Rheumatic diseases: Classification and Immunology

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General Objectives
- Approach to pathophysiology and clinical presentation of OA, RA and SpA
- Overview of the immune system
- Introduction to the principles of autoimmune disease

Detailed Objectives
1. Describe the classification system for rheumatic disease
2. In OA, RA and SpA, understand:
   - Where the disease fits into the classification table
   - Epidemiology
   - Etiology and pathogenesis
   - Disease course and clinical manifestations
   - Pertinent laboratory and radiological tests
3. Understand the basic pathogenesis of immune-mediated disease

OA
- Also known as degenerative joint disease
- Most common form of arthritis
- Classified as:
  - Idiopathic (localized or generalized) or
  - Secondary (traumatic, congenital, metabolic/endocrine/neuropathic and other medical causes)
- Characterized by focal and progressive loss of the hyaline cartilage of joints, underlying bony changes

OA
- Usually defined by symptoms, pathology or combination
- Pathology = radiographic changes
  - Joint space narrowing
  - Osteophytes
  - Bony sclerosis
- Symptoms = pain, swelling, stiffness
# Rheumatic Diseases: Classification and Immunology

## OA Prevalence
- Overall OA affects
  - 13.9% of adults aged 25 and older
  - 33.6% (12.4 million) of those 65+
  - an estimated 26.9 million US adults in 2005
  - up from 21 million in 1990
- Estimated that 59.4 million patients will have OA by the year 2020

## OA Unique features
- Disease in weight bearing joints has greater clinical impact.
- About 20-35% of knee OA and ~50% of hip and hand OA may be genetically determined.

## OA Risk Factors

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
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<tbody>
<tr>
<td>Excess body mass (especially knee OA)</td>
<td>Gender (women higher risk)</td>
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<tr>
<td>Joint injury (sports, work, trauma)</td>
<td>Age (increases with age and levels around age 75)</td>
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<tr>
<td>Occupation (excessive mechanical stress: hard labor, heavy lifting, knee bending, repetitive motion)</td>
<td>Race (some Asian populations have lower risk)</td>
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<tr>
<td>Men: Often due work that includes construction/mechanics, agriculture, etc.</td>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Women: Often due work that includes cleaning, construction, agriculture, etc.</td>
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<tr>
<td>Structural malalignment, muscle weakness</td>
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</tbody>
</table>

## OA Clinical
- A.M. stiffness
- Gel phenomenon
- Joint pain and tenderness
- Crepitus
- Bony swelling
- Angulation deformities
- Functional Impairment

## OA Features

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Radiographic</th>
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</thead>
<tbody>
<tr>
<td>Noninflammatory synovial fluid</td>
<td>Osteophytes</td>
</tr>
<tr>
<td>Usually &lt; 2000 WBC</td>
<td>Joint space narrowing</td>
</tr>
<tr>
<td></td>
<td>Subchondral</td>
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<tr>
<td></td>
<td>Cysts and sclerosis</td>
</tr>
<tr>
<td></td>
<td>Malalignment</td>
</tr>
</tbody>
</table>

## Osteoarthritis-Diagnosis
- Clinical
- Supported by X-rays
- Non-inflammatory lab data, if any

## OA Unique features
- Disease in weight bearing joints has greater clinical impact.
- About 20-35% of knee OA and ~50% of hip and hand OA may be genetically determined.
Natural history of OA
- Progressive cartilage loss, subchondral thickening, marginal osteophytes

Inflammatory Arthritis
- Rheumatoid arthritis
- Spondyloarthropathies
  - Undifferentiated
  - Ankylosing spondylitis
  - Psoriatic arthritis
  - Reactive arthritis (formerly Reiter’s syndrome)
  - Enteropathic arthritis / IBD associated
- SLE, Sjogrens, Scleroderma, Polymyalgia rheumatica, Vasculitis, Infectious (bacterial, viral, other), Undifferentiated connective tissue disease

Rheumatoid Arthritis-Background
- Symmetric, inflammatory polyarthritis
- Affects ~1% of our population
- Occurs in women 3x more than men
- Etiology
  - Genetic, class II molecules (HLA-DRB1)
  - Autoimmune
  - ?Environmental

Introduction
- RA is a common chronic inflammatory joint condition
- Multi-factorial etiology
- Variable course with exacerbations and remissions of activity
- Inflammation leads to joint damage (erosions)
- Can result in severe disability

Historical
- ‘Rheumatoid’ first used in 1859 by Garrod
- Little evidence for RA prior to 16th Century
- Possibly earlier in New World
- In contrast to OA and Gout

Epidemiology
- Incidence
  1.4/10000 male, 3.6/10000 females
- Prevalence 0.5-2%
- Male:female 1:3
- Worldwide distribution
  - Higher in Native populations
  - Absent in some parts of Africa
- Onset any age but maximum
  40 - 70 years in women
  60 - 70 years in men
**Genetic factors**
- Small increased risk in siblings
- Monozygotic twins
  - 15% concordance
- Dizygotic twins
  - 4% concordance
- HLA DR4

**Rheumatoid arthritis is a systemic disease**
- Symmetrical polyarthritis
- Prolonged morning stiffness (>45 min)
- Extra-articular manifestations
- Constitutional features (weight loss, fatigue)

**History**
- Insidious onset
- Slow development of signs & symptoms
- Stiffness
- Polyarticular
- Most common: PIP & MCP of hands
- Morning stiffness > 1 hr
- Fatigue, malaise, depression

**Clinical course of rheumatoid arthritis**

![Diagram showing progression of joint involvement]
- **Mild, limited disease**
  - Often leading to remission
- **Severe, refractory, progressive disease**
  - Leading to disability and/or premature death
- **Moderate, poly cyclic disease**
  - Usually leading to disability

**Clinical features**
- Symmetrical deforming polyarthritis
  - Affects synovial lining of joints, bursae and tendons
  - More than just joint disease
- Presentation
  - Variable
  - Gradual or acute/subacute
  - Palindromic
  - Monoarticular
  - Symmetrical, diffuse small joint involvement

**Progression of joint involvement**
- Spread occurs within months to years to other joints
  - Almost any joint may be involved
  - Spontaneous remission can occur (after acute onset)
  - Poor prognosis factors exist
- Symptoms
  - Of inflammation
    - Stiffness, pain, swelling, warmth, redness
Pattern of joint involvement
- symmetrical
- small joints of hands - DIP spared
- characteristic features
  - Boutonniere
  - Swan neck
  - Z thumb
  - Volar subluxation
  - Ulnar deviation

Functional impairment
- related to underlying disease activity
- joint damage due to previous activity

Rheumatoid Arthritis
Morbidity and Mortality
RA Patients with Severe Disease (>30 Active Joint Count), 10 year survival is comparable to:
- 3 vessel coronary artery disease
- stage IV Hodgkins Disease
  At 2 years, over 50% RA patients would already have suffered irreversible joint damage

Extra-articular manifestations
- Rheumatoid Nodules
- Eye inflammation
  - episcleritis, scleritis
  - corneal melt
- Interstitial lung disease
- Sicca Symptoms
- Felty’s
- Rheumatoid Nodules
- Vasculitis
- Pleuritis
- Pericarditis
- Neuropathy
  - mononeuritis
  - symmetrical
  - peripheral

Investigations
- Hematology
  - CBC, ESR (anemia of chronic disease)
- Biochemistry
  - LFT, CRP
- Immunology
  - RF, ANA, anti-CCP
- Microbiology
  - viral titres
- Radiology
  - XRay, bone scan, MRI

Laboratory Tests
- ESR: elevated
- Serology: Rheumatoid factor
  - Fc of IgG
    (+) not pathognomonic for RA
    - erosive joint disease, aggressive
    (-) milder disease course
  Detectable in non RA pts w/ prolonged infection
Anti-Cyclic Citrullinated Peptide Antibodies (anti-CCP)
- Sensitivity 47-76%
- Specificity 90-96%
- Can occur in active other conditions (TB, SLE, Sjogren's, Polymyositis, Dermatomyositis, Scleroderma)
- (+) CCP Ab
  - more likely to have aggressive disease and progressive radiographic joint damage

<table>
<thead>
<tr>
<th></th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
<th>Serositis SpA</th>
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<tbody>
<tr>
<td>Ankylosis</td>
<td>Rare</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Alignment</td>
<td>++</td>
<td>+ (irregular)</td>
<td></td>
</tr>
<tr>
<td>Bone density</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sclerosis</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Osteophytes</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Periosteal</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cartilage space</td>
<td>++ (symmetric)</td>
<td>+ (symmetric)</td>
<td></td>
</tr>
<tr>
<td>Cysts</td>
<td>Subchondral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>PIP/MCP/DCP/supracarpal</td>
<td>DIP/PIP/CMC</td>
<td></td>
</tr>
<tr>
<td>Erosions</td>
<td>+++</td>
<td>- (erosive OA)</td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>+++ (fluid)</td>
<td>+ (H&amp;B nodes)</td>
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Differential diagnosis
- Post viral (parvo, rubella)
- Reactive arthritis
- SLE
- Polyarticular Gout
- Polyarticular OA

Diagnostic criteria
- ARA 1958
  - 11 inclusion criteria
    - 7+ classical RA
    - 5-6 definite RA
    - 3-4 probable RA
  - 20 exclusion criteria
- ACR 1987 (4/7 necessary)
  1. Morning stiffness (> 1 hour)
  2. Arthritis of at least 3 areas (> 6 weeks)
  3. Arthritis of hand joints
  4. Symmetrical arthritis
  5. Rheumatoid nodules
  6. Serum rheumatoid factor
  7. Radiographic changes

Prognosis
- Life expectancy reduced by
  - 7 years in men
  - 3 years in women
- Severe morbidity
- Sudden onset do better than gradual
- Early knee involvement bad
- Bad RA has a worse prognosis than IHD or Hodgkin's

Two Types of Immunity
- Innate
  - "possessed at birth, possessed as an essential characteristic"
  - Always present

- Adaptive
  - "to make suitable to or fit to a specific use or situation"
  - Created and modified
Lymphocytes

- Two types of lymphocytes
  - **T-Cells** (Thymus derived)
    - Natural Killer Cells (Innate Immunity)
    - CD4+ T-Cells (helper cells)
    - CD8+ T-Cells (cytotoxic cells)
  - **B-Cells** (Bone Marrow derived)

Adaptive Immunity

- Two Components of Adaptive Immune System
  - Humoral (humoral mediated immunity)
    - **B-Cells** → Plasma Cells → Antibodies
  - Cellular (cellular mediated immunity)
    - CD8+ T-Cells → Direct Cellular Killing
    - CD4+ T-Cells → Recruitment of other immune cells (inflammatory response)

Immune Response *Glossary*

- **Antigen** – “any substance when introduced into the body stimulates the production of an antibody”
- **Antibody** – “a Y-shaped protein, found on the surface of B-Cells or free in the blood, that neutralize antigen by binding specifically to it”
- Also known as an Immunoglobulin

Cellular Mediated Immunity

- Via T-Cells
  - **CD8+ T-Cell**
    - Stimulated → Direct Killing
  - **CD4+ T-Cell**
    - Th1: Stimulated → Macrophage Activation
    - Th2: Stimulated → B-Cell Activation

*Rheumatoid Arthritis (RA)*

- RA is thought to be **T-Cell** mediated
- Most widely accepted hypothesis:
  - Professional APC encounters some “unknown” antigen
  - It presents this “unknown” antigen to a CD4+ T-helper Cell
  - In a genetically predisposed individual, this starts an immune chain reaction

Damage

- Cytokine cascade results in attraction of PMNs to the joint, penetration through synovial vessels and into joint space
- In active RA up to ONE BILLION cells may gain access to the knee joint EACH DAY and they don’t leave!
### Rheumatoid Arthritis

- **Drugs against TNF-α**
  - Infliximab (Remicade®) – Chimeric monoclonal antibody
  - Etanercept (Enbrel®) – Soluble receptor
  - Adalimumab (Humira®) – Humanized monoclonal antibody
  - Certolizumab/golimumab (Cimzia®/Simponi®) - Humanized monoclonal antibody
- **Drugs against IL-1**
  - Anakinra (Kineret®) - humanized receptor antagonist
- **Drugs against IL-6**
  - Tocilizumab (Actemra®) humanized monoclonal antibody
- **Drugs against T-cell costimulation**
  - Abatacept (Orencia®) - Soluble fusion protein which prevents CD28 from binding to its counter-receptor
- **Drugs against B-cells**
  - Rituximab (Rituxan®) - Chimeric monoclonal antibody directed against CD20 on B-cells
- **Drugs against intracellular targets**
  - Tofacitinib (Xeljanz®) – Janus kinase 3 (JAK3) inhibitor which influences intracellular signalling

### Summary

- **Innate and Adaptive Immunity**
  - **B-Cells**
    - Act as Professional APCs
    - With Th2 response - turn into plasma cells and synthesize antibodies
  - **T-Cells**
    - Natural Killer Cells – Innate Immunity
- **CD8 T-Cells**
  - Interact with MHC Class I (any cell)
  - Direct Cellular Killers
- **CD4 T-Cells**
  - Interact with MHC Class II (professionals)
  - Th1 – Cellular activation - Macrophages
  - Th2 – B-Cells - Antibody

### Ankylosing Spondylitis Features

- **Chronic & progressive form of sero-negative arthritis with axial skeleton predominance**
- **Affects 0.1-0.2% of the population**
- **90-95% of patients are HLA-B27 positive**
  - 7% of general population is B27 positive, only 1% of positives will develop ankylosing spondylitis
- **Male:female 4-10:1**

### Features cont.

- **Age of onset 15-35 years old**
  - Juvenile onset associated with more frequent & severe hip & peripheral joint involvement
- **Life expectancy generally unaffected**
  - Most patients able to maintain a normal lifestyle
**Rheumatic Diseases: Classification and Immunology**

**Features cont.**
- Starts with sacroiliac joints
  - begins with sclerosis, eventually get ankylosis
- Progresses to include facet joints, spine, iliac crest, ischial tuberosity, greater trochanter, hips, patella, calcaneus, glenohumeral joints
  - peripheral joint involvement in 30%

**Features cont.**
- Enthesopathy - calcification & ossification of ligaments, tendons, joint capsules at insertion into bone
- Erosion of subligamentous bone due to inflammatory response
- Fusion of interspinous ligament

**Features cont.**
- Syndesmophytes - bony bridges between vertebrae & ossification of joint capsule
  - Bamboo spine
- Resorption of vertebral endplates
- Soft tissue findings are new bone formation in outer layers of annulus fibrosis as well as chronic synovitis and capsular fibrosis

**Physical Findings**
- Patients usually present with low back pain and stiffness, which improves with activity
- Decreased range of motion in lumbar spine
- Thoraco-cervical kyphosis (late)
- One-third of patients will have acute, unilateral uveitis

**Other Complications**
- Cervical spine fracture, C1-C2 subluxation, cauda equina syndrome
- Peripheral joint ankylosis
- Restrictive lung disease, upper lobe fibrosis
- Aortic root dilation (20%) & murmur (2%)

**Genetic Predisposition for Development of Ankylosing Spondylitis (AS)**
- AS and HLA-B27 – strong association
- Ethnic and racial variability in presence and expression of HLA-B27

<table>
<thead>
<tr>
<th></th>
<th>HLA-B27 positive</th>
<th>AS and HLA-B27 positive</th>
</tr>
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<tbody>
<tr>
<td>Western Europeans</td>
<td>8%</td>
<td>90%</td>
</tr>
<tr>
<td>African Americans</td>
<td>2% to 4%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Ankylosing Spondylitis
- Up to 90% of Caucasian patients with AS are positive for HLA-B27
- HLA-B27 is an MHC Class I molecule

Ankylosing Spondylitis
- Remember – MHC is part of the adaptive immune system – so everybody is different
- Those people with HLA-B27 type of MHC Class I are at higher risk for developing AS
- But Why?

Ankylosing Spondylitis
- The HLA-B27 molecule has a specific binding groove
- Only certain peptide fragments will fit into this binding groove
- Big Question: What peptide fragment could be responsible for the initiation of Ankylosing Spondylitis?

Natural History of AS
- Highly variable
- Early stages: spontaneous remissions and exacerbations
- Spectrum of severity
  - Mild with limited sacroiliac or lumbar joint involvement to severe, debilitating disease
- "Pre-spondylitic" phase – unrecognized period of progressive structural damage over a 5-to-10-year period
  - Average delay in diagnosis is 8.9 years

Burden of Illness
- Functional disability
- Potential complications
- Quality-of-life issues
  - Pain, stiffness, fatigue, sleep problems
- Healthcare costs = $6720 annually
  - 75% indirect medical costs
    - Missed workdays
    - Limited-activity days
- Treatment options: NSAIDs, COX-2 inhibitors, DMARDs
  - Mostly symptomatic relief only
  - Minimal impact on natural course of disease

Obstacles to Desirable Outcomes in AS Until Recently
- Diagnostic and classification limitations
- Lack of universally accepted instruments to assess AS
- Until recently, limited treatment options
  - NSAIDs, COX-2 inhibitors, DMARDs
    - Mostly symptomatic relief only
    - Minimal impact on natural course of disease
Clinical Features of AS

**Skeletal**
- Axial arthritis (eg, sacroiliitis & spondylitis)
- Arthritis of 'girdle joints' (hips & shoulders)
- Peripheral arthritis uncommon
- Others: enthesitis, osteoporosis, vertebral fractures, spondylodiscitis, pseudoarthrosis

**Extra-axial**
- Acute anterior uveitis
- Cardiovascular involvement
- Pulmonary involvement
- Cauda equina syndrome
- Enteric mucosal lesions
- Amyloidosis

Modified New York Criteria for the Diagnosis of AS

- **Clinical Criteria**
  - Low back pain, > 3 months, improved by exercise, not relieved by rest
  - Limitation of lumbar spine motion, sagittal and frontal planes
  - Limitation of chest expansion relative to normal values for age and sex

- **Radiologic Criteria**
  - Sacroiliitis grade ≥ 2 bilaterally or grade 3 – 4 unilaterally

- **Grading**
  - Definite AS if radiologic criterion present plus at least one clinical criteria
  - Probable AS if:
    - Three clinical criterion
    - Radiologic criterion present, but no signs or symptoms satisfy clinical criteria

Disease Activity Assessment

<table>
<thead>
<tr>
<th>Index</th>
<th>Metric</th>
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<tbody>
<tr>
<td>BASFI</td>
<td>Disability level</td>
</tr>
<tr>
<td>BASDAI</td>
<td>Disease activity level</td>
</tr>
<tr>
<td>ASAS - IC</td>
<td>Composite sum of disease activity</td>
</tr>
</tbody>
</table>

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

- A self-administered instrument (using 10-cm horizontal visual analog scales) that comprises 6 questions:
  - Over the last one week, how would you describe the overall level of:
    - Fatigue/tiredness
    - AS spinal (back, neck) or hip pain
    - Pain/swelling in joints other than above
    - Level of discomfort from tender areas
    - Morning stiffness from the time you awake
    - How long does morning stiffness last?

Bath Ankylosing Spondylitis Functional Index (BASFI)

- Visual analog scale (VAS) – 10 cm
- Mean score of 10 questions
- Questions level of functional disability, including:
  - Ability to bend at the waist and perform tasks
  - Looking over your shoulder without turning your body
  - Standing unsupported for 10 minutes without discomfort
  - Rising from a seated position without the use of an aid
  - Exercising and performing strenuous activity
  - Performing daily activities of living
  - Climbing 12 to 15 steps without aid

Assessment in Ankylosing Spondylitis (ASAS)

- **ASAS 20:** An improvement of ≥ 20% and absolute improvement of ≥ 10 units on a 0–100 scale in ≥ 3 of the following 4 domains:
  - Patient global assessment (by VAS global assessment)
  - Pain assessment (the average of VAS total and nocturnal pain scores)
  - Function (represented by BASFI)
  - Inflammation (the average of the BASDAI's last two VAS concerning morning stiffness intensity and duration)
- Absence of deterioration in the potential remaining domain (deterioration is defined as ≥ 20% worsening)
Patterns of Psoriatic Arthritis

- **Distal arthritis**
  - involvement of the distal interphalangeal (DIP) joints
- **Asymmetric oligoarthritis**
  - less than five small and/or large joints are affected in an asymmetric distribution
- **Symmetric polyarthritis**
  - Similar to rheumatoid arthritis
- **Arthritis mutilans**
  - A deforming and destructive arthritis
- **Spondyloarthropathy**
  - both sacroiliitis and spondylitis