ANKYLOSING SPONDYLITIS: Etiopathogenesis, Involvement Pattern & Clinical Spectrum

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Chronic Inflammatory autoimmune disease that mainly affects axial skeleton; peripheral joints and extra-articular structures

Sacroiliac joints (SIJs) and their adjacent soft tissues, such as tendons and ligaments causing severe, chronic SPINE pain.....Spine fusion.

Ankylosing spondylitis (Marie-Strumpell disease, Bechterew's disease)

- Named for the French neurologist Pierre Marie (1853-1940) and the German neurologist whose full name was Ernst Adolf Gustav Gottfried von Strumpell (1853-1925)

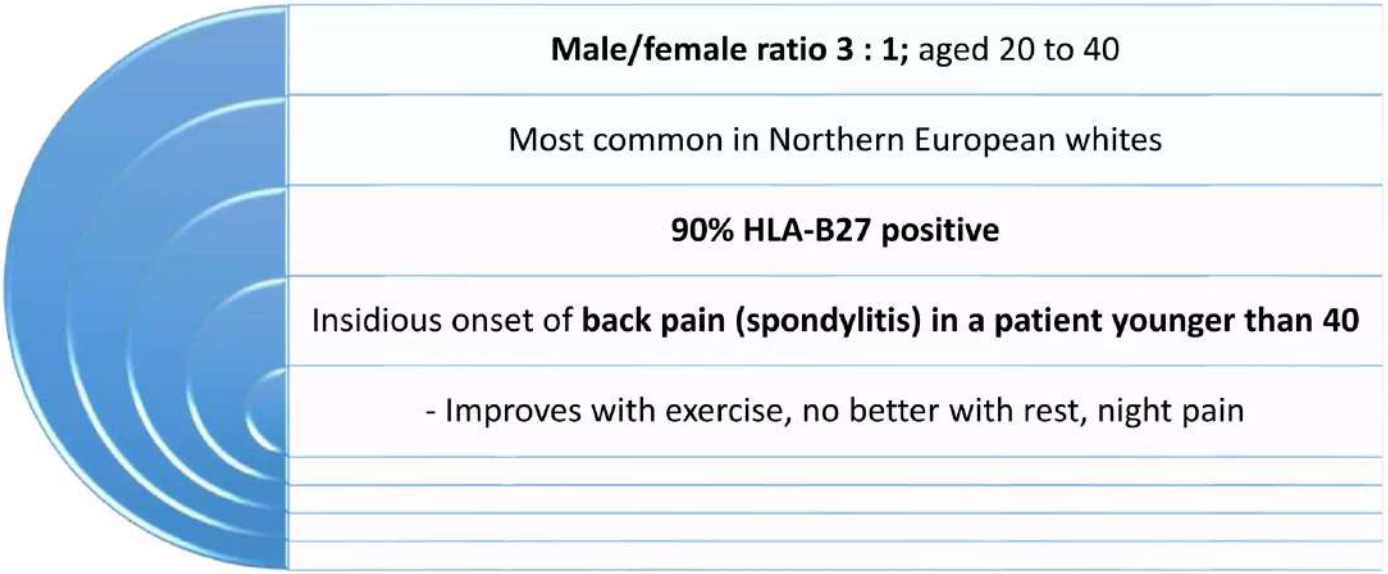
Seronegative spondarthropathies are closely asso. with the presence of HLAB27 on chromosome 6;

Frequently used as a confirmatory test in patients suspected of having ankylosing spondylitis or Reiter's disease, but it should not be regarded as a specific test because it is positive in about 8% of normal western Europeans.

- Etiology unknown; association with HLA-B27.

Ankylosing spondylitis,
Reiter's disease &
psoriatic arthritis

characteristically test negative for rheumatoid factor; they have been grouped together as the 'seronegative spondarthopathies'

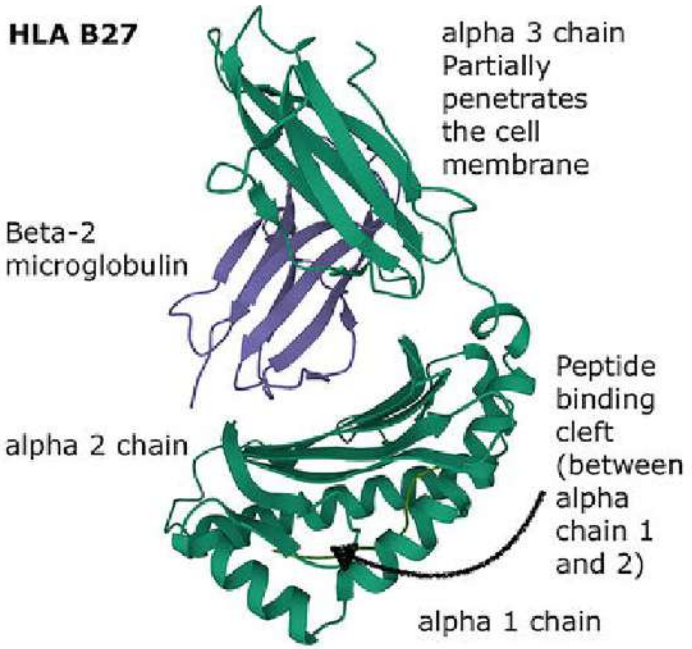


Genetic background

- Higher concordance between monozygotic twins (63%) than between dizygotic twins (23%).
- (MHC) class I allele HLA-B27 ..... 90%–95% of AS patients are HLA-B27 (MORE WITH FIRST DEGREE RELATIVES) positive, while 1%–2% of HLA-B27-positive populations develop AS.
- HLA-B27-positive patients showed a significantly lower average onset age and a higher prevalence of acute anterior uveitis than did HLA-B27-negative patients.
- HLA-B60 is related to HLA-B27-negative AS and increases the disease susceptibility by 3–6-fold.

HLA

- HLA-B2705 (Caucasian populations)
- HLA-B2704 (Chinese populations)
- HLA-B2702 (Mediterranean populations)
- Additional β2m reduces HLA-B27 misfolding and promotes arthritis and spondylitis, implying that B27 misfolding is associated with intestinal inflammation.



Features distinguish HLA B27 from most other HLA class I molecules.

1. Glutanine is substituted for methanine located at the 45 position.
2. Unpaired cysteine (Cys67) . This feature enables formation of homodimers and oligomers of free heavy chains which are thought to contribute to development of AS .
3. Lys residue at position 70 that increases reactivity of the cysteine at position 67

- WHICH AMONG THE FOLLOWING IS A/W HLA-B27-negative AS?

a) HLA-B7,

b) HLA-B16,

c) HLA-B35,

d) HLA-B38

e) HLA-B39

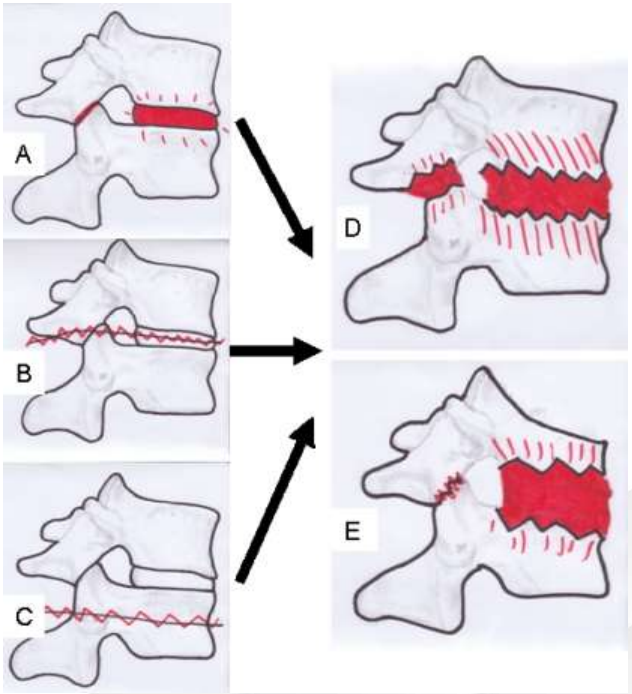
2 basic lesions:

synovitis of diarthrodial jts &

inflammation at the fibro-osseous junctions of syndesmotic jts & tendons.

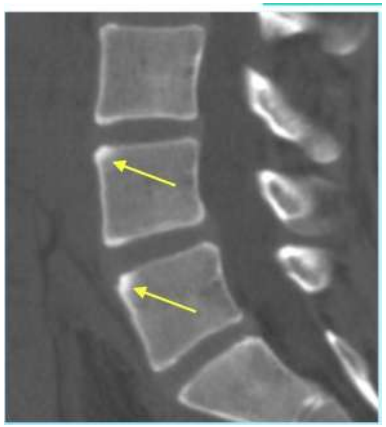
The preferential involvement of the insertion of tendons & ligaments

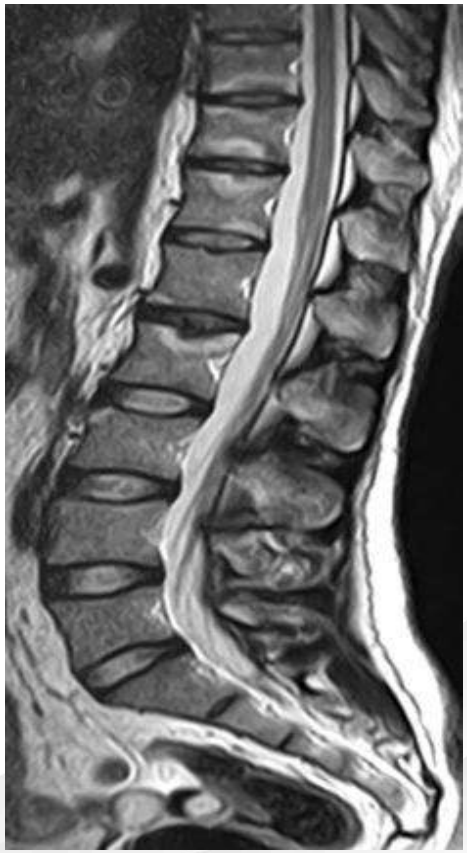
(the entheses) has resulted in the unwieldy term *enthesopathy*.



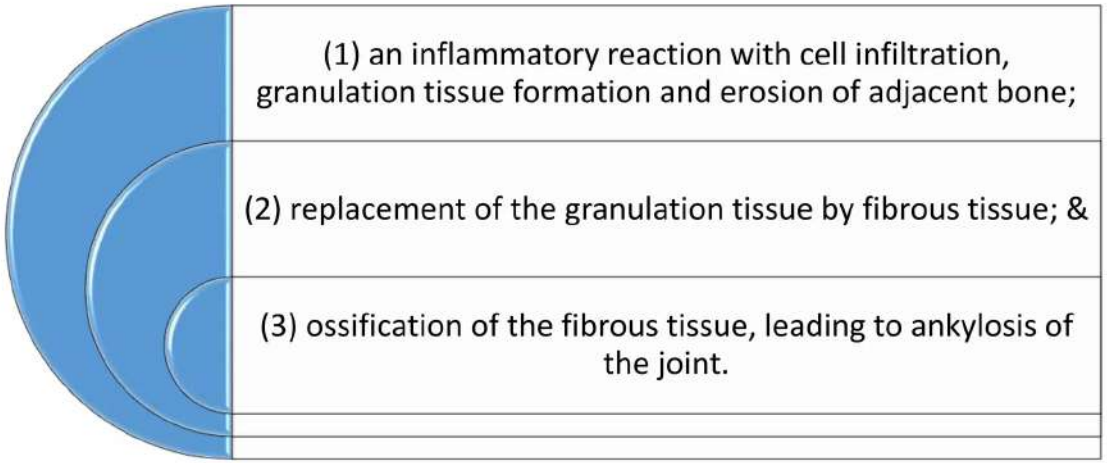
- A 35 year-old male with known ankylosing spondylitis presented with a history of chronic low back pain. Which of the following MR features is shown on this sagittal T2 sequence?

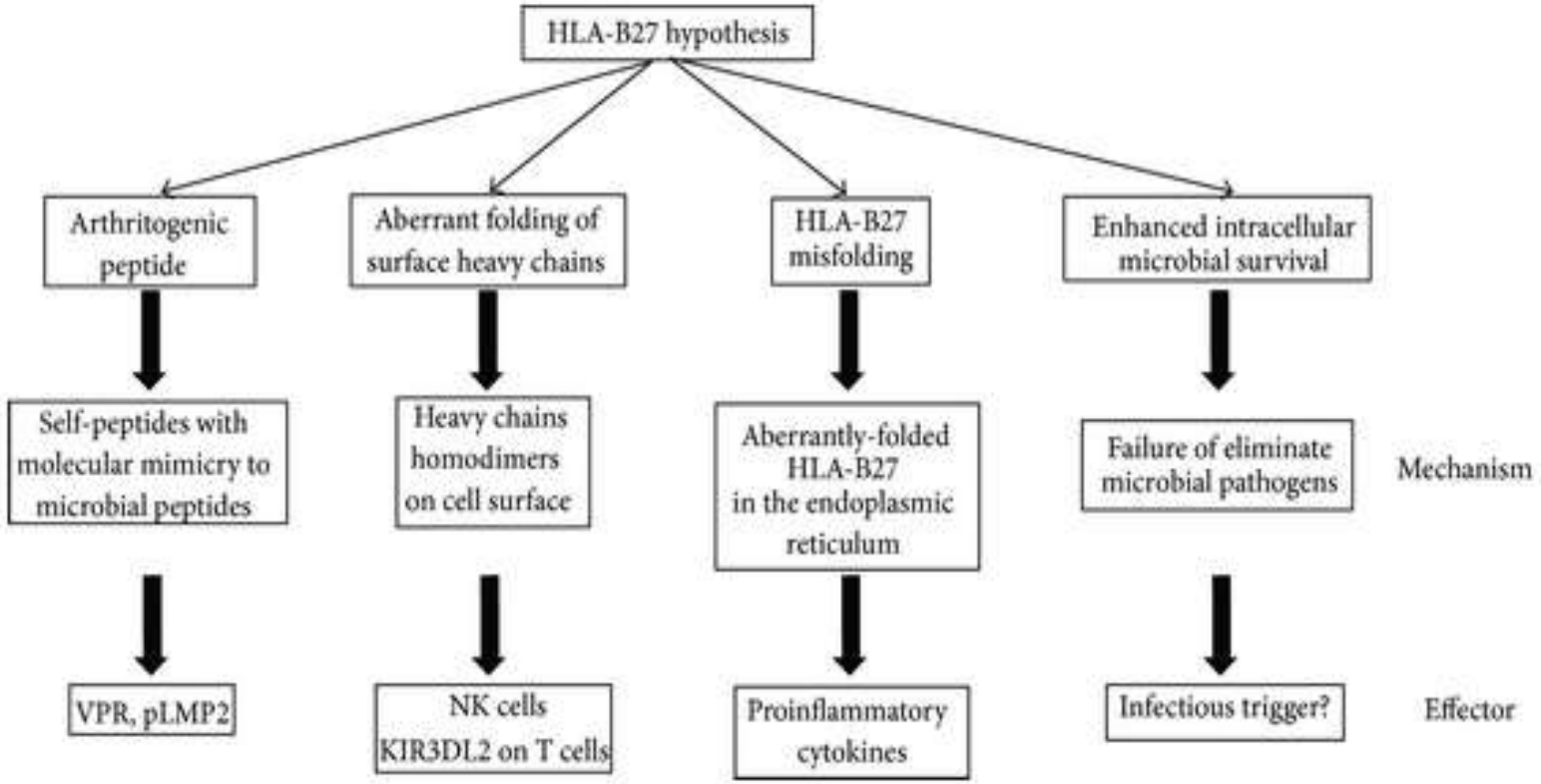
1. Andersson and Romanus lesions
2. Andersson lesions
3. Bamboo spine
4. Infectious spondylodiscitis
5. Romanus lesions





PATHOLOGICAL CHANGES



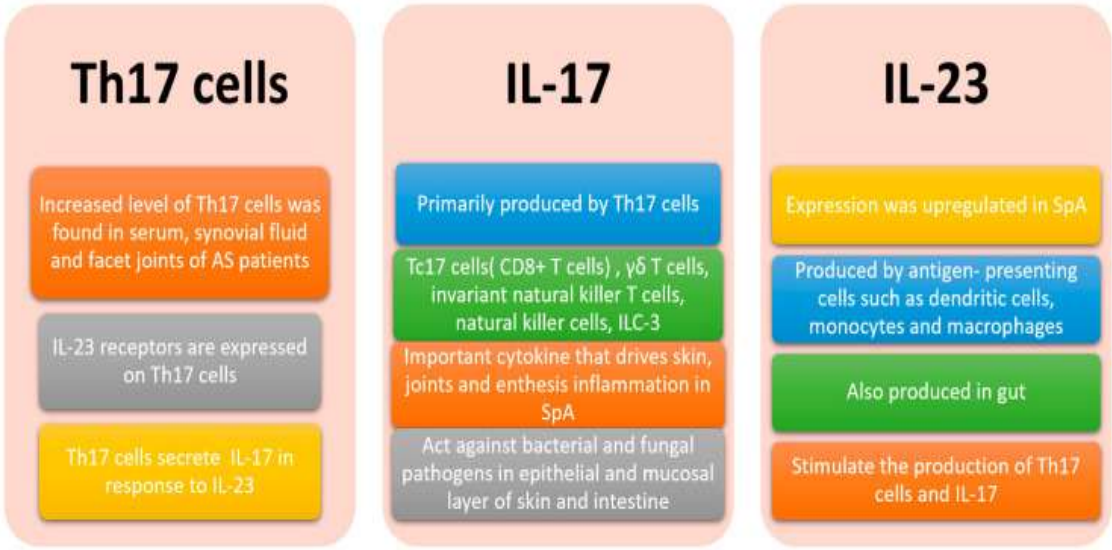


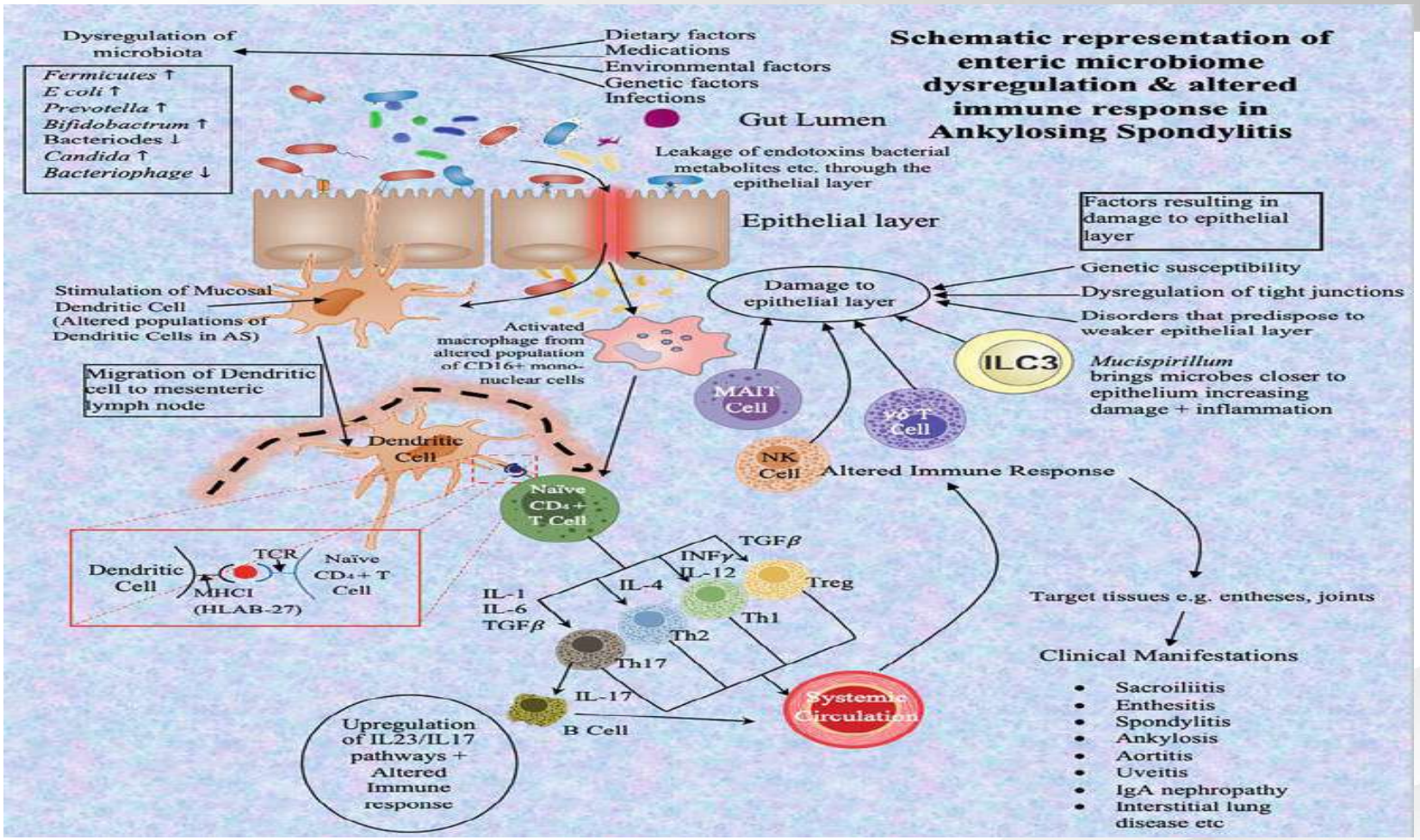
Arthritogenic Peptide Theory

Presentation of either bacterial peptides by HLA-B27 or self-mimicking HLA-B27-binding peptides from certain bacteria could initiate a cell-mediated immune reaction leading to AS

Key Cytokine Pathways in the Pathogenesis of Inflammatory Bowel Disease and Spondyloarthritis

- IL-17 promotes T cell priming and stimulates fibroblasts, endothelial and epithelial cells and immune cells such as macrophages, to produce pro-inflammatory cytokines and chemokines.
- IL-17A and IL-17F also stimulate the production of anti-microbial peptides β-defensins at the epithelial layer which is important for maintaining gut permeability.





Immunological and microbial factors

1. The gut microbiome, including Lachnospiraceae,
2. Veillonellaceae (Dialister),
3. Prevotellaceae(Prevotella melaninogenica, Prevotella copri, and Prevotella spp.),
4. Porphyromonadaceae,
5. Bacteroidaceae,
6. Klebsiella pneumoniae (opportunistic pathogen in the normal human gut)
7. Akkermansia muciniphila
8. Mucispirillum schaedleri
9. IgA coated E coli

- Fungal bioproducts including β-glucan
- Caudovirales bacteriophages

GRAM NEGATIVE

- Shigella, Salmonella, Yersinia,Campylobacter species, Clostridium difficile, Brucella, and Giardia

Role of Endocrine

1. Sex Hormones -

Male

a. Diminished testicular testosterone (T) reserve,
b. Elevated luteinizing hormone (LH) level,
c. Estradiol/testosterone ratio (E2:T) inversion
d. Slightly increased estradiol (E2) level

Female

a. Lower estradiol levels(menstruation period).

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

- Diagnostic Test to determine the effectiveness of a current drug therapy, or the need to institute a new drug therapy for the treatment.

- The BASDAI consists of a 0 - 10 scale measuring discomfort, pain, and fatigue (0 being no problem and 10 being the worst problem) in response to six questions asked of the patient pertaining to the five major symptoms of AS:

- Fatigue
- Spinal pain
- Arthralgia (joint pain) or swelling
- Enthesitis, or inflammation of tendons and ligaments (areas of localized tenderness where connective tissues insert into bone)
- Morning stiffness duration
- Morning stiffness severity

To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken.

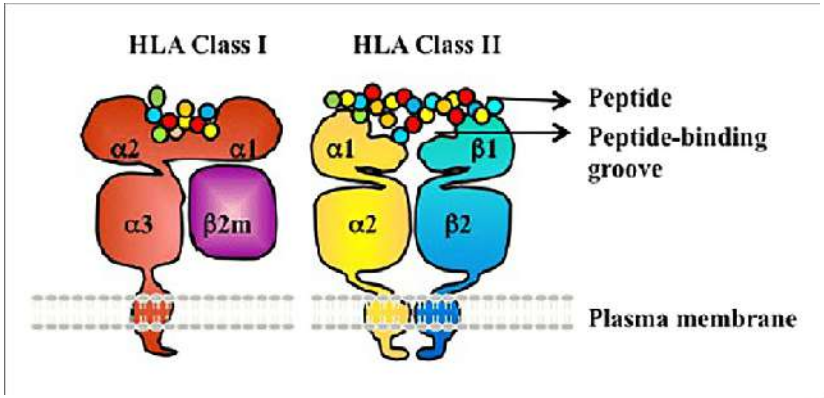
The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score.

Scores of 4 or greater suggest suboptimal control of disease, and those patients are usually good candidates for a change in their medical therapy, may benefit by treatment with biologic therapies, or may be candidates for enrollment in clinical trials evaluating new drug therapies directed at treating the AS disease process.

Inflammatory effects of HLA-B27 as a Mechanism in Ankylosing Spondylitis

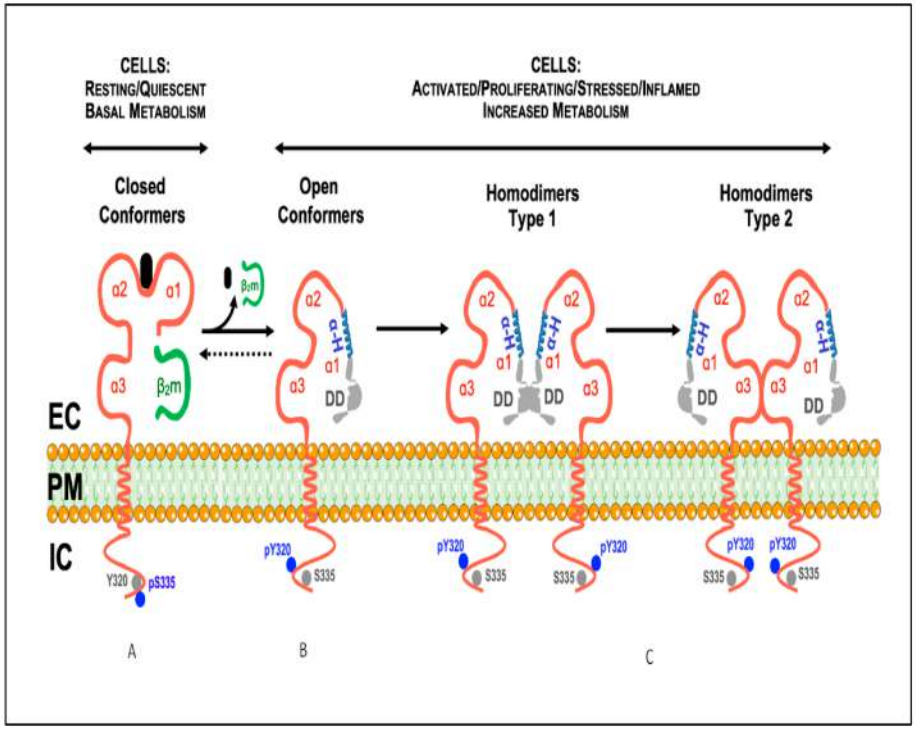
MHC genetics

- There are three class I α-chain genes in humans MHC gene family: class I, II, and III.
- MHC class I encodes HLA-A, HLA-B, and HLA-C
- MHC class II α- and β-chain genes, called HLA-DR, -DP, and -DQ.



MHC

- The heterodimer MHC class I subgroup consists of a polymorphic heavy chain. The chain contains three domains, i.e., α1, α2, and α3.
- The α1 domain links noncovalently with the non-MHC molecule β2m followed by transport to the cell surface as a trimolecular complex, while α3 spans the plasma membrane and interacts with the CD8 coreceptor of T cells
- The MHC class I complex can link to peptides of 8–10 amino acids in length via one cleft spaced by both α1 and α2, leading to the initiation and propagation of immune responses.



Misfolding and creating dimers and even multimers

Without proper folding, these defective HLA-B27 proteins continually gather in the ER

Improperly folded HLA-B27 proteins accumulate in the ER and activate autophagy and the interleukin (IL)-23/IL-17 pathway.

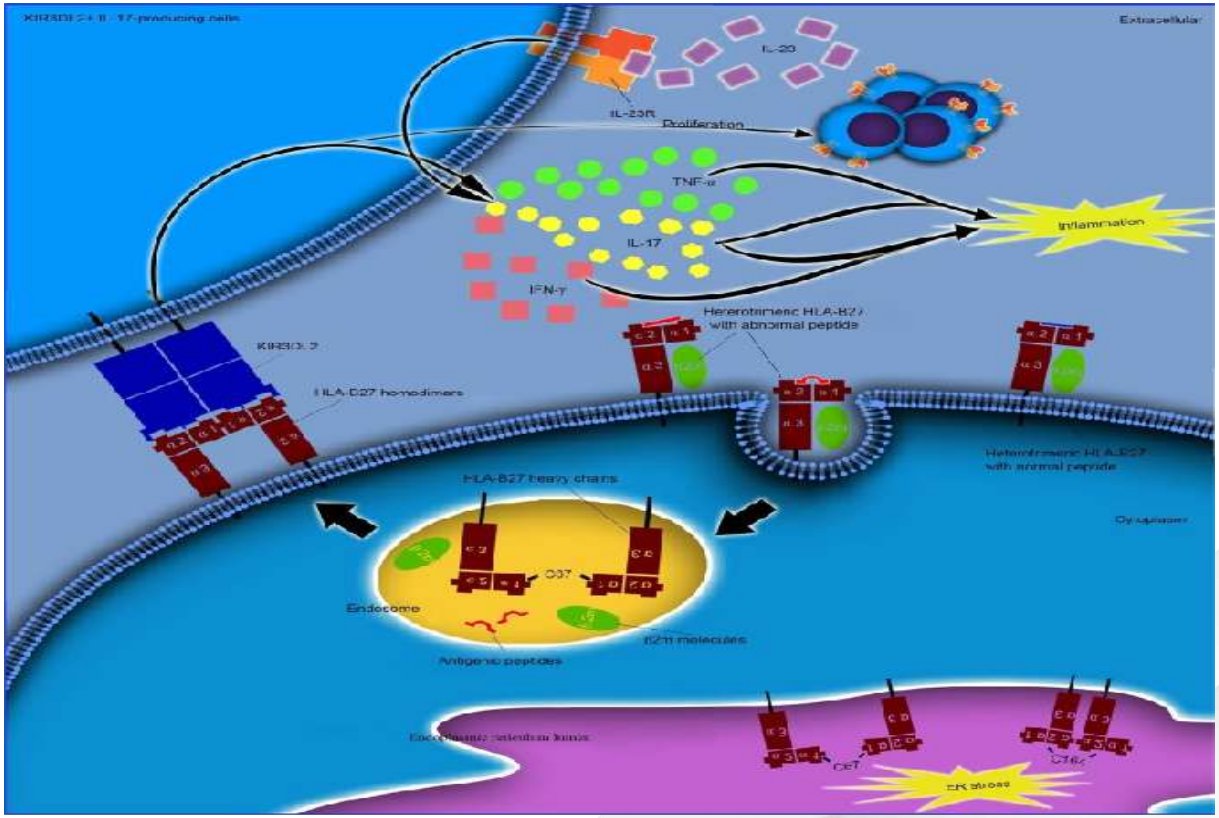
These misfolded molecules can interfere with ER function, leading to ER stress and even triggering the pro-inflammatory endoplasmic reticulum unfolded protein response (ERUPR)

Which further activates the IL-23/IL-17 pathway.

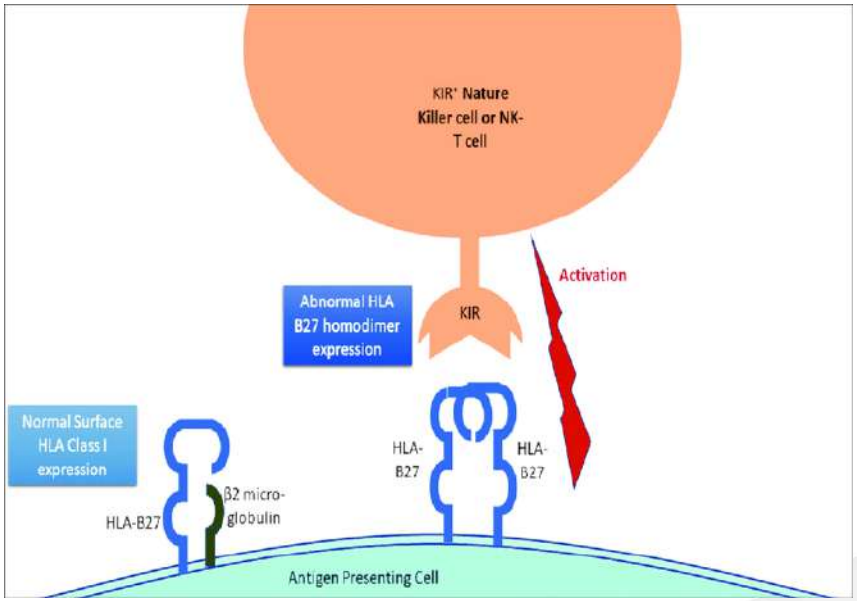
HLA-B27 homodimer formation

- HLA-B27 heavy chains tend to form homodimers without β2m via the disulfide bonds of the cysteine at C67.

- These HLA-B27 dimers could occur on antigen-presenting cells, thus stimulating IL-23 receptor + T lymphocytes to produce IL-17.



- HLA-B27 homodimers have been linked to receptors expressed on natural killer (NK) immunocytes, myelomonocytes and lymphocytes. The binding is realized via killer cell immunoglobulin-like receptors (KIRs) and leucocyte immunoglobulin-like receptors (LILRs), thus acting in the processes related to autoimmune disorder.
- The 3 immunoglobulin domains and the long cytoplasmic tail 2 (KIR3DL2) receptor expressed by certain increased immune cells, including NK cells and Th17 cells, can recognize cell-surface HLA-B27 homodimers via a greater affinity than that with the classic HLA-B27 heterotrimers.



- The binding of KIR3DL2 with HLA-B27 homodimers was revealed to stimulate the survival and differentiation of KIR3DL2+CD4+ T lymphocytes in patients with SpA.

Non-HLA-B27 MHC alleles

- HLA-B40, HLA-B60, HLA-A, HLA-DRB1, HLA-DQA1, HLA-DPB1
- HLA-G
- HLA-A0201 tag SNP rs2394250

ERAP1 and ERAP2

- Aminopeptidases were recognized as genetically related to AS vulnerability,

1. ERAP1 (coding for endoplasmic reticulum aminopeptidase 1 (ERAP1))
2. ERAP2 (coding for ERAP2),
3. NPEPPS (coding for puromycin-sensitive aminopeptidase (PSA)

- Genes at chromosome 5q15.

ERAP1

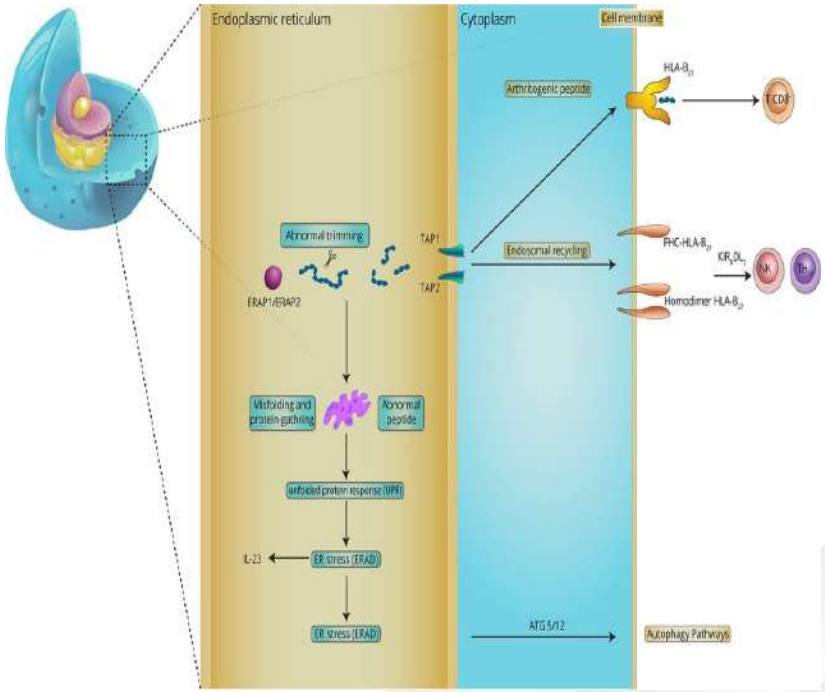
- ERAP1 is associated with HLA-B27− and HLA-B40positive.
- ERAP1 is also involved in the development of juvenile idiopathic arthritis, psoriasis, and Behçet's disease

ERAP2

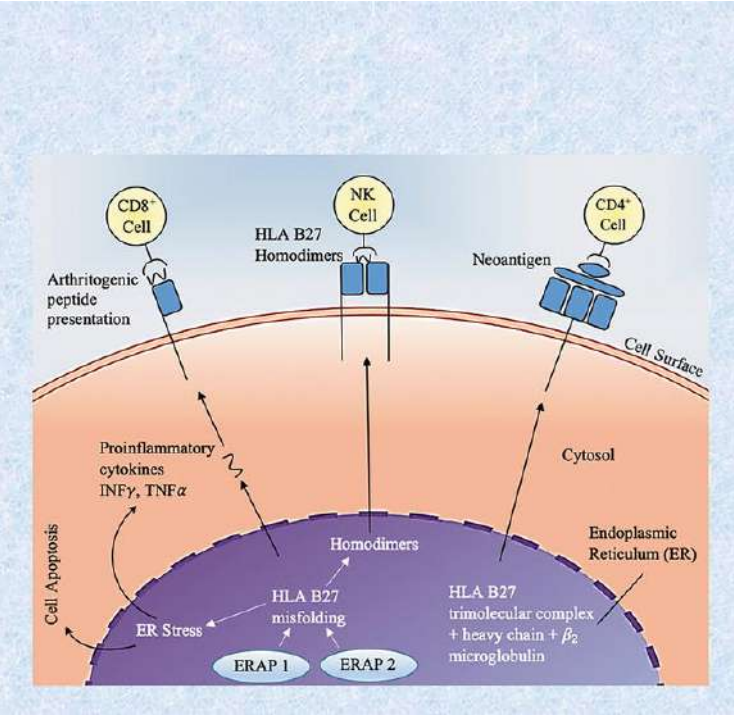
- ERAP2 is related to HLA-B27+ and HLA-B27− AS.
- ERAP2 is related to Crohn's disease and psoriasis, as well as birdshot chorioretinopathy

Role of HLA-B27 and ERAP1/2 in AS pathogenesis.

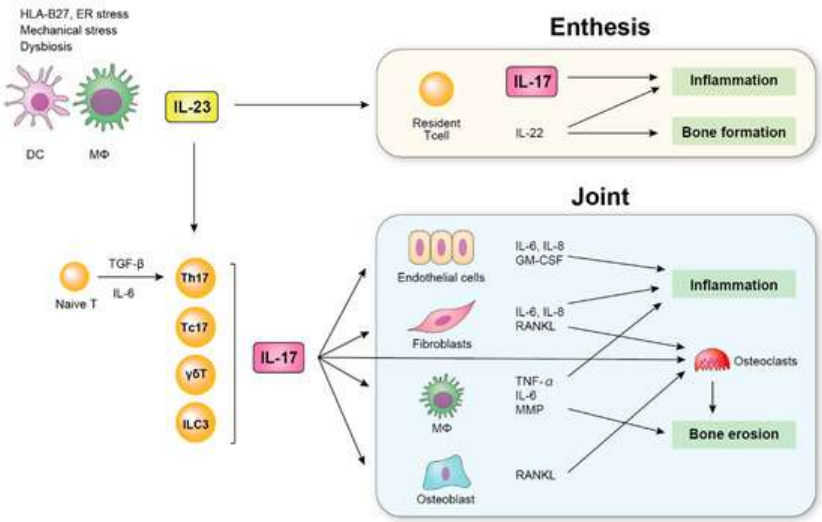
1. HLA-B27 can present arthritogenic peptides to CD8+ T lymphocytes, which trigger AS initiation.
2. Peptides enter the ER and are further trimmed by ERAP1 and ERAP2.
3. Unusual peptides will be produced because of incorrect ERAP1 or ERAP2 trimming, leading to HLA-B27 free heavy chains (FHCs) and homodimers through endosomal recycling from the cell membrane and then to NK cell and Th17 cell activation by KIRs, particularly KIR3DL2.
4. Abnormal peptide-HLA-B27 complexes gather in the ER, triggering UPR, ER stress, ER-associated protein degradation (ERAD) and autophagy.

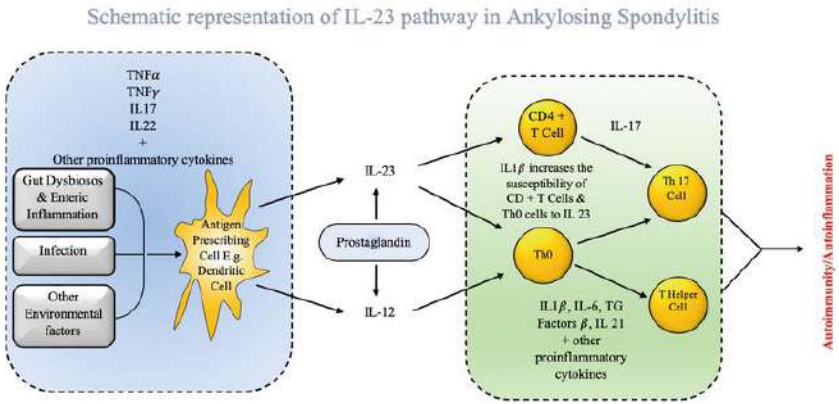


Role of HLA B27 & ERAP genes in pathogenesis of ankylosing spondylitis.

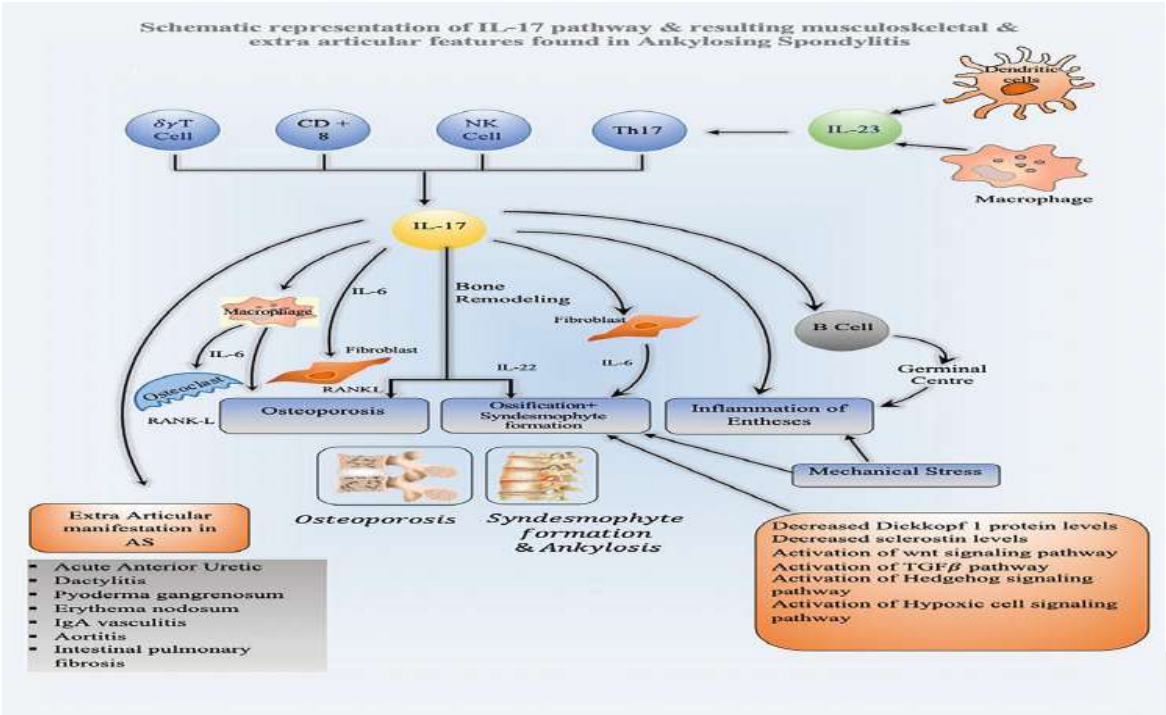


IL-23/17 pathway in AS pathogenesis.





IL-17 pathway & resulting musculoskeletal & extra articular features found in ankylosing spondylitis.

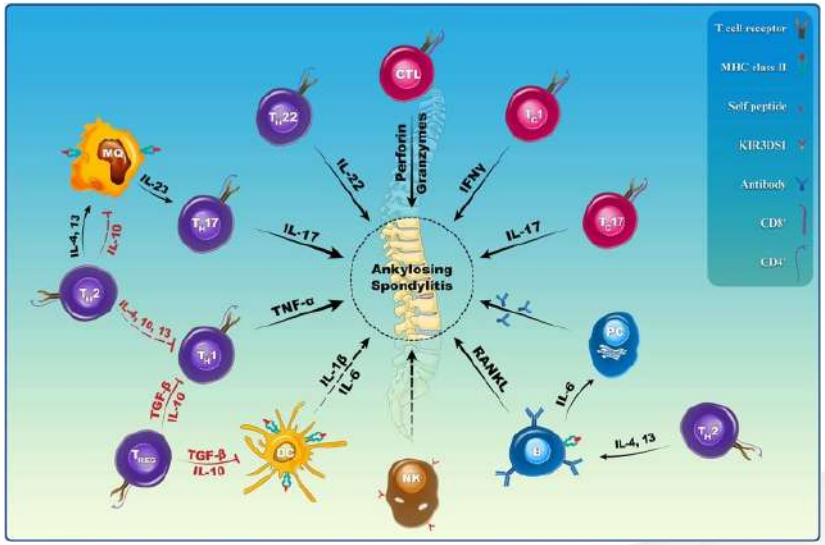


Lymphocyte Activation and Differentiation

- RUNX3, EOMES, ZMIZ1, IL7, TBX21, and IL7R....genes modulating the activation and differentiation of either CD4+ or CD8+ T lymphocytes.
- Runt-related transcription factor 3 (RUNX3), can stimulate T cell differentiation to CD8+ T lymphocytes in thymopoiesis.
- RUNX3 stimulates eomesodermin expression encoded by the EOMES gene and is the transcription factor related to the differentiation of CD8.

Killer immunoglobulin-like receptor (KIRLR)

- KIR3DL2 R is up-regulated on activated CD4+ T-cells and that there are increased levels of these cells in patients with AS .



Clinical manifestations- Symptoms

- PAIN --- The initial symptom is typically a Dull Deep Pain that is insidious in onset.
- Accompanied by morning stiffness in the same area that lasts for a few hours, improves with activity, and returns with inactivity.
- The pain becomes persistent and bilateral within a few months and is usually worse at night.

- Axial skeleton:
- Bilateral sacroiliitis—earliest symptom
- Associated morning stiffness
- Progressive spinal flexion deformities over life
- Ascending ankyloses from thoracic to entire
- "Chin-on-chest" deformity
- Hip involvement at young age—poor prognosis
- Enthesitis: inflammation of tendon insertion

Clinical Features of AS

Skeletal	Axial arthritis (eg, sacroiliitis and spondylitis)
	Arthritis of ‘girdle joints’ (hips and shoulders)
	Peripheral arthritis uncommon
	Others: enthesitis, osteoporosis, vertebral, fractures, spondylodiscitis, pseudoarthrosis
Extraskeletal	Acute anterior uveitis
	Cardiovascular involvement
	Pulmonary involvement
	Cauda equina syndrome
	Enteric mucosal lesions
	Amyloidosis, miscellaneous

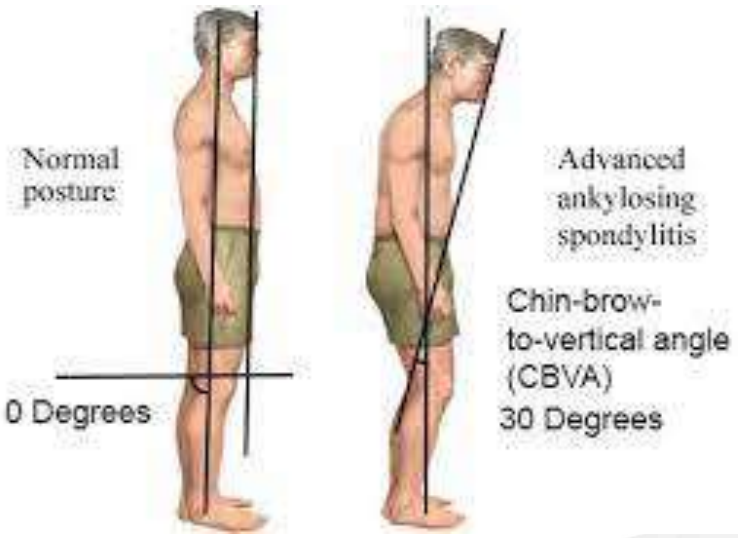
CLINICAL FEATURES

Initial symptom-

- Insidious onset dull pain in the lower lumbar or gluteal region
- Low-back morning stiffness of up to a few hours duration that improves with activity and returns following periods of inactivity.
- Pain usually becomes persistent and bilateral. Nocturnal exacerbation +.
- Predominant complaint- Back pain or stiffness.
- Bony tenderness may present at- costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels.
- Neck pain and stiffness from involvement of the cervical spine : late manifestations

Physical findings

- A principal physical finding is loss of Spinal mobility, with restrictions of flexion, extension of the lumbar spine, and expansion of the chest.



EXAMINATION

The cardinal clinical feature is marked stiffness of the spine.

Chest expansion loss:

- Circumference at fourth rib space
- Max inspiration versus max expiration
- Normally over 5 cm

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Laboratory findings

- Laboratory findings in ankylosing spondylitis (AS) are generally nonspecific but may help assist with diagnosis.
- About 50% to 70% of patients with active AS have elevated acute phase reactants, such as erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP).
- A normal ESR and CRP, however, should not exclude the disease.

1984 MODIFIED NEW YORK CRITERIA FOR AS

- CLINICAL CRITERIA
  - Low back pain ≥ 3 months, improved by exercise and not relieved by rest
  - Limitation of lumbar spine in sagittal and frontal planes
  - Limitation of chest expansion (relative to normal values corrected for age and sex)
- RADIOLOGICAL CRITERIA
  - Bilateral grade 2-4 sacroiliitis, or;
  - Unilateral 3-4 sacroiliitis

Modified New York Criteria for Ankylosing Spondylitis

Clinical criteria

- Low back pain and stiffness which improves with activity for more than three months
- Limited range of motion of the lumbar spine in both forward and lateral bending.
- Limitation of chest expansion relative to normal values correlated for age and sex

Radiological criteria

- Sacroiliitis grade $\geq$2 bilaterally
- Sacroiliitis grade 3 to 4 unilaterally

Note: Diagnosis of AS is made if the patient fulfills at least one radiological and one clinical criteria. Source: Copyright © 1984 American College of Rheumatology. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361–368.[24]

ASAS CRITERIA FOR AXIAL SPA

ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

RheumTutor.com

In patients with ≥ 3 months back pain and age of onset < 45 years

Sacroiliitis on imaging AND ≥ 1 SpA feature	OR	HLA-B27 positive AND ≥ 2 other SpA features

SpA features

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

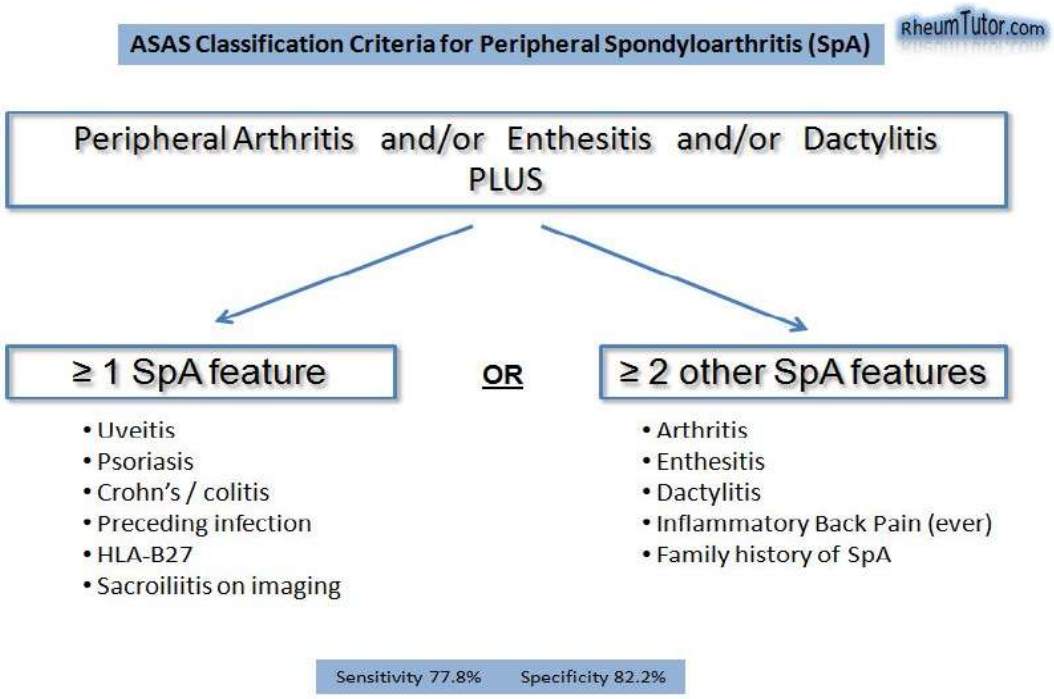
Sacroiliitis on imaging

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

Sensitivity 82.9% Specificity 84.4%

Rudwaleit M et al. Ann Rheum Dis 2009;68:777-783

ASAS CRITERIA FOR PERIPHERAL SPA



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

to be continued...

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