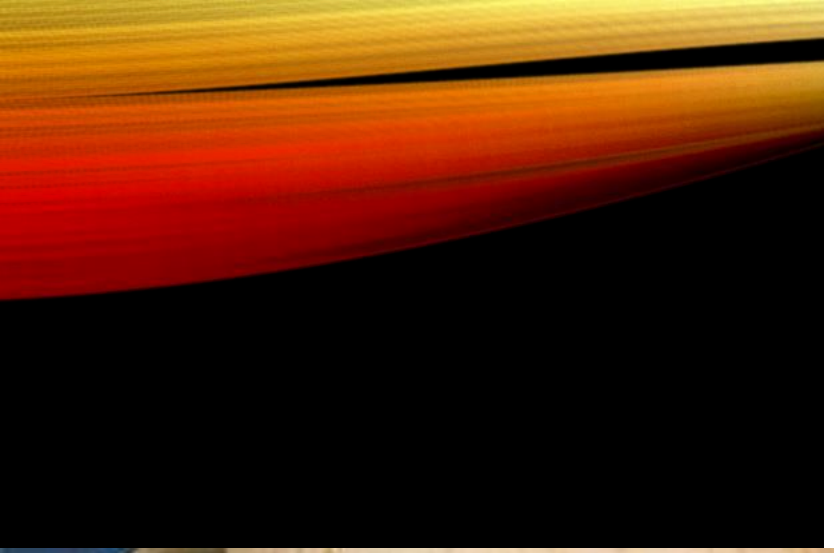
ENTHESITIS:

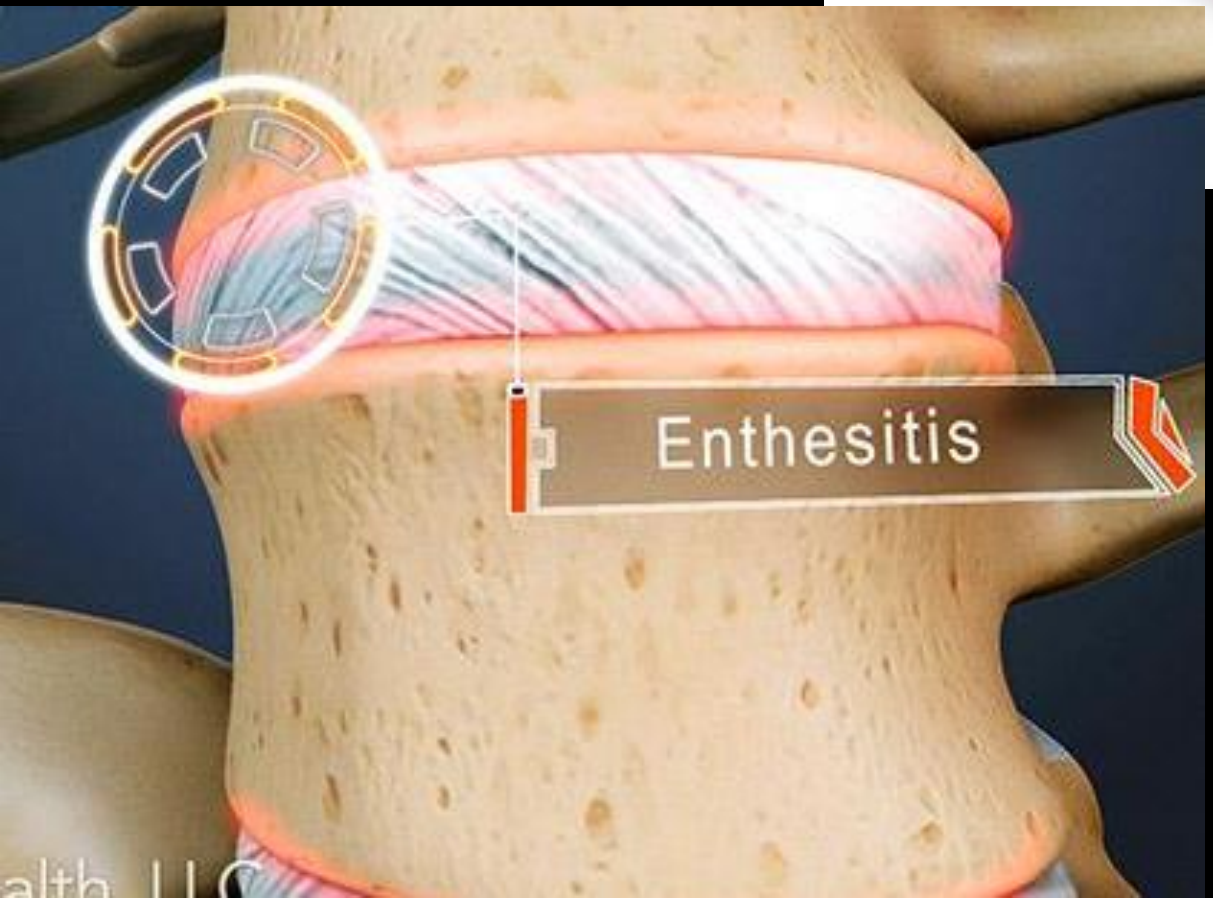
Positive Arrow Sign:

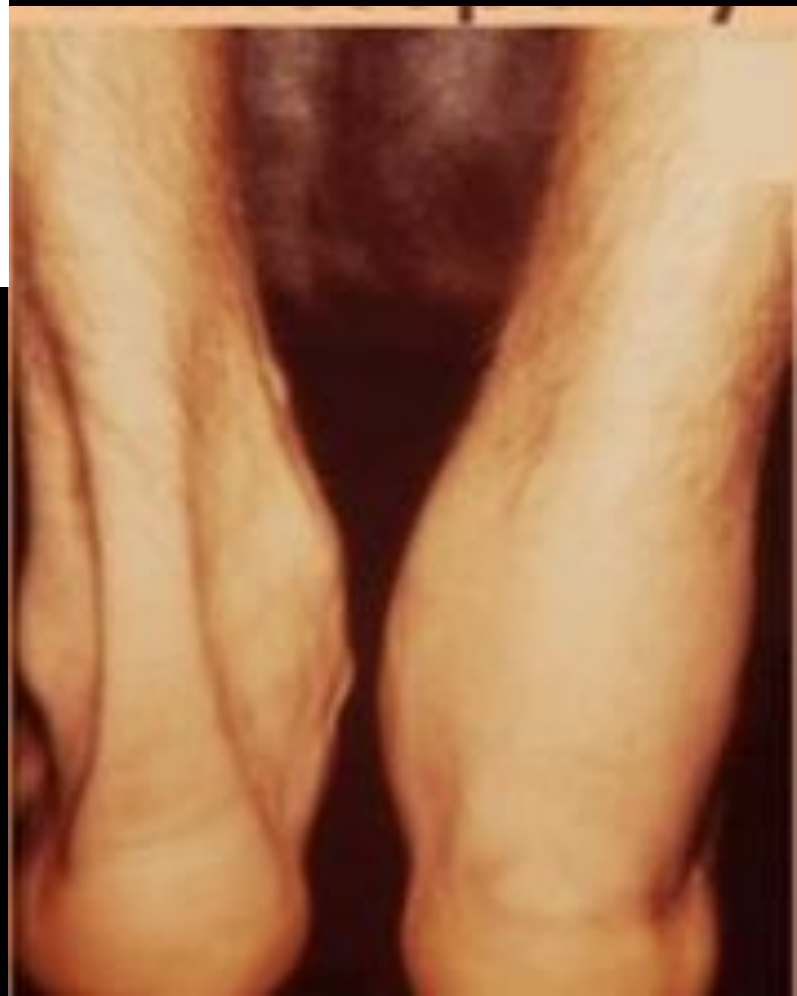


- Enthesitis (Enthesopathy):
  - Inflammation around the insertion of ligaments, tendons, joint capsules or fascia to bone.
  - Specific to SpA's.
  - Enthesis: Dense collagen, fibrocartilage, adjacent bursae and synovial fold
  - Most common: Achilles tendon inflammation and plantar fascia at the calcaneal bursa.
  - Other less common sites: Greater trochanters, iliac crests (**whiskering**), epicondyles, tibial plateaus, costochondral junctions at the sternum, humeral tuberosities, manubrial-sternal joints, occiput, and spinous processes.

ENTHESITIS:



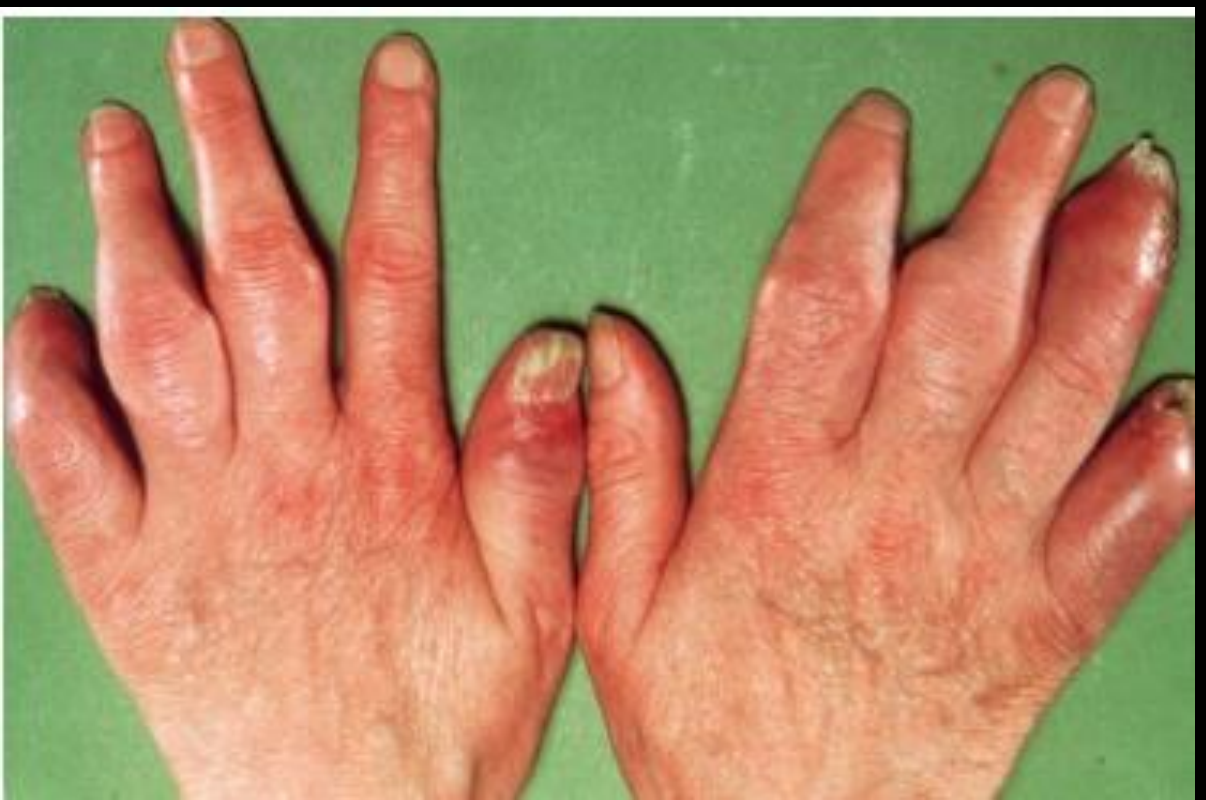


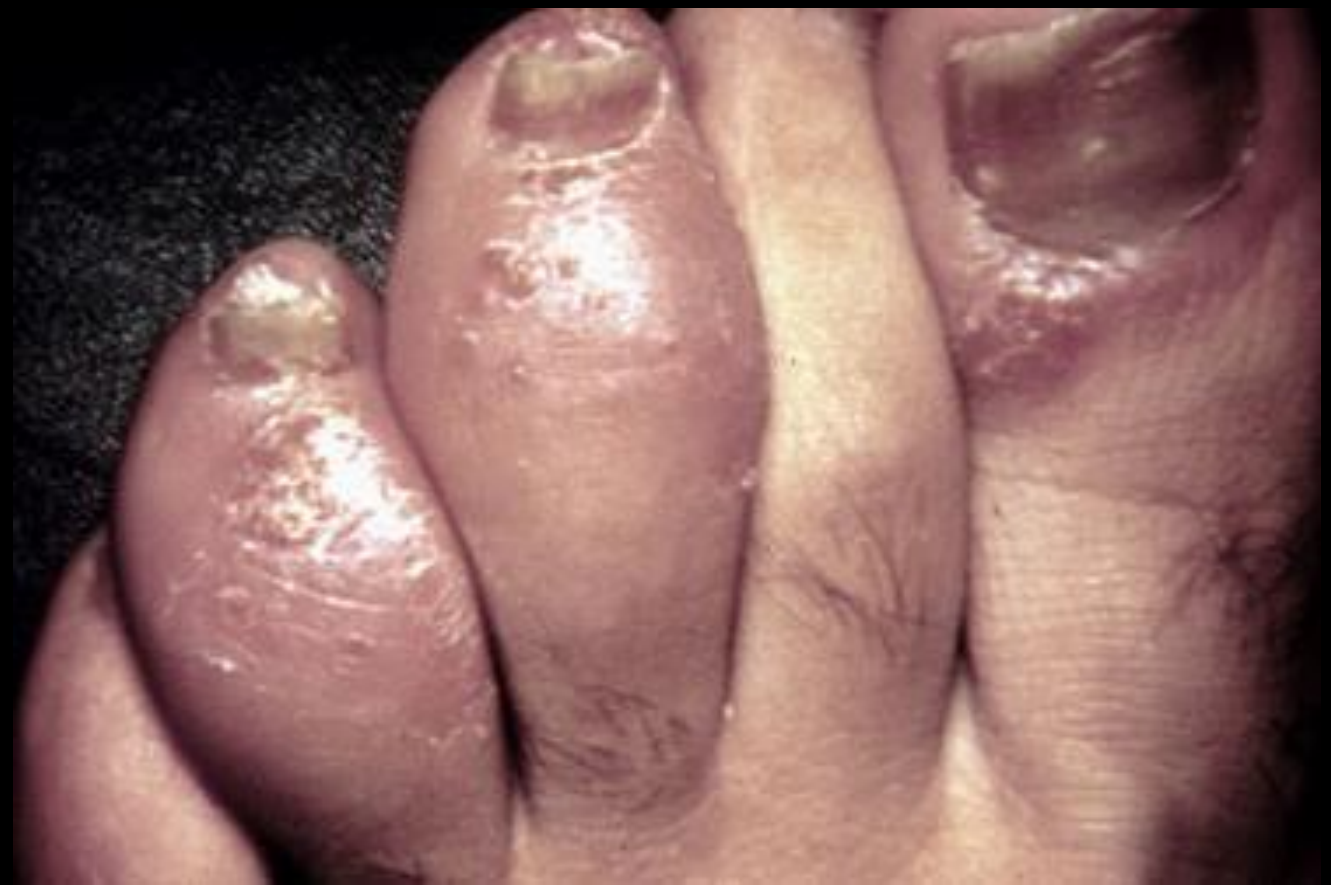


DACTYLITIS:

- AKA Sausage digits
- Can be seen in ALL forms of SpA, however MC seen in PsA and ReA
- Entire digit is swollen w/ surprisingly less pain and tenderness w/ palpation.
- Is due to involvement of the flexor tendon, sheath, and soft tissue tenosynovitis. Joints can be involved as well.
- Dactylitis can also be seen in TB, Syphilis, **sarcoidosis**, **sickle cell disease** and tophaceous gout as well.

DACTYLITIS (SAUSAGE DIGITS):





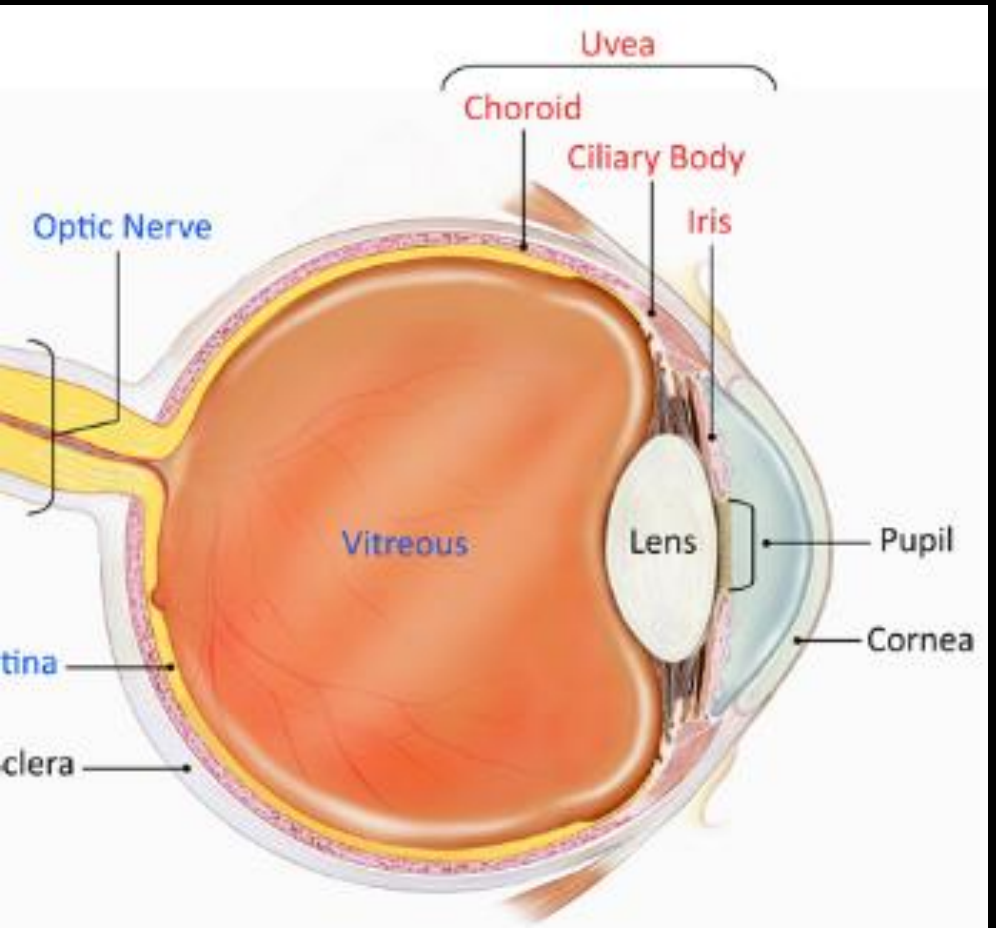
NON-MSK FINDINGS:

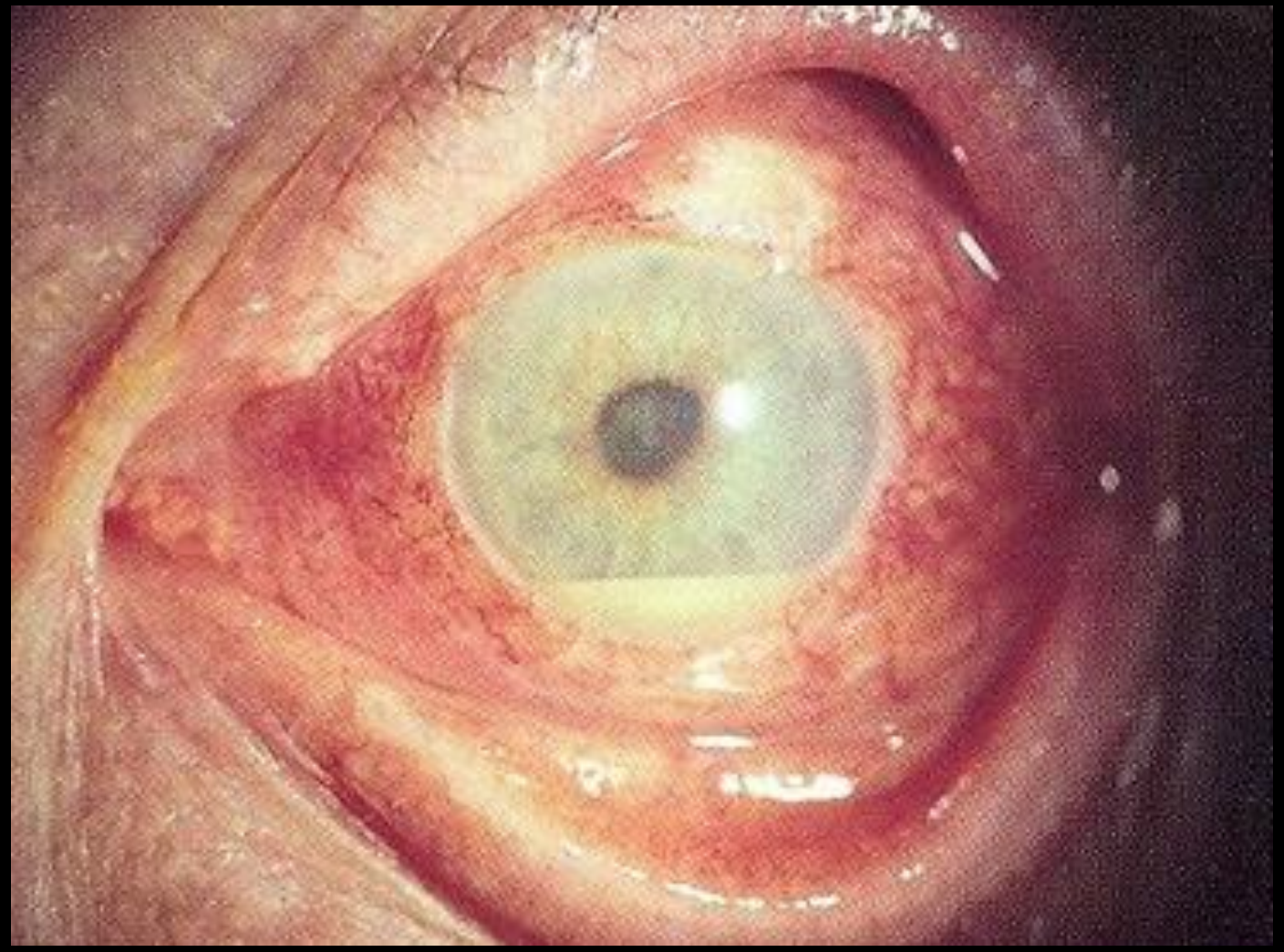
- Inflammatory Eye Disease:
  - Conjunctivitis (reactive arthritis): Non-purulent. Transient (weeks).
  - Anterior Uveitis (iritis):
    - Usually unilateral and may be initial presenting features of SpA
    - Redness, pain, photophobia
    - 50% of patients with recurrent anterior uveitis have a form of SpA
    - 10% can become chronic and threaten vision impairment
- Inflammatory Bowel Mucosa:
  - Either microscopic or macroscopic
  - Symptomatic and Asymptomatic.
- Psoriasis:
  - Can be seen with all forms of SpA
  - 10% of A.S. cases have psoriasis of some type

UVEITIS (A FORM OF ENTHESITIS?):

Likelihood of Iritis

Disease	Percent
•Ank spondylitis	20-30
•Reiter's	12-37
•Psor Spondylitis	7-16
•IBD	2-9
•Undiff SA	ND

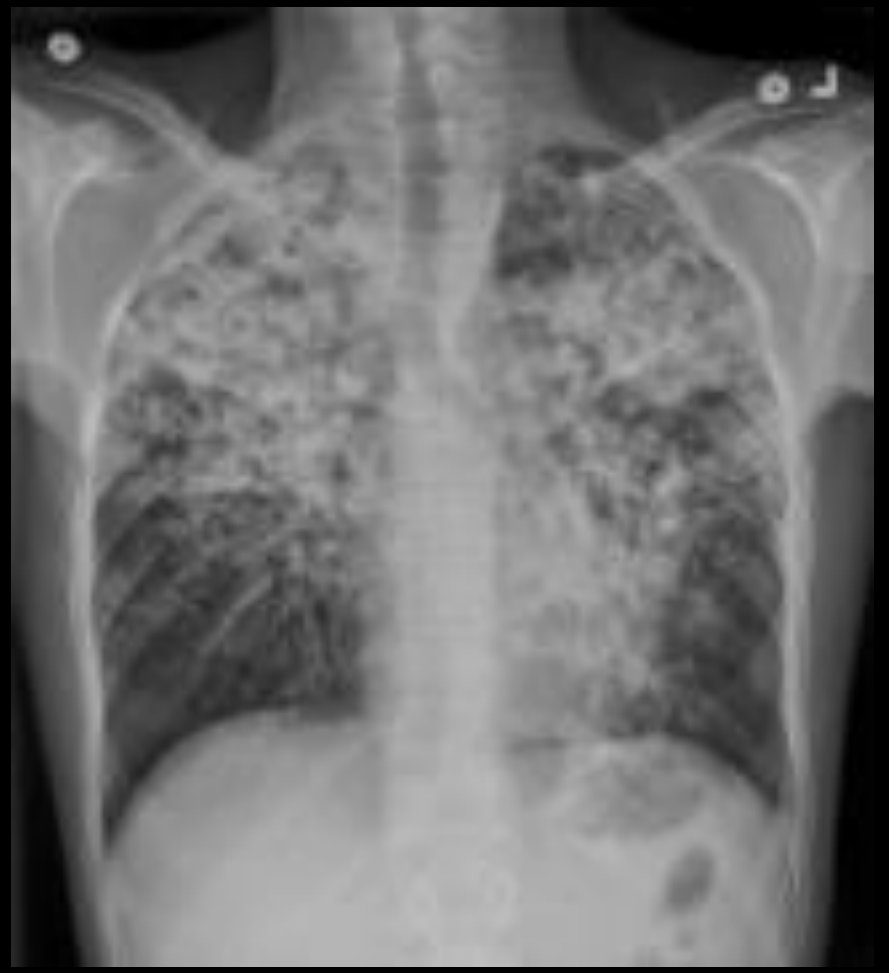




PULMONARY MANIFESTATIONS:

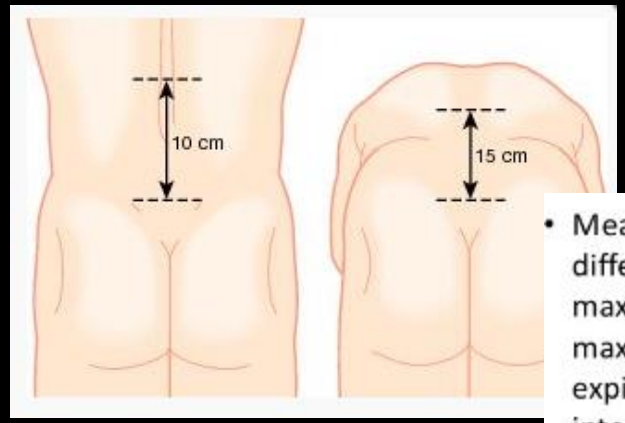
- Upper Lobe, Bilateral Reticulonodular infiltrates w/ cyst formation.
- Restrictive Changes

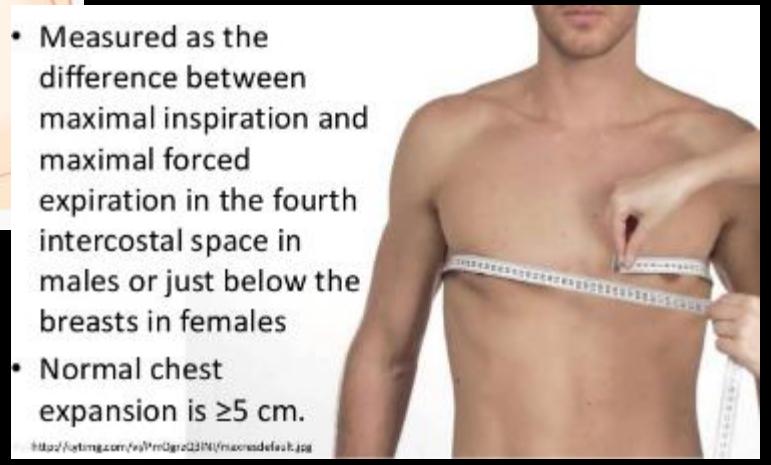
- Upper lobes:
  - R/o TB, Sarcoidosis, Pneumoconiosis, histiocytosis X and Radiation-induced.



PHYSICAL EXAM:

- Modified Schober Test:
  - Landmark: PSIS (Dimples of Venus)
  - > than 5 cm change when patient bends forward
- Reduced Chest Expansion
  - From costovertebral and costochondral joint involvement leading to impaired chest expansion. (dec TLC).
  - Normal: ~5 cm
  - Less than 2.5 cm is abnormal.
- Wall-To-Occiput test
  - From inability to extend the neck
  - With heels/scapulae touching the wall, the occiput should be able to touch the wall.
- Pelvic Compression, Gaenslen's Test, Patrick Test.

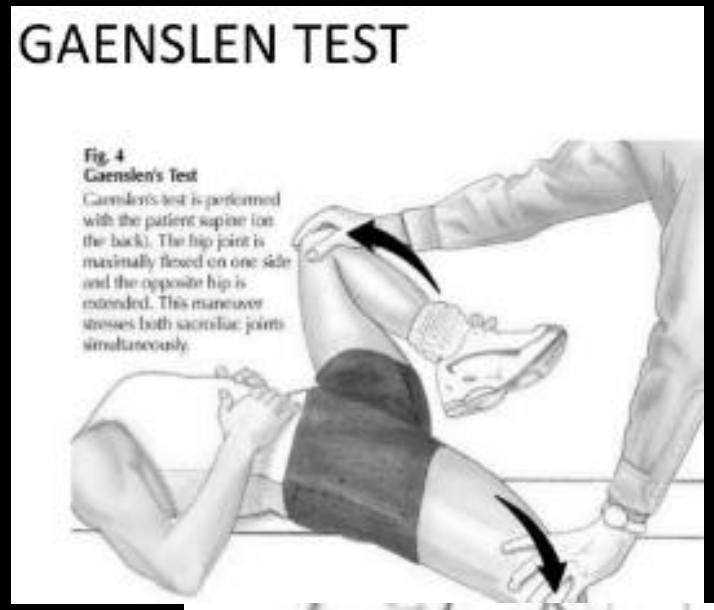




PHYSICAL EXAM:

- Gaenslen's Test: Supine, leg dropped over side of exam table while other leg drawn toward chest. Pain elicited in the SI joint on the side of the dropped leg.

- Patrick Test: FABER test should elicit contralateral SI joint tenderness

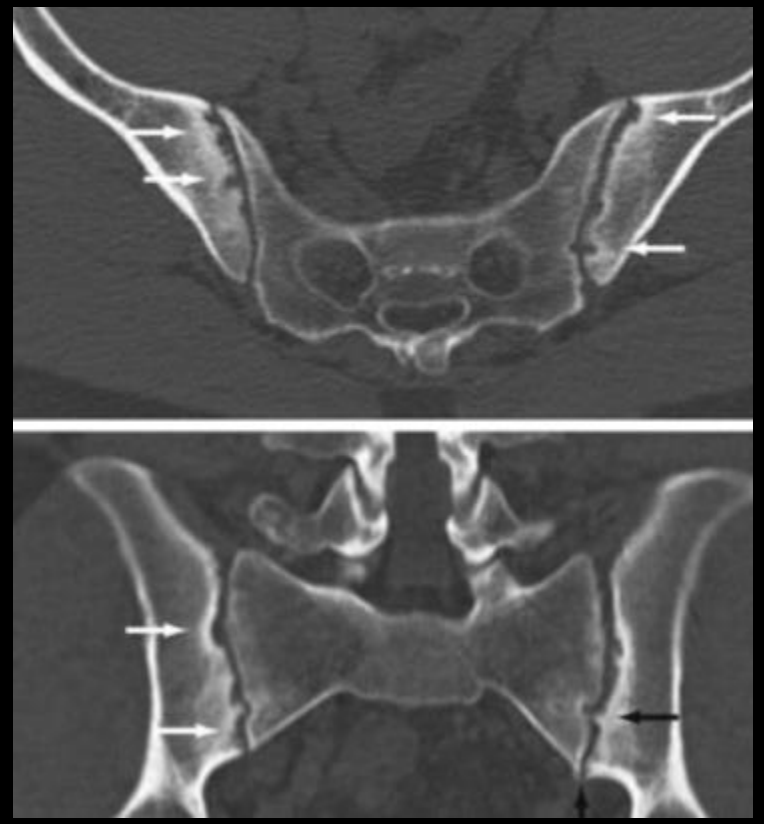


IMAGING:

- General findings:
  - Sacroiliitis seen on plain radiographs is relatively specific for SpA.
  - Syndesmophytes and changes of spondylitis in the spine are also relatively specific for SpA but are seen more in longstanding disease.
  - Other findings: Enthesitis and erosive joint disease
- Plain Radiographs:
  - In early disease, the x-rays are normal
  - Axial X-rays:
    - Sacroiliitis is the most specific finding (Takes years before it is apparent)
    - Syndesmophytes (Bridging) w/o sacroiliitis seen in 5% of cases
    - At least 50% of patients with AS develop syndesmophytes of the spine at some point in the course of the disease.

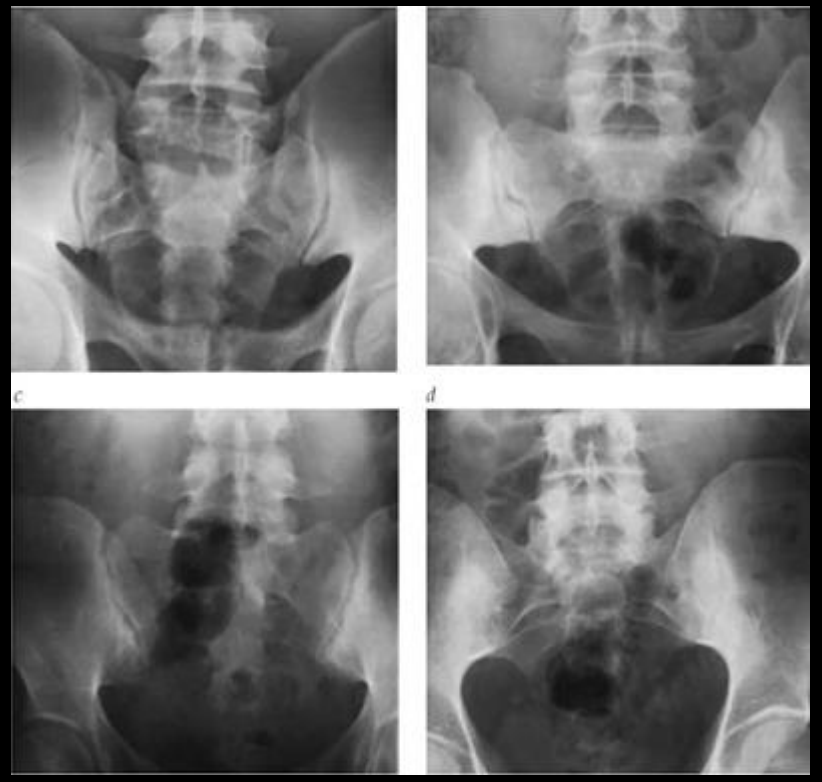
IMAGING:

- X-rays of the SI joints:
  - Views:
    - AP pelvis – evaluates inferior aspects of the SI joints.
    - **Ferguson** (AP w/ tube angled 25 to 30 degrees cephalad) enables full view of the SI joints.
    - Alternatively: Dedicated Oblique views can be done
  - Iliac Erosions: "Postage Stamp Serrations"
  - Erosions become more prominent and produce a "pseudowidening" of the SI joints.
  - Then there is fusion w/ complete obliteration of the SI joint



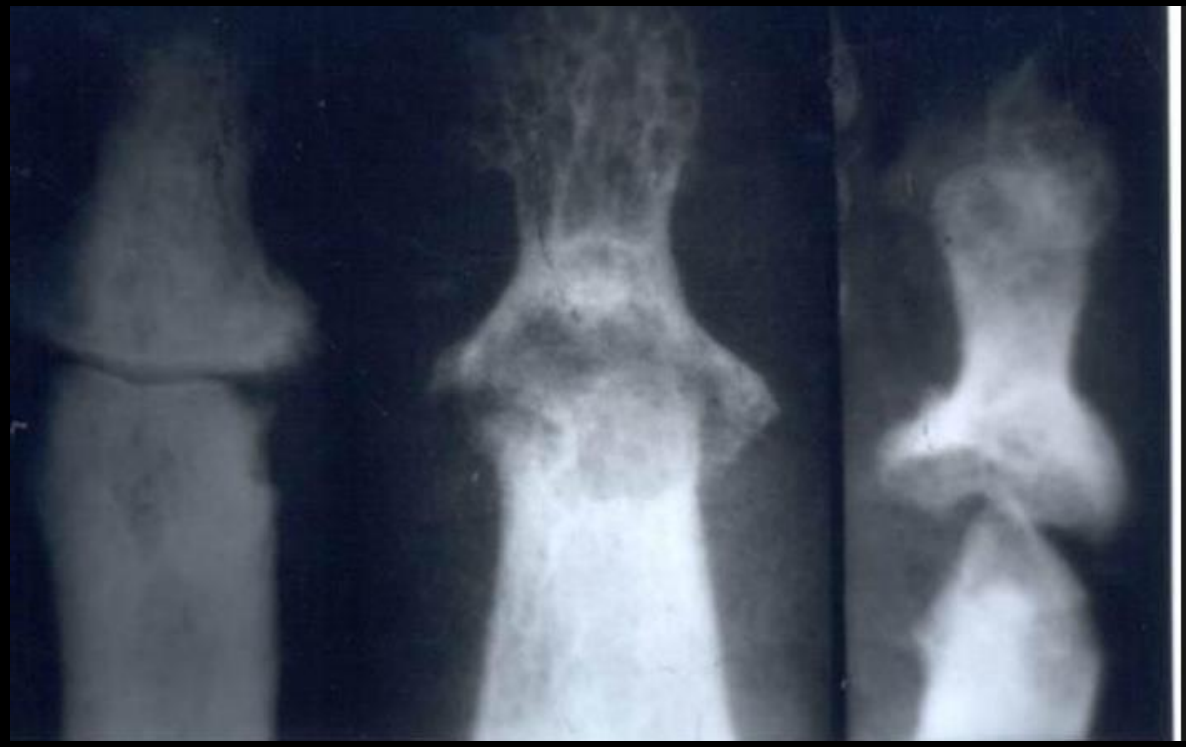
IMAGING:

- Plain radiographs continued:
  - Axial Radiographs (SI joint grading)
    - Grade 0: Normal
    - Grade 1: Suspicious changes
    - Grade 2: Minimal abnormalities, small localized areas w/ erosions or sclerosis with normal joint width
    - Grade 3: Unequivocal abnormalities, moderate to advanced sacroiliitis w/ erosions and sclerosis with widening, narrowing or partial ankyloses
    - Grade 5: Severe, total ankyloses.
  - Radiographic Sacroiliitis: Grade 2 bilaterally or Grade 3 unilaterally.
  - Non-Radiographic SpA: No definite radiographic sacroiliitis **(On X-ray)**
  - Use of x-ray for diagnosis of A.S. is a matter of debate due to disagreement among radiologist, rheumatologist reading the same film (False +/-).



IMAGING:

- Peripheral Joint & Enthesis Radiographs:
  - The most severely involved peripheral joints are the hips (Destructive)
  - In contrast, even if severely symptomatic, the knees and shoulder x-rays typically show minimal destructive changes.
  - **"Fluffy erosions"** can be seen at areas of enthesitis.
  - In PsA radiographic changes in peripheral joints are more common even early in the disease
    - Classic changes: Erosions w/ new bone formation within the same joint occurring in the same joint.
    - **Pencil-in-cup appearance**: Fluffy periostitis, bone formation and gross destruction of isolated joints
    - More knee destruction in PsA vs other SpA subtypes.



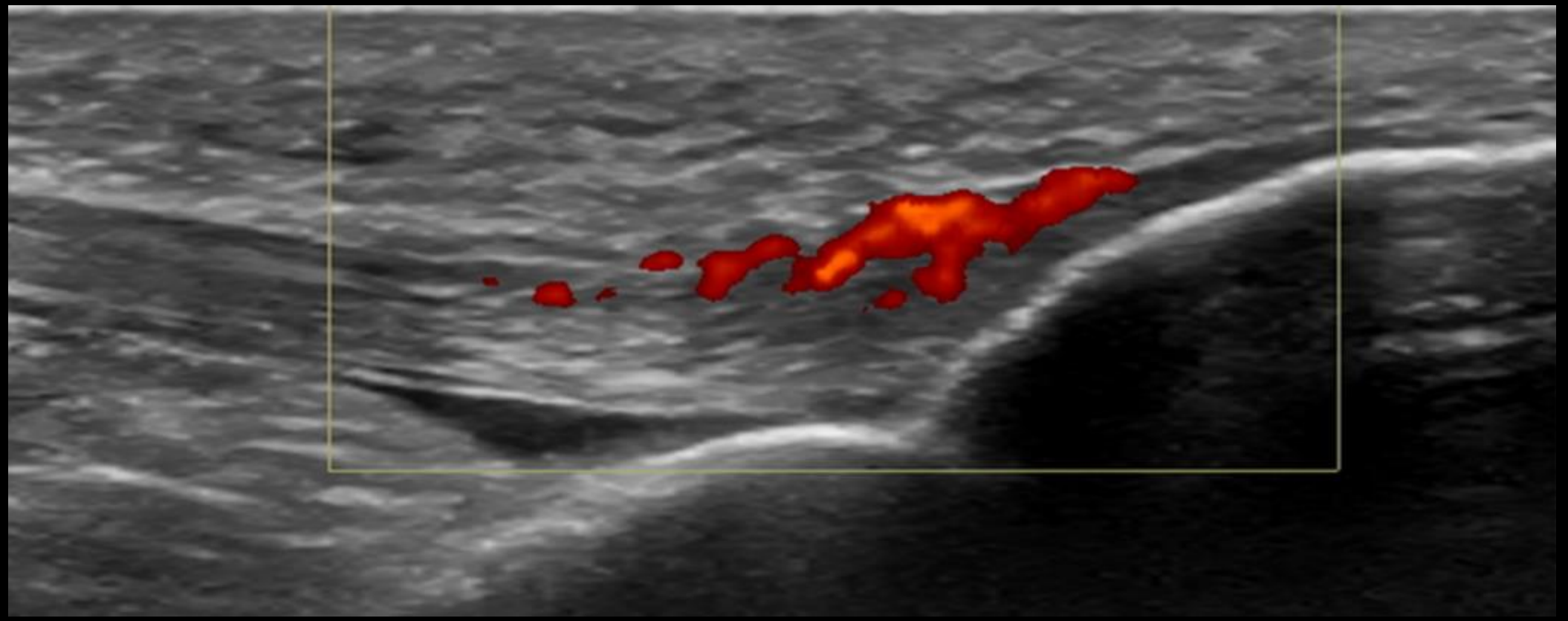
IMAGING:

- Magnetic Resonance Imaging (MRI):
  - Usually not necessary in patients with abnormalities seen on plain films and clinical s/s of SpA.
  - MRI can help establish the diagnosis of nr-axSpA.
  - MRI of the sacroiliac joints:
    - Active inflammatory lesions of the SI joints which appear as high-intensity bone marrow edema on STIR or T2 images.
    - Typical locations including the subchondral or periarticular bone marrow
    - Bone Marrow Edema can be seen in infections, malignancy, and osteitis condensans ilii.

IMAGING:

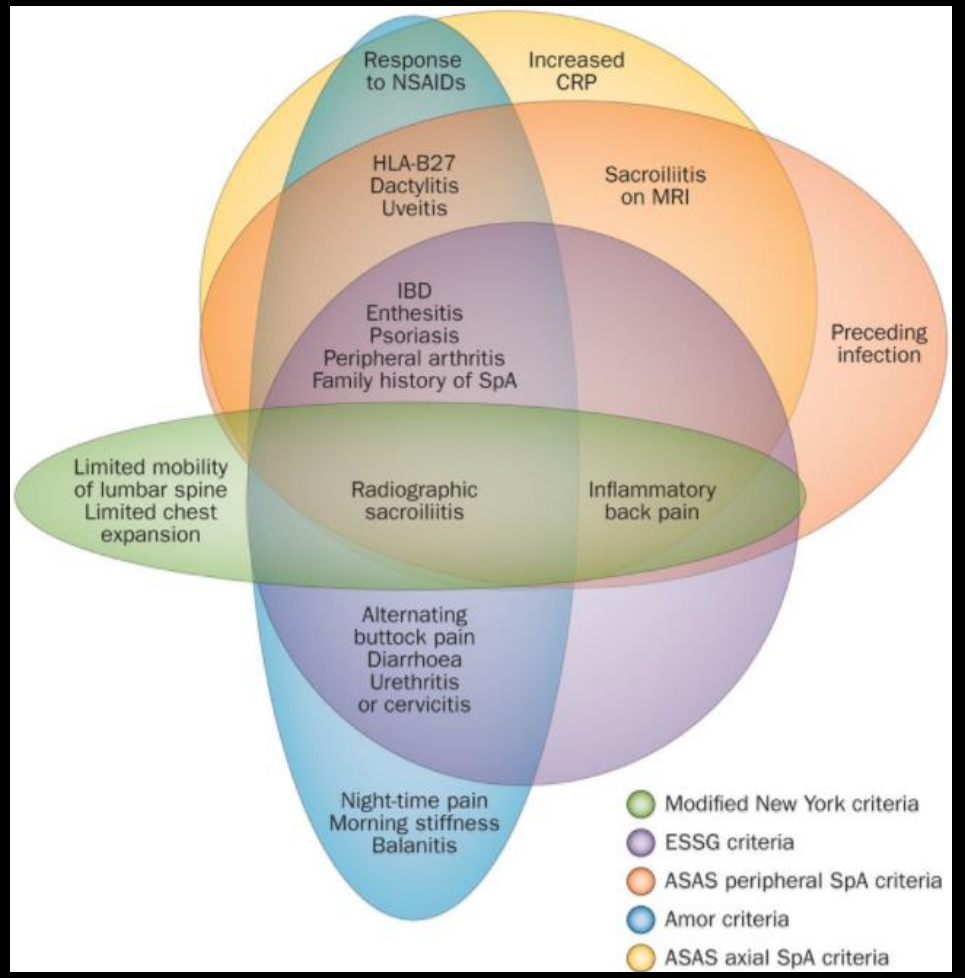
- MRI of the Spine
  - Triangular lesions seen at one or more of the four corners of the vertebrae.
  - Bone marrow edema on STIR or T2 as well as fatty deposites seen as high-intensity lesions in the T1-image.
- Ultrasound for enthesitis:
  - U/s features; Hypoechogenicity, increased tendon thickness, calcifications, enthesophytes (bone spur), and positive power doppler activity.
- CT Scan:
  - CT is more sensitive than x-rays for the detection of structural changes n the SI joint. Several disadvantages compared with MRI.
  - CT = MRI when detecting bony changes such as erosions and sclerosis
  - MRI however shows changes in subchondral bone and entheses, which CT cannot do.
  - CT has more radiation
- Scintigraphy: reveals high uptake in areas of inflammation, however too nonspecific in the diagnosis of SpA.

ULTRASOUND OF ENTHESITIS:

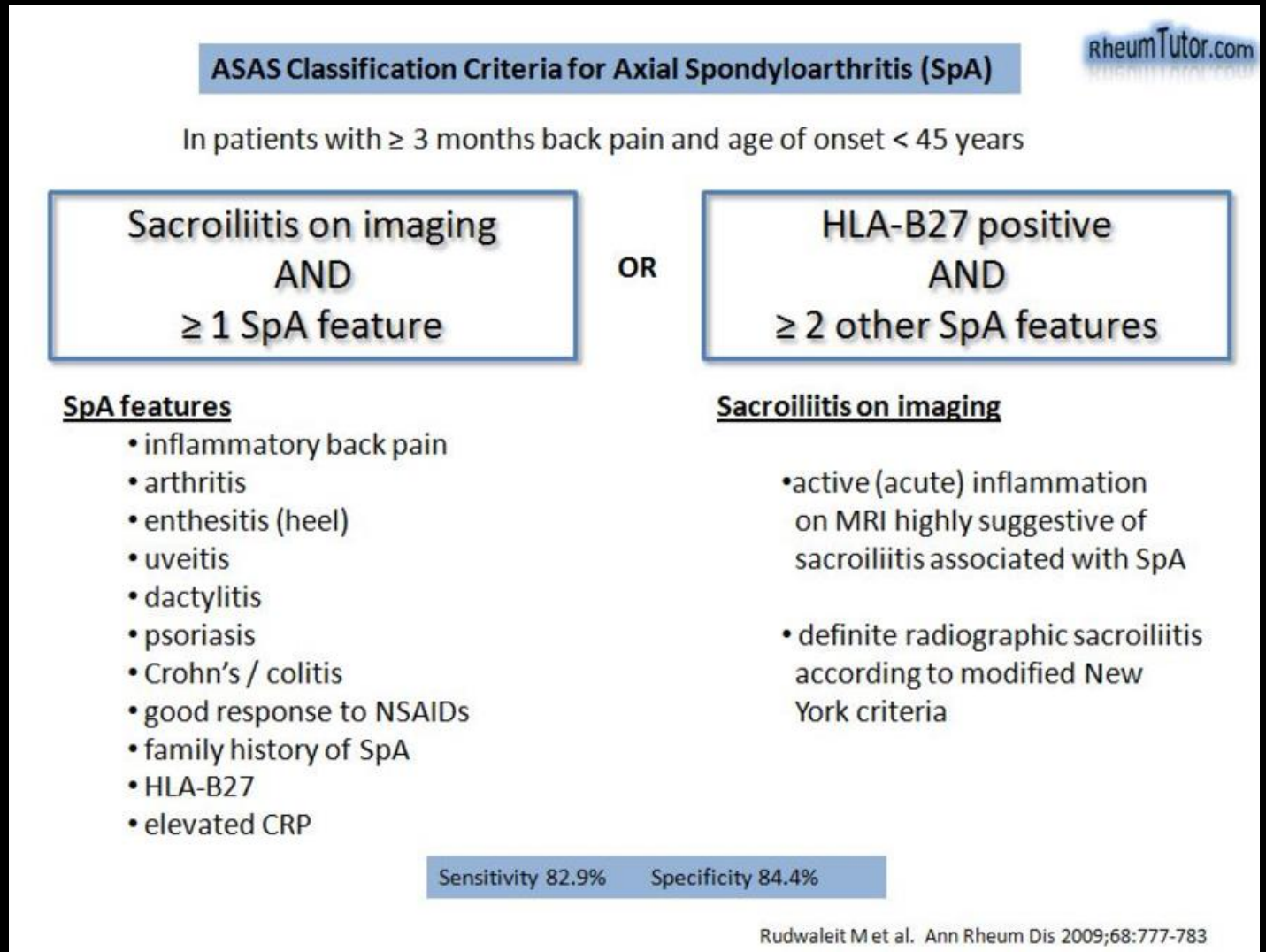


CLASSIFICATION OF SPONDYLOARTHRITIS:

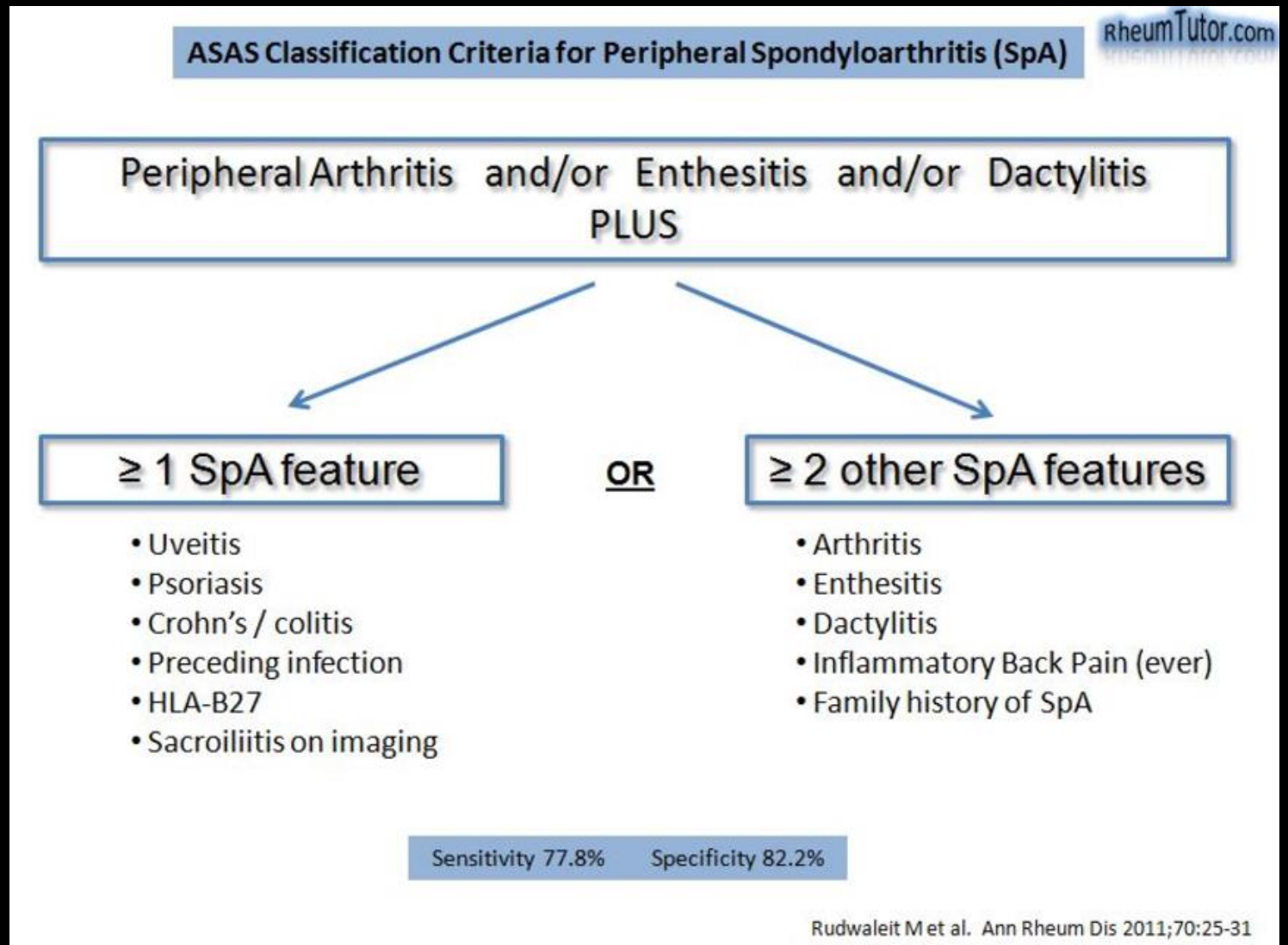
- Classification criteria does not equal diagnostic criteria
- **ASAS: Assessment of SpondyloArthritis international Society**
- Modified New York Criteria (no longer used)
- European Spondyloarthritdes Study Group (no longer used)
- Amor Criteria (no longer used)



ASAS CRITERIA FOR "AXIAL SPA":



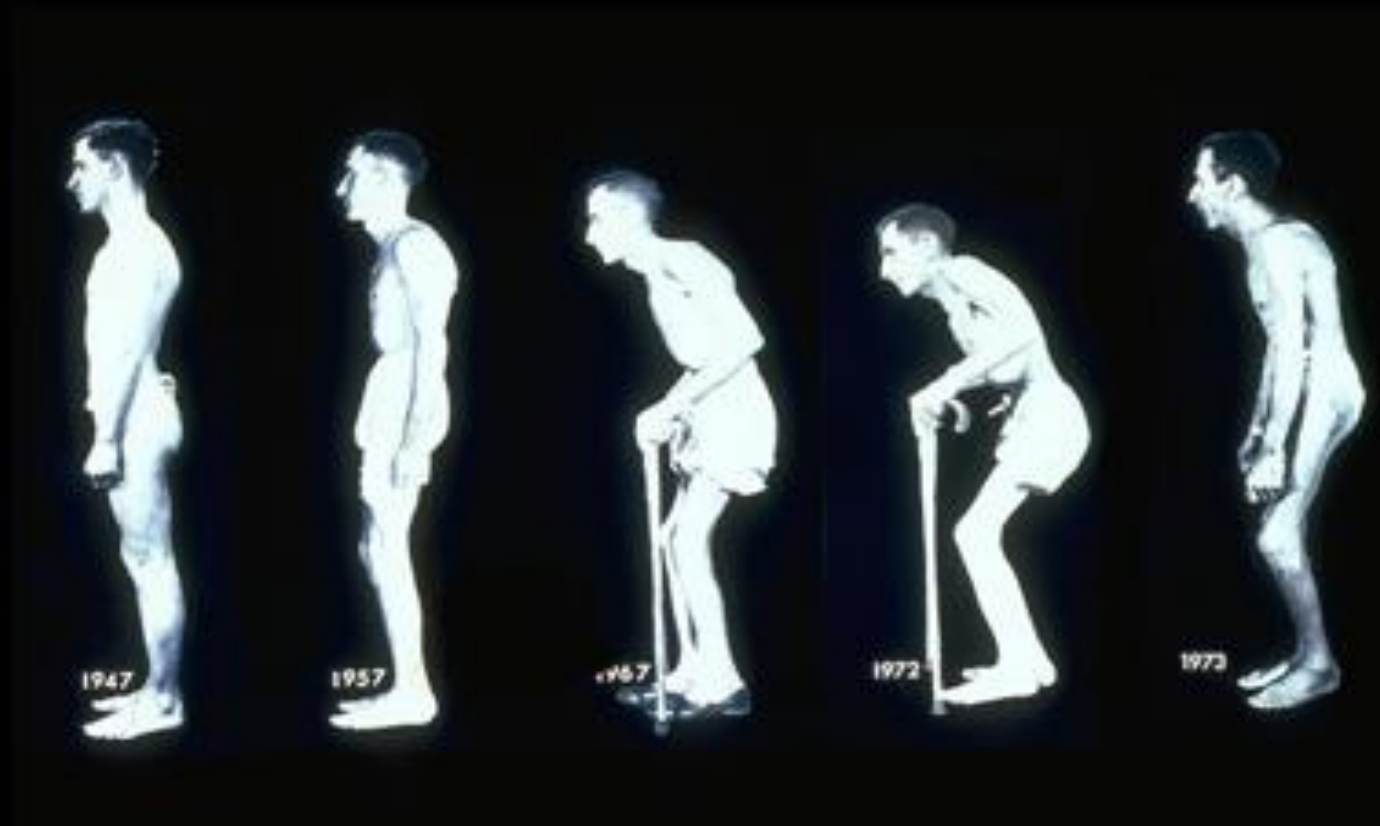
ASAS CRITERIA FOR PERIPHERAL SPA:



ASAS CLASSIFICATION CRITERIA:

- Interesting Points:
  - Prior infection is a clinical feature in peripheral but not axial SpA.
  - "Sacroiliitis on Imaging" includes MRI in order to detect early axial SpA.
  - "Non-Radiographic" Axial SpA means that changes were not present on X-ray, but are seen on MRI.
    - A "pre-radiographic" diagnosis which was missed by old criteria
  - 70% of patients will not have X-ray findings at the time of diagnosis

ANKYLOSING SPONDYLITIS



ANKYLOSING SPONDYLITIS:

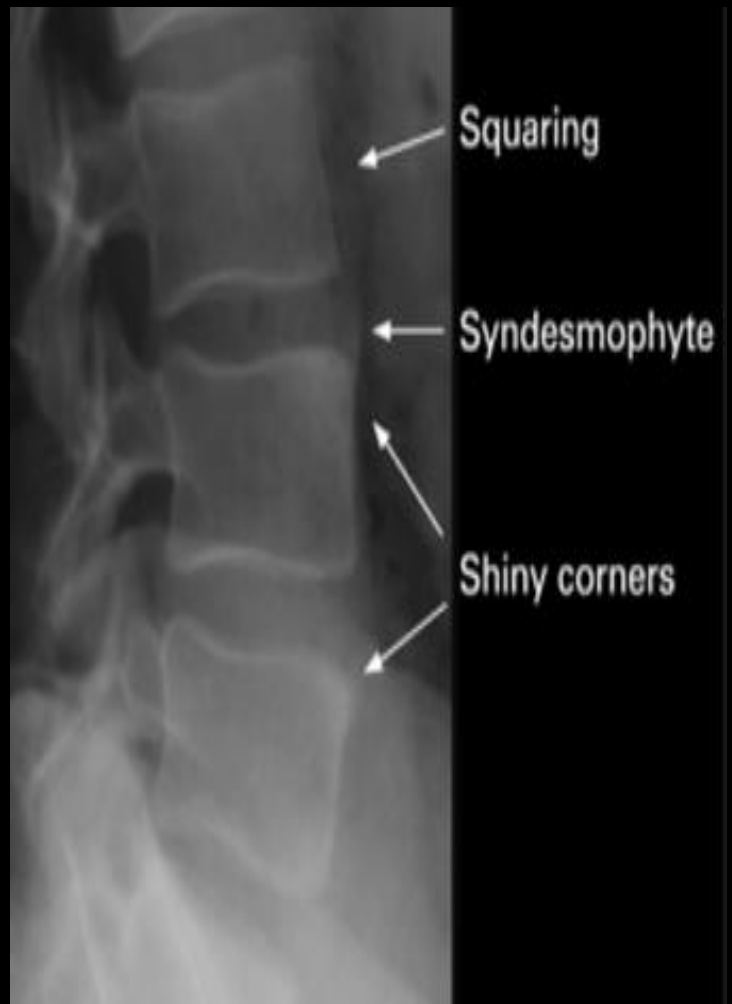
- AKA: Marie-Strumpell's or van Bechterew's disease (physician's)
- Inflammation involves the insertion of the annulus fibrosis to the corners of the vertebrae.
- Affects 0.1-1% overall, but is higher in certain Native American populations.
- Male to Female Ratio is 3:1
  - C/w PsA: 1:1
- Typically begins in the teens to 40's
- Can be associated with Ascending aortitis, aoritic regurgitation.
- Genes: HLA-B27, ERAP-1, IL-23R genetic mutations.
- Highest Ethnic risk: Scandinavians, Lowest with African Blacks and Asians.

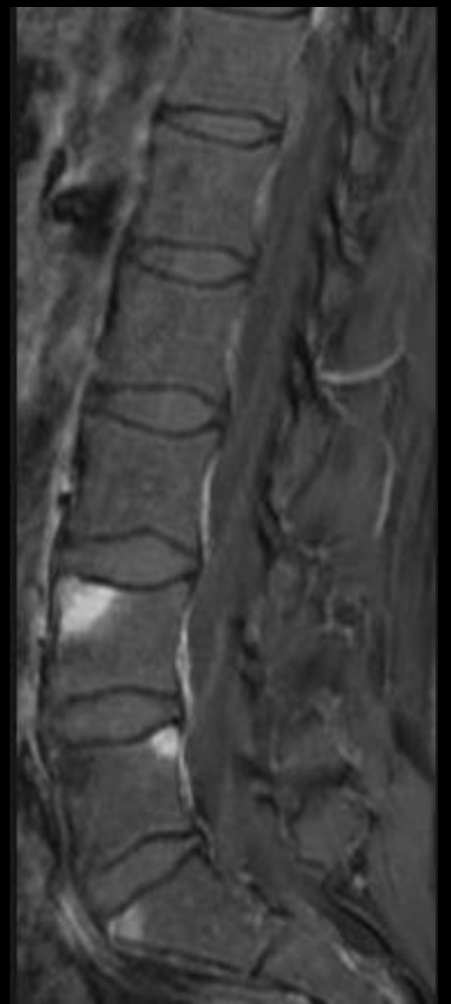
ANKYLOSING SPONDYLITIS:

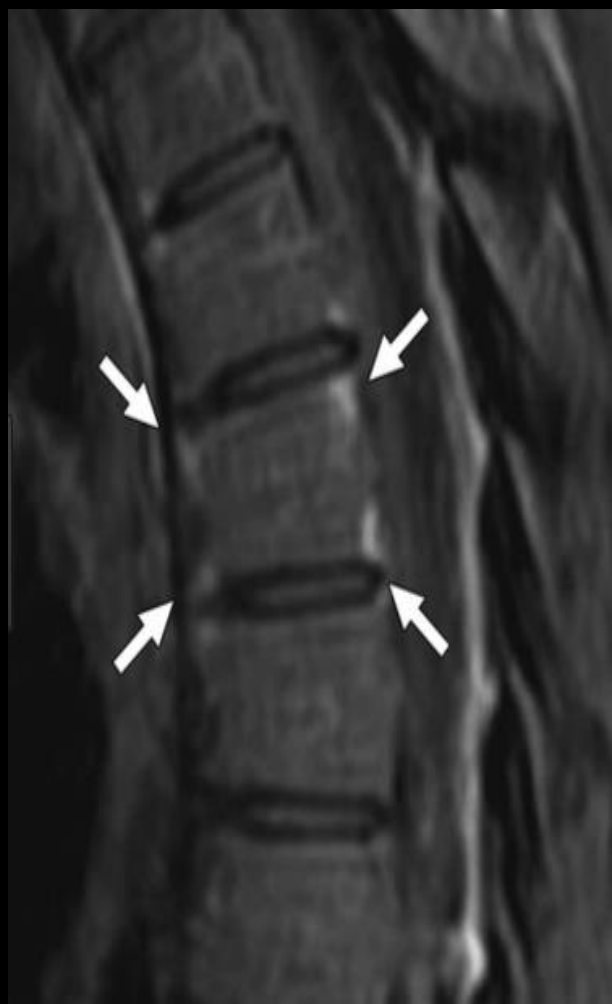
- "ANKSPOND"
  - **A**- Aortic insufficiency (3-10%), Aoritis, Conduction abnormalities, diastolic dysfunction, pericarditis, and ischemic heart disease.
  - **N**- Neurologic (C1/2 subluxation), Cauda Equina, Arachnoiditis, Spinal stenosis.
  - **K**- Kidney: Secondary amyloidosis, IgA nephropathic and chronic prostatitis.
  - **S**- Spine: Cervical fracture, spinal stenosis, and osteoporosis
  - **P**- Pulmonary: UPPER lobe fibrosis, restrictive lung changes.
  - **O**- Ocular: Anterior uveitis (25-30%)
  - **N**- Nephropathy: IgA nephropathy and nephrolithiasis
    - With associated peripheral elevated IgA.
  - **D**- Discitis or spondylodiscitis (Andersson lesions)
  - ALSO: 30-60% of pt's with A.S. have asymptomatic microscopic colitis or Crohn's-like lesions in the terminal ileum and colon. MC in those with peripheral arthritis.

ANKYLOSING SPONDYLITIS:

- X-ray finding explained:
  - **Romanus Lesions: "Shiny corners"** – inflammation of the insertion of the annulus fibrosis to the corners of the vertebral bodies.
  - Leads to **"squaring"** of the vertebrae.

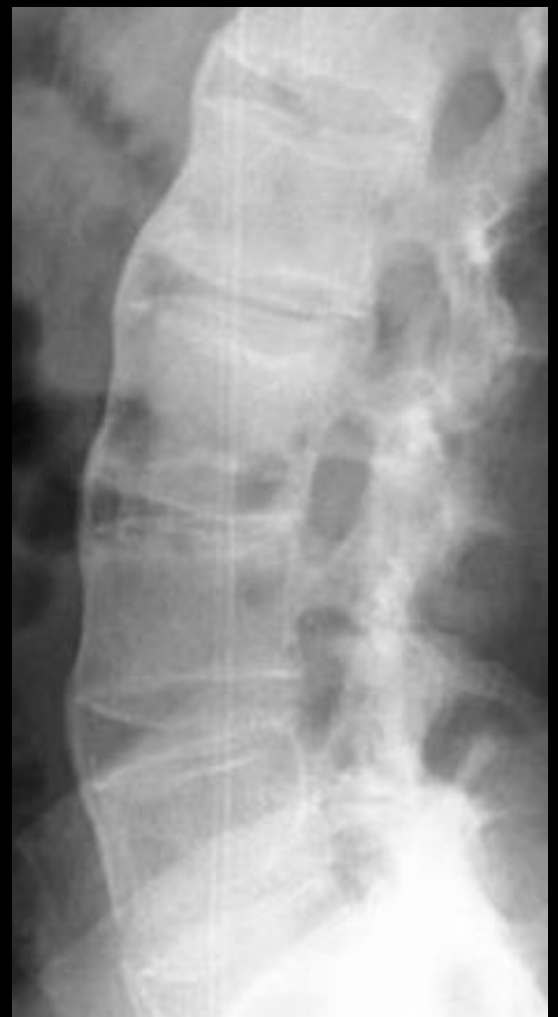


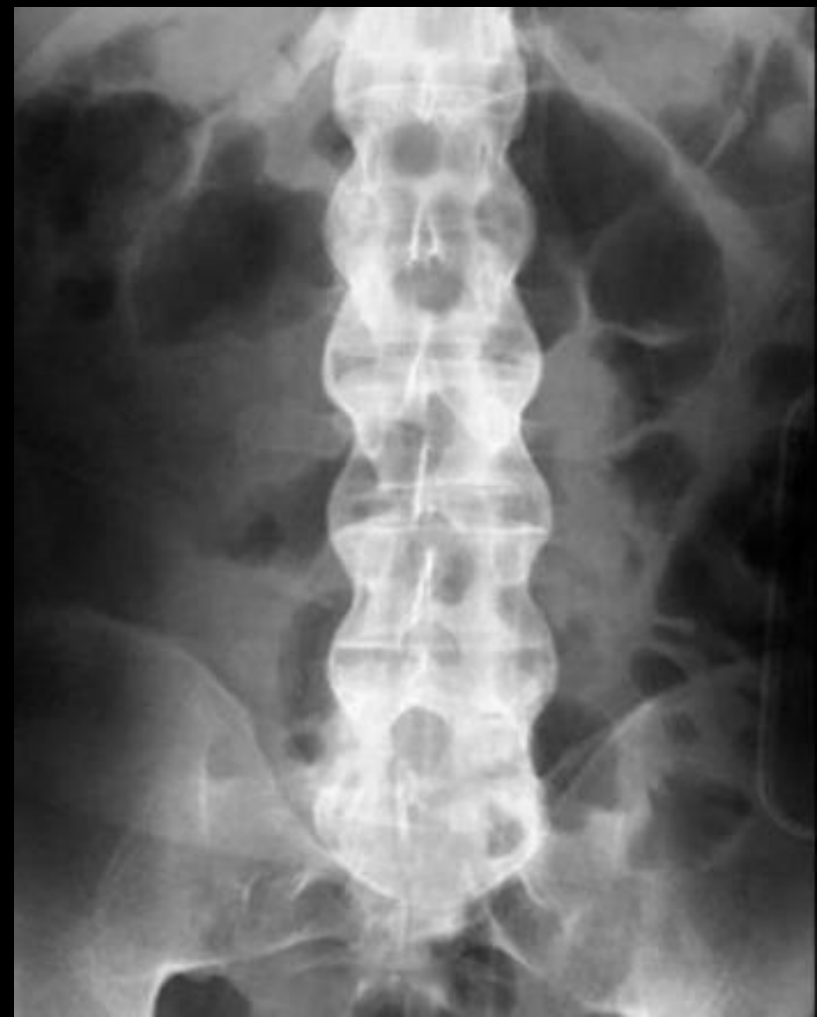




ANKYLOSING SPONDYLITIS:.

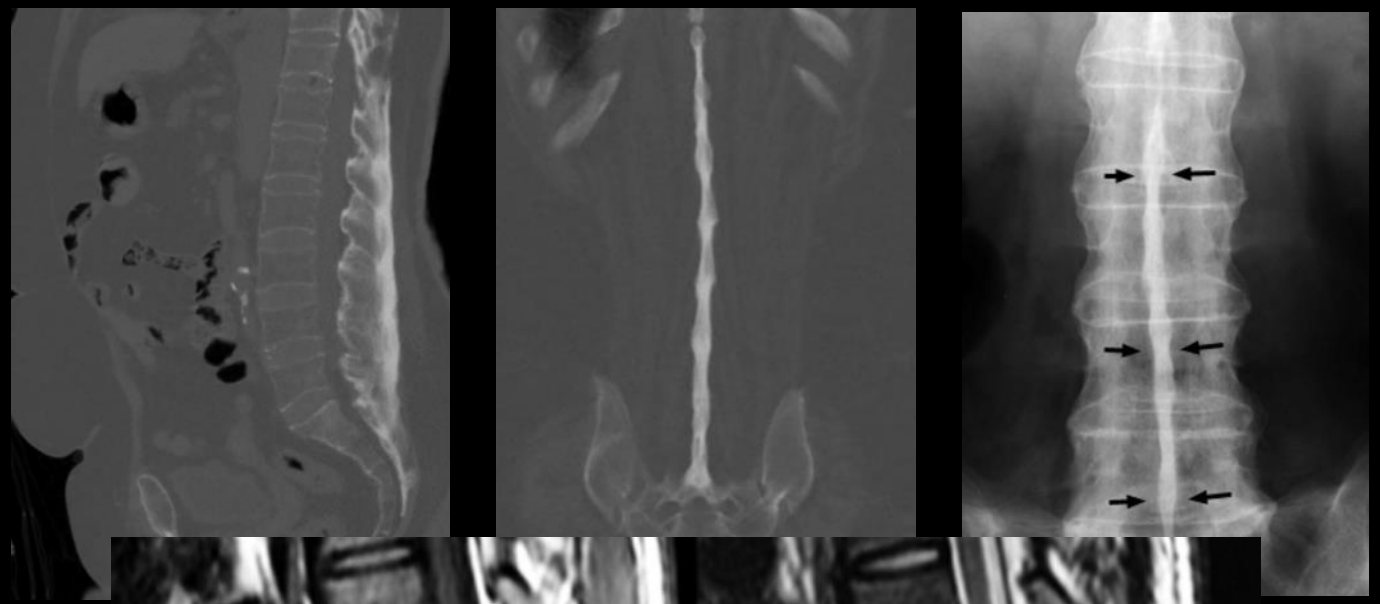
- X-ray findings explained:
  - **“Sharpy Fibers”:** Ossification of the outer layer of the annulus fibrosis.
  - Fusion of the apophyseal joints and calcification of spinal ligaments results in **Bamboo spine.**

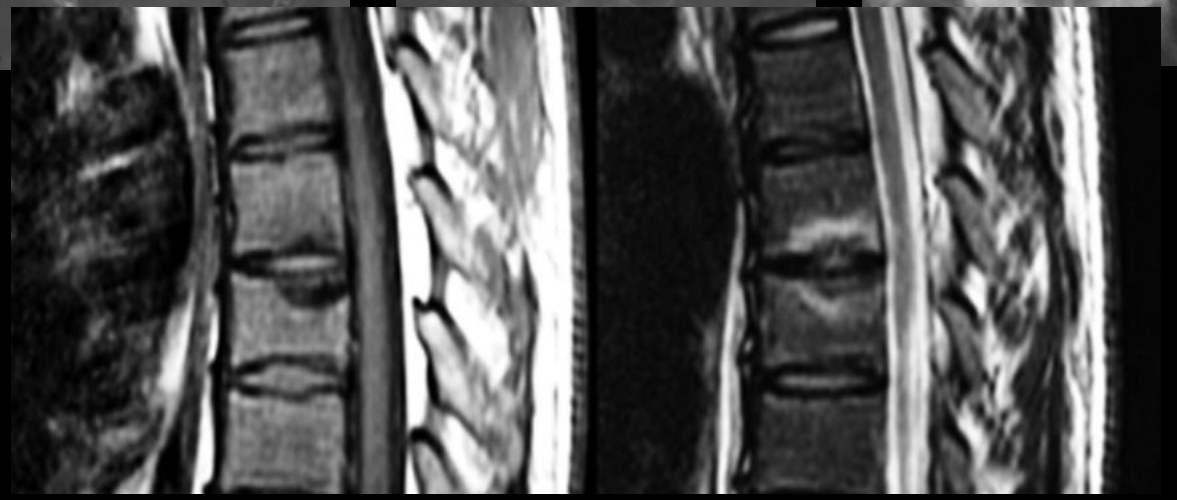




ANKYLOSING SPONDYLITIS:

- X-ray findings explained:
  - Calcification of the supraspinous ligament can end in a tapering point: **Dagger spine.**
  - Some develop destructive spondylodiscitis which is called **Andersson lesions** that mimic infection.





ANKYLOSING SPONDYLITIS CONT.

- Disease Activity Measures:
  - BASDAI (Disease Activity) Bath Ankylosing Spondylitis Disease Activity Index
  - BASMI (Spinal Mobility) ….Metrology Index
  - BASFI (Functional Index) ….Functional Index
- Early Features that predict poor prognosis:
  - Hip involvement
  - ESR >30 or persistently high CRP.
  - Poor NSAID response
  - Early syndesmophyte formation.
  - Uveitis
  - Cardiovascular disease
  - Pulmonary Fibrosis (upper lungs).

PSORIATIC ARTHRITIS:

- Quick summary:
  - HLA-Cw6 – associated with early, severe skin disease
  - HLA-B38 and B39 – associated with psoriatic arthritis
  - HLA-DR*04 – associated with worse radiographic progression.
  - HLA-B27 – associated with sacroiliitis and spondylitis.
  - HIV can cause difficult to treat skin disease (CD8 driven disease).
  - Can be associated with gout/metabolic syndrome.
  - 6 pits/nail (>60 pits) = Pathognomonic for PsA.

PSORIATIC ARTHRITIS:

- **Five Subtypes:**
  - Asymmetrical/Oligoarticular Arthritis
  - Symmetrical Polyarticular or RA-like
  - DIP-predominant w/ nail involvement
  - Arthritis Mutilans w/ telescoping digits and opera hands → → → →
  - Axial predominant, Sacroiliitis
    - Sacroiliitis tends to be more asymmetrical or one sided at least early in the disease.

PSORIATIC ARTHRITIS:

- CASPAR Criteria for PsA (3 points or more):
  - Current PsO (2)
  - History of PsO (1)
  - Family hx of PsO (1)
  - Dactylitis (1)
  - Juxta-articular bone formation (1)
  - Negative RF (1)
  - Nail Dystrophy (1)

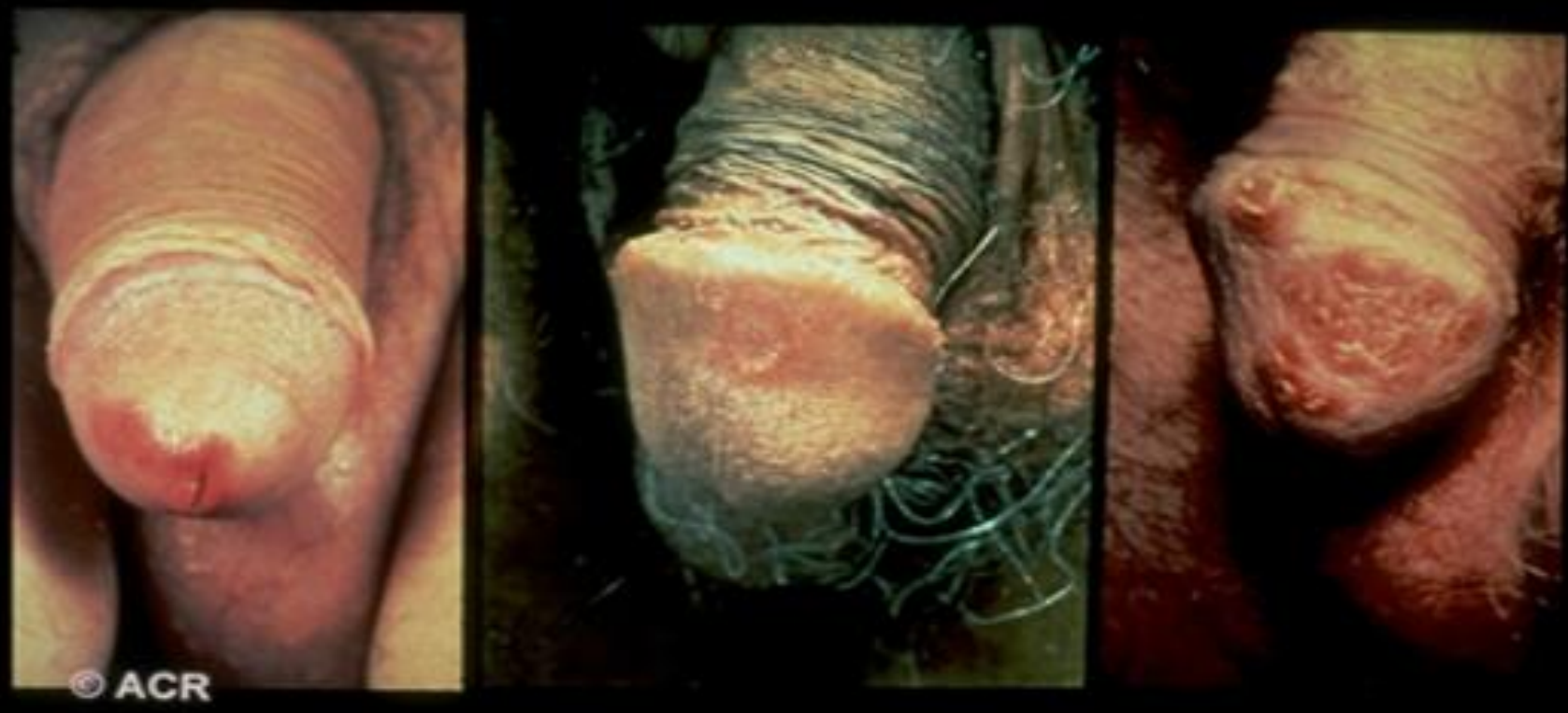
REACTIVE ARTHRITIS:

- Prior "Reiter's syndrome"
- Urethritis, conjunctivitis and arthritis first described in a young German officer with bloody dysentery. ("Can't pee, can't see, can't climb a tree")
- Genetics: 60-80% of ReA pts have HLA-B27.
- Develops within 4 weeks after bacterial infections
- Physical:
  - Keratoderma blennorhagica
  - Circinate Balanitis.
  - Oral/genital ulcers, conjunctivitis.

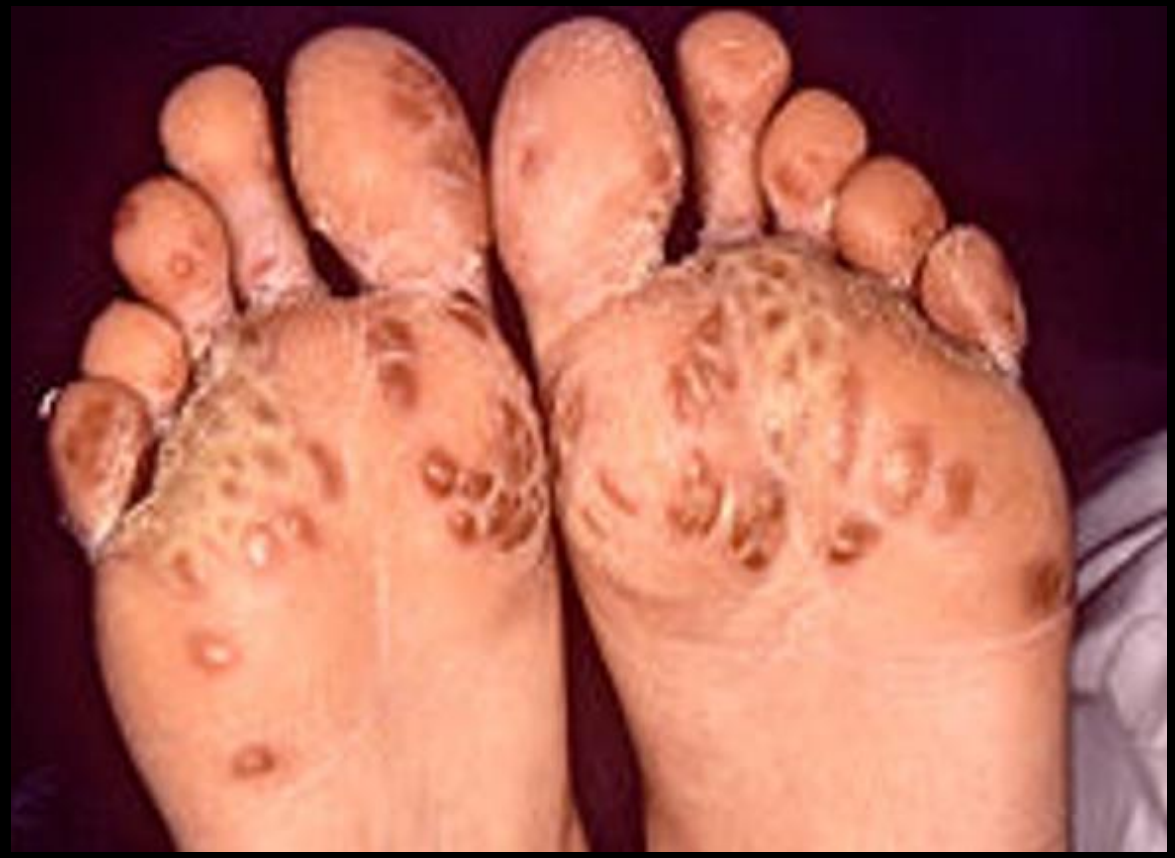
REACTIVE ARTHRITIS:

- Causes:
  - GU: Chlamydia Trachomatis, Neisseria Gonorrhea and Ureaplasma Urealyticum
  - GI: Shigella, Campylobacter, Yersinia, Salmonella, C. Diff, Vibrio
  - Others:
    - Chlamydia Pneumonia
    - Borellia Burgdorferi
    - Streptococcus
    - Hepatitis C
    - Giardia Lamblia
    - Mycoplasma

REACTIVE ARTHRITIS:



REACTIVE ARTRITIS: KERATODERMA BLENORHAGICUM:



ENTEROPATHIC ARTHRITIS:

- Associated with IBD (UC/CD), Microscopic colitis and collagenous colitis
- Also associated with Whipple's disease, Celiac disease and also
- Intestinal bypass arthritis.
- 5/100,000, M:F 1:1

- Clinically: abdominal pain, bloody diarrhea.
- Can have an axial form AND a peripheral arthritis form.

ENTEROPATHIC ARTHRITIS:

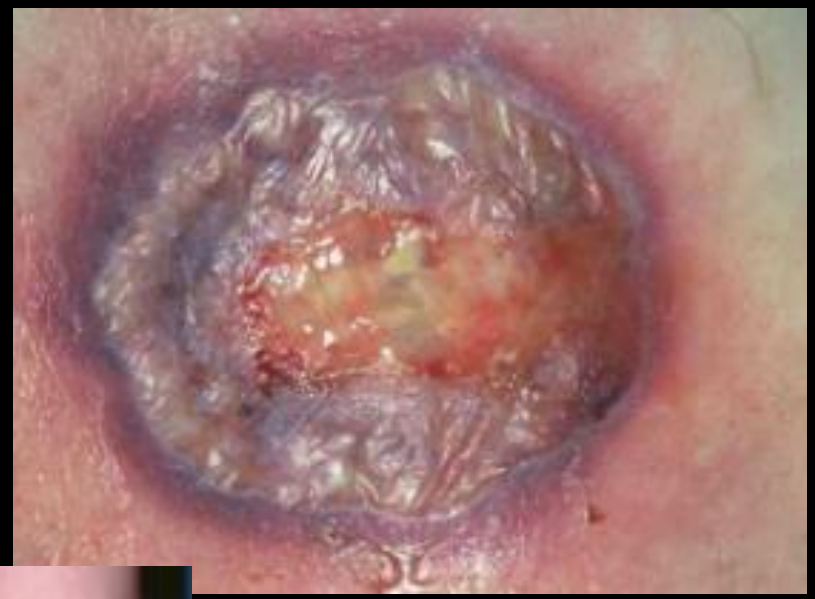
- Why?
  - Associations:
    - 60% of asymptomatic A.S. and ReA patients have microscopic evidence Crohn's disease.
    - 6-10% of A.S/ReA develop symptoms over time.
    - 10% of IBD develop SpA over time.
  - There are 400 m2 surface area of gut
  - Lymphoid tissue, Payer's patches, lamina propria, intraepithelial T-cells help exclude harmful antigens from entering systemic circulation.
  - The Human Microbiome is 10x the number of human cells.
  - IBD interrupts the normal barrier:
    - Antigen can either deposit directly into the joints OR.
    - Cause systemic immune response resulting in immune complex formation which then deposit in the joints and other tissues (i.e. IgA-nephropathy).

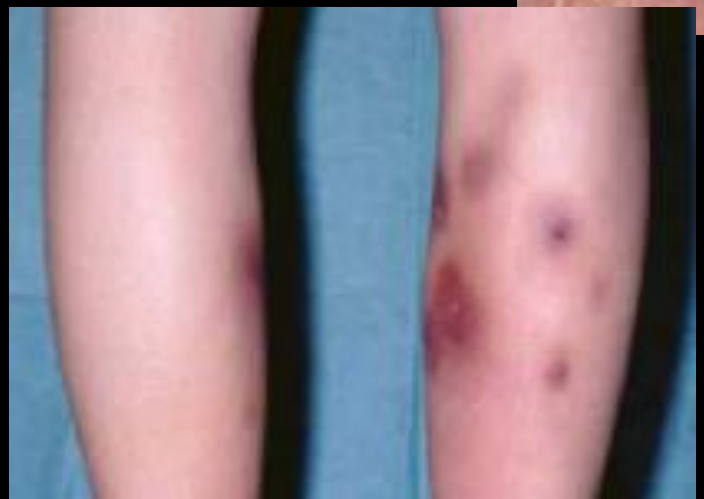
ENTEROPATHIC ARTHRITIS:

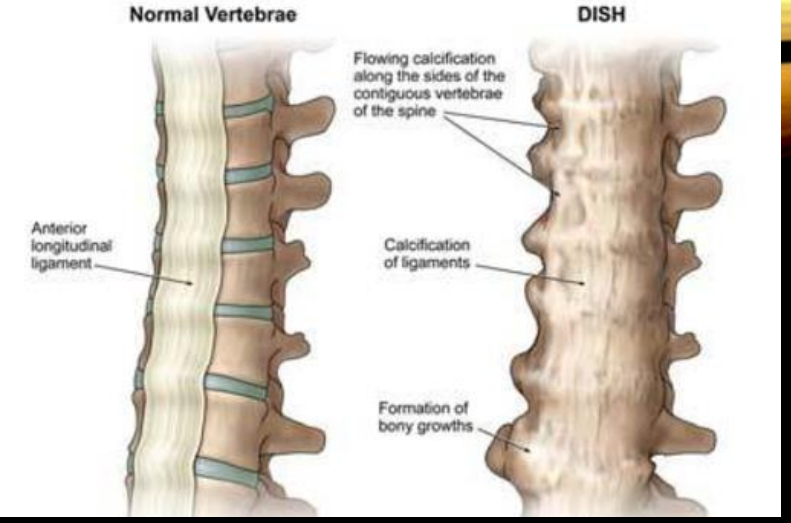
- Peripheral Type 1: Arthritis parallels IBD
  - More common
  - No real association with radiographic changes/deformities
  - Associated with HLA-B27, B35, DRB1*0103
- Peripheral Type 2: Arthritis is independent of IBD
  - Less common
  - More chronic in nature leading to radiographic changes/deformities
  - Associated with HLA-B44
- Axial disease does NOT however correlate with IBD activity.
- X-rays are similar to A.S. with thin marginal syndesmophytes.

ENTEROPATHIC ARTHRITIS:

- "PAIN"
  - **P**- Pyoderma Gangrenosum (2-5%)
  - **A**- Apthous Stomatitis (more common in UC)
  - **I**- Inflammatory Eye Disease (more common in Crohn's)
  - **N**- Nodosum (erythema) – up to 15%

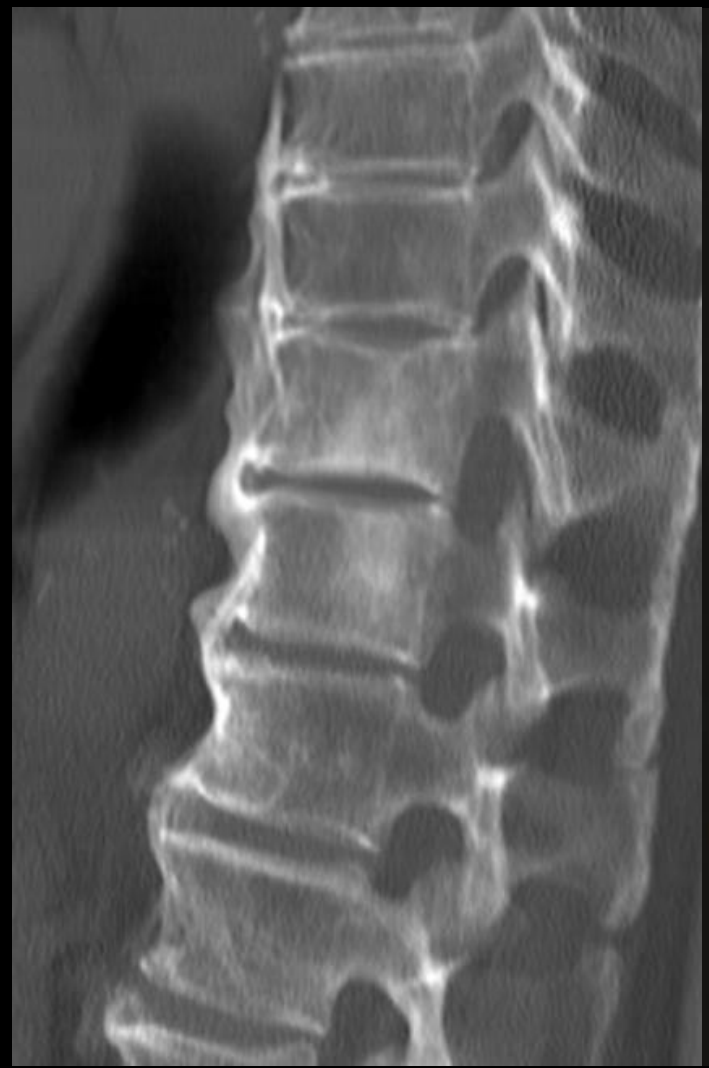






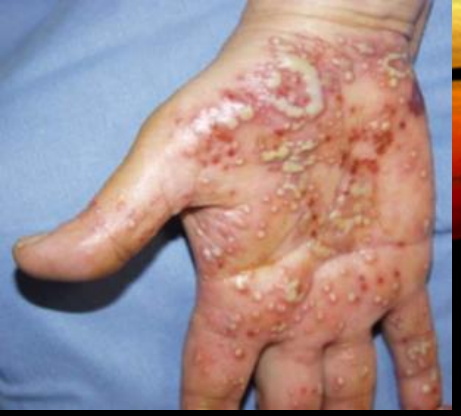
OTHER RELATED ODDITIES:

- D.I.S.H.
  - Diffuse Idiopathic Skeletal Hyperostosis
  - AKA **Forestier's Disease**
  - Risks: Obese, Diabetes, >50 yrs of age.
  - Characteristics: Flowing hyperostosis, calcification of the anterior longitudinal ligament of at least FOUR contiguous vertebrae with non-vertebral whiskering.
  - Interesting tid-bit: Has a predisposition to the right side of the vertebrae opposite the side fo the heart/aorta.
  - Not associated with A.S. or HLA-B27.



OTHER RELATED ODDITIES:

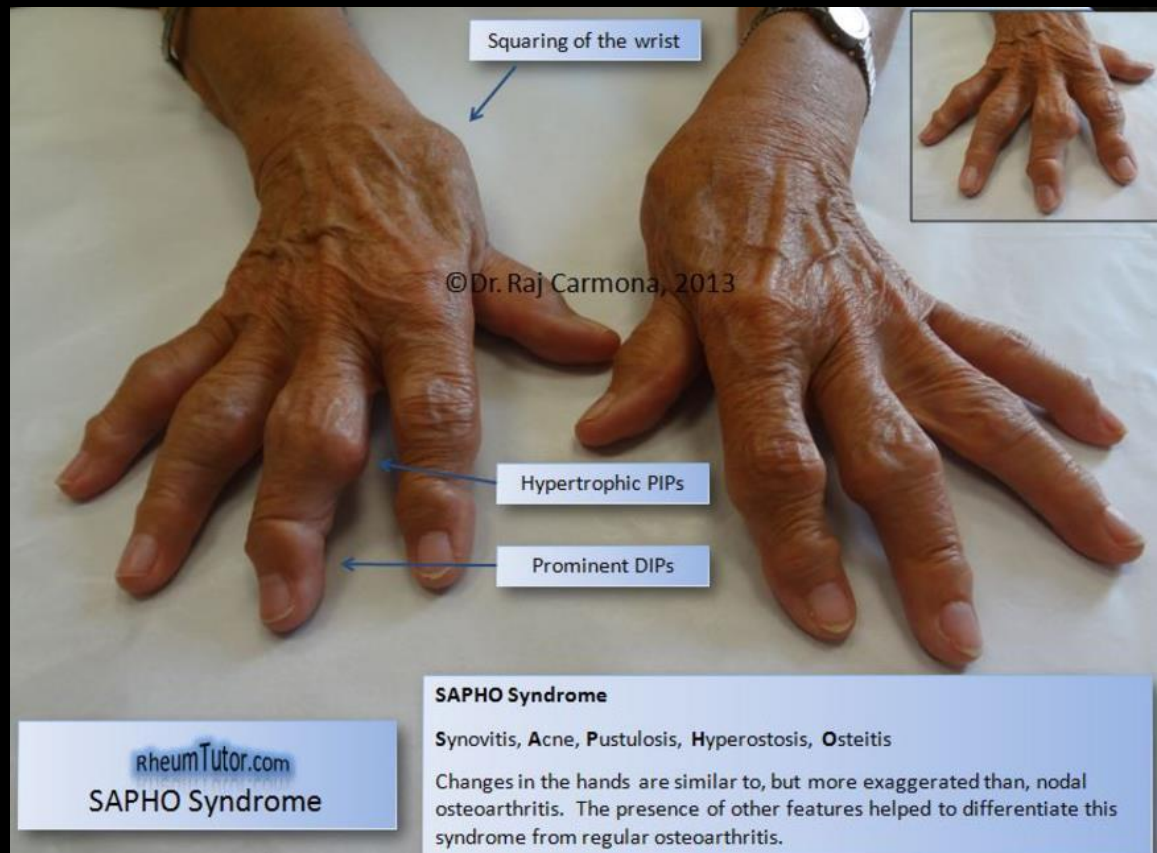
- PPP Syndrome: Pancreatic, Panniculitis and Polyarthritis Syndrome.
  - Occurs in those with pancreatitis or Pancreatic Acinar Cell Carcinoma
  - Due to release of trypsin, lipase and amylase causing fat necrosis.
  - PANCREAS:
    - P – Pancreatitis
    - A – Arthritis – Ankle/knees – synovial fluid is creamy due to lipid droplets +sudan black.
    - N – Nodules – Lobular panniculitis with fat necrosis +/- fasciitis
    - C – Cancer – of the pancreas
    - R – Radiographic osteolytic bone lesions from bone marrow necrosis.
    - **E – Eosinophilia – Arthritis + Nodules + Eosinophils = Schmidt's triad.**
    - A – Amylase, lipase, trypsin are elevated – causes the fat necrosis.
    - S – Serositis – pleural/pericardial with fever.



OTHER RELATED ODDITIES:

- SAPHO syndrome: Anterior chest pain and Skin disease associations.
  - Synovitis – Large/Oligoarticular disease, Axial and SI joints.
  - Acne – Cystic acne conglobata, acne fulminans.
  - Pustulosis – Pustular Psoriasis, palmoplantar pustulosis or H.S.
  - Hyperostosis – Anterior chest/Sternoclavicular hyperostosis
  - Osteitis – Symphysis pubis, Sacroiliitis, Spondylodiscitis, anterior chest wall, vertebral sclerosis

  - HLA-B27 + in 13% of cases.
  - Proprionibacterium is possible causative agent.



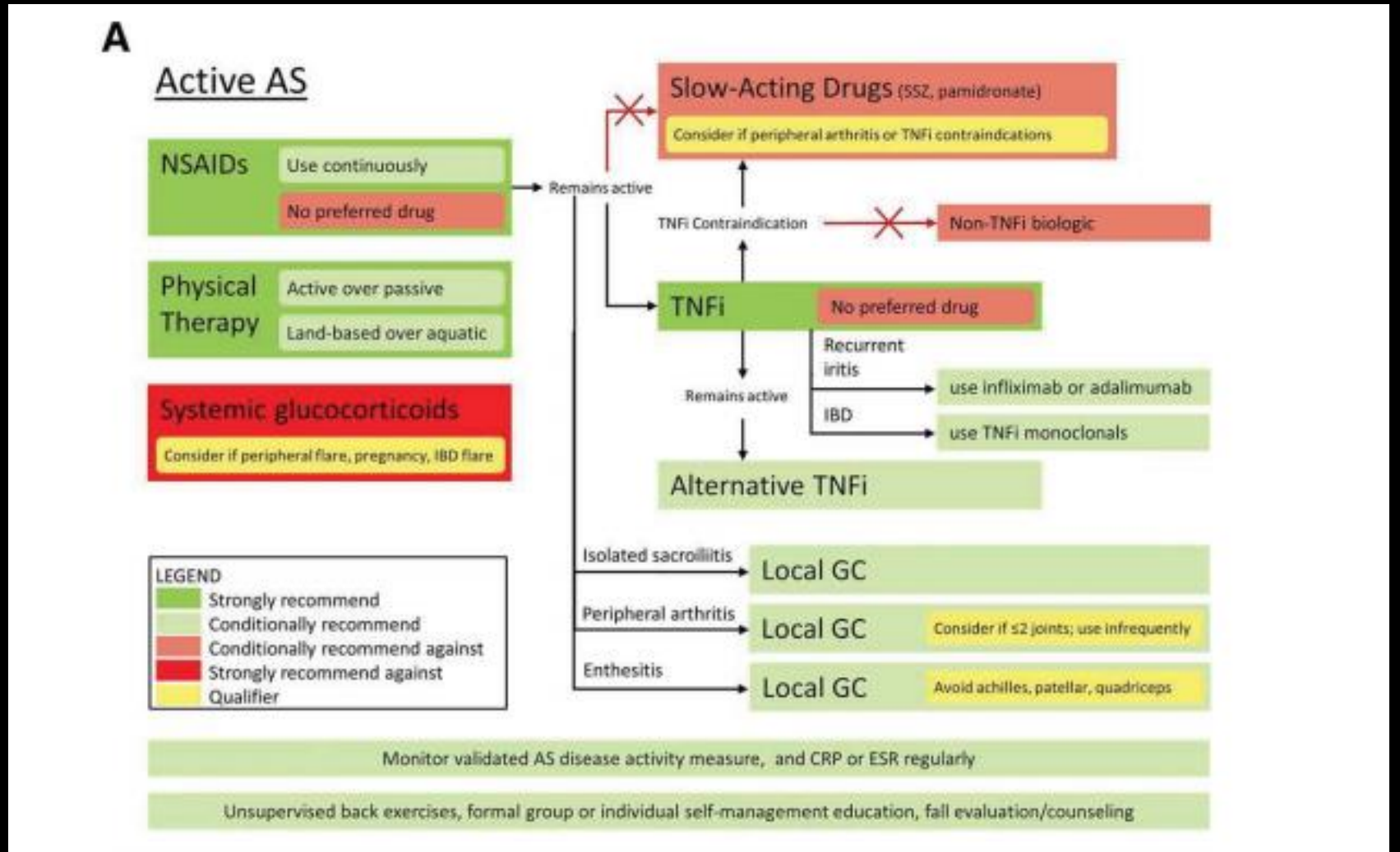
SPA TREATMENTS:

- NSAIDs
- Anti-TNF's agents: Etanercept, Adalimumab, Golimumab, Cirtulizumab, and Infliximab.
- Anti-IL17 agents: Secukinumab (AS, PsA), Ixekizumab (PsA)
- Anti-IL12/23 agents: Ustekinumab (PsA)
- PDE-4 inhibitors: Apremilast – only for PsA/PsO. can be used in combination
- Jak inhibitors: Toficitinib recently approved in PsA/PsO.
- CTLA-4: Abatacept – Now approved for PsA and PsO.
- Non-Biologic DMARDS are not effective for axial SpA (e.g., MTX)
- Other biologics such as Tocilizumab and Rituxan are not effective.
- Steroids have no value in the treatment of MSK aspect of A.S.
- Local Steroid injections are useful in the treatment of enthesopathies, synovitis and sacroiliitis.

TREATMENT NUANCES:

- Anti-TNFs, while a treatment for PsA/PsO can flare PsO.
- Anti-IL17 agents, while treatment of A.S. and PsA can actually flare IBD.
- Etanercept ineffective for treatment of iritis and IBD.
- Anti-12/23 medications (Ustekinumab) inhibit TWO interleukins by inhibiting a common subunit: The p40 subunit!

SPARTAN/GRAPPA RECOMMENDATIONS:



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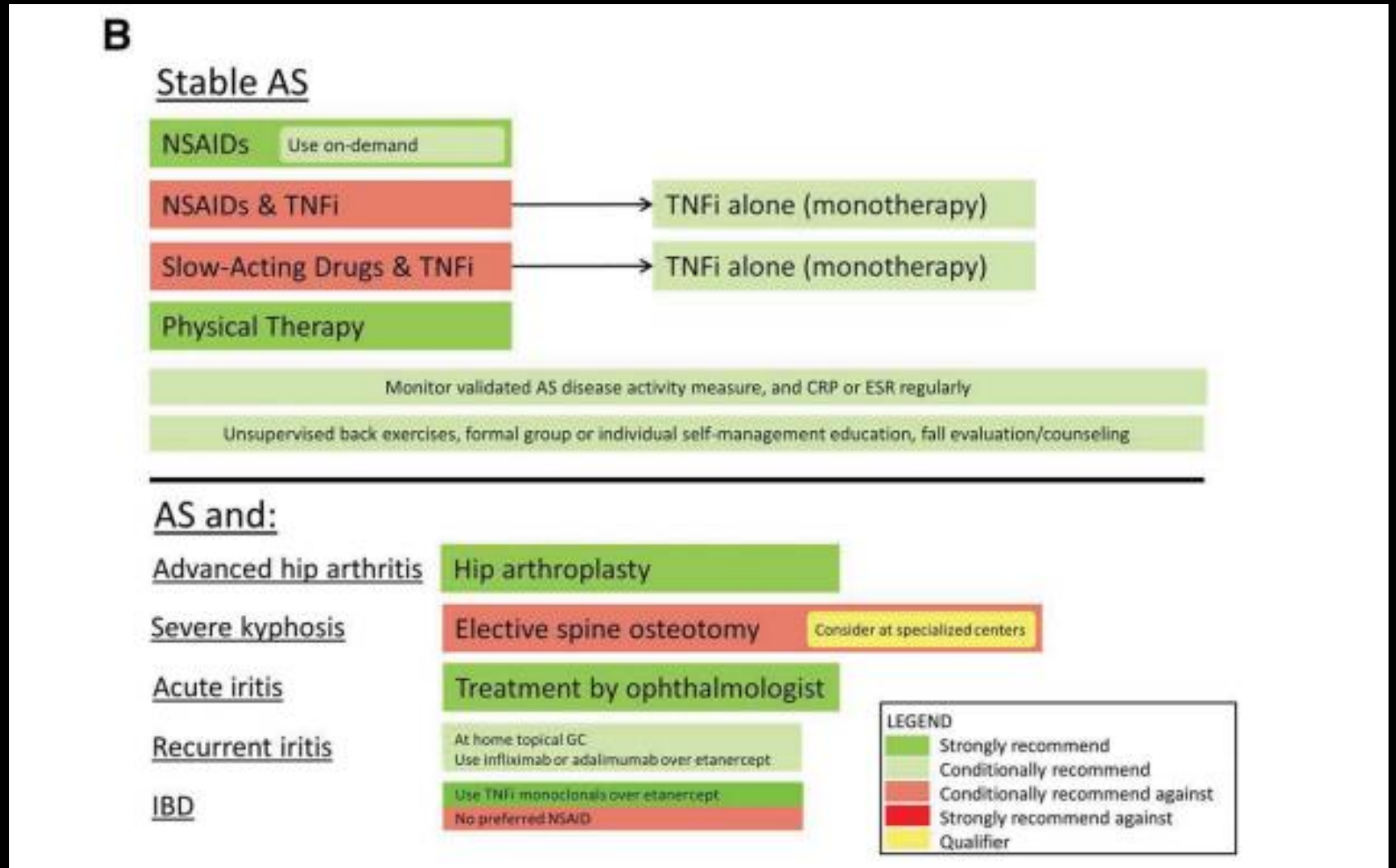

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