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MECHANISMS OF RHEUMATIC DISEASE

IMMUNE MECHANISMS FOR DISEASE
- Many rheumatological conditions are characterized by abnormal types or amounts of serum immunoglobulins/antibodies
- Antibodies function by binding their ligand (antigen), marking them for destruction
- Antibodies can cause disease by two main mechanisms
  1. Cytotoxic mechanism (a type II immune reaction)
     * Antibodies are formed against inappropriate targets (e.g., normal tissues)
  2. Immune complex mechanism (a type III immune reaction)
     * Antibody-antigen complexes are formed and are deposited in tissues
- Inflammatory response is initiated
  * Complement is activated
  * Leukocytes are recruited
  * Cells coated with antibody are destroyed
  * Cell functions are altered
- Immune-mediated disease represents an imbalance of inflammatory vs. anti-inflammatory mediators

IMMUNOGENETICS AND DISEASE
- Cell surface molecules called human leukocyte antigen (HLA) or major histocompatibility complex (MHC) play a role in mediating immune reactions
- The genes that encode HLAs are on chromosome 6
- There are three classes of MHC

### Table 1. Classes of Major Histocompatibility Complexes (MHCs)

<table>
<thead>
<tr>
<th>MHC Class</th>
<th>Types</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HLA–A, –B, –C</td>
<td>All cells</td>
<td>Recognized by CD8+ (cytotoxic) T lymphocytes</td>
</tr>
<tr>
<td>II</td>
<td>HLA–DP, –DO, –DR</td>
<td>Antigen presenting cells (mononuclear phagocytes, B lymphs, others)</td>
<td>Recognized by CD4+ (helper) T lymphocytes</td>
</tr>
<tr>
<td>III</td>
<td>Complement components</td>
<td>In plasma</td>
<td>Chemotaxis, opsonization, lysis of bacteria and cells</td>
</tr>
</tbody>
</table>

HLA and Disease
- Individuals with certain HLA types may have increased risk of certain immune-mediated disease
- Mechanism is not well understood
- May be due to
  * Molecular mimicry
  * Effects on T-cell development
  * Inheritance with other pathogenic alleles
  * Spurious correlations

### Table 2. HLA-Associated Rheumatic Disease

<table>
<thead>
<tr>
<th>HLA Type</th>
<th>Associated Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>Ankylosing spondylitis</td>
<td>In AS, relative risk = 70-90</td>
</tr>
<tr>
<td></td>
<td>Reiter’s syndrome</td>
<td>In Reiter’s, relative risk = 40</td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td>Psoriatic also associated with B38</td>
</tr>
<tr>
<td></td>
<td>IBD arthropathy (spine)</td>
<td></td>
</tr>
<tr>
<td>DR4, DR1</td>
<td>Rheumatoid arthritis</td>
<td>93% of patients have HLA type</td>
</tr>
<tr>
<td>DR3</td>
<td>Sjögren’s syndrome</td>
<td>DR3 associated with many non-rheumatic conditions (celiac disease, Type 1 DM, Graves’ disease, chronic active hepatitis)</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
</tbody>
</table>
### APPROACH TO DIAGNOSIS OF RHEUMATIC DISEASES

#### Figure 1. The Joint and Its Pathology

![Joint and Pathology Diagram]

#### Table 3. Classification of Arthritis and Characteristic Features

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seropositive rheumatic diseases</strong></td>
<td>Skin - nodules, ulceration, rash, mucosal ulcers</td>
</tr>
<tr>
<td>1. Connective Tissue Disease</td>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Neurological involvement</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome (APS)</td>
<td>Renal involvement</td>
</tr>
<tr>
<td>Scleroderma/progressive systemic sclerosis (PSS)</td>
<td>Vascular involvement</td>
</tr>
<tr>
<td>Polymyositis (PM)/dermatomyositis (DMY)</td>
<td>Positive serology</td>
</tr>
<tr>
<td>Mixed connective tissue disease (MCTD)</td>
<td>Constitutionally unwell</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td></td>
</tr>
<tr>
<td>2. Vasculitides</td>
<td>Involvement of axial skeleton</td>
</tr>
<tr>
<td>Polymyositis nodosa (PAN)</td>
<td>Anterior uveitis, conjunctivitis</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Enthesitis, sacroiliitis, dactylitis, urethritis</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Predominantly cutaneous vasculitis</td>
<td>Family history</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>HLA-B27 association</td>
</tr>
<tr>
<td><strong>Seronegative rheumatic diseases</strong></td>
<td>Remitting, recurring pattern</td>
</tr>
<tr>
<td>Ankylosing spondylitis (AS)</td>
<td>Mono or oligoarthritis</td>
</tr>
<tr>
<td>Reactive Arthritis</td>
<td>Tophi</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Renal involvement</td>
</tr>
<tr>
<td>Inflammatory bowel disease (IBD)</td>
<td></td>
</tr>
<tr>
<td><strong>Crystal-induced</strong></td>
<td>Acute monoarthritis or migratory polyarthritis</td>
</tr>
<tr>
<td>Gout (monosodium urate)</td>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Pseudogout (calcium pyrophosphate dihydrate)</td>
<td>Insidious onset</td>
</tr>
<tr>
<td>Hydroxyapatite deposition disease</td>
<td></td>
</tr>
<tr>
<td><strong>Septic/Infectious</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Degenerative</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-articular rheumatism</strong></td>
<td></td>
</tr>
</tbody>
</table>
HISTORY

Onset/Duration
- acute (hours): e.g. gout, infectious, palindromic rheumatism
- subacute (days): e.g. pseudogout, infectious
- insidious (months): e.g. degenerative, inflammatory
- trauma and prodromes: e.g. diarrhea, infection

Course
- intermittent with periods of complete remission (e.g. gout)
- gradual progression over time with acute exacerbations (e.g. pseudogout)
- wax and wane with slow progression over time (e.g. RA)

Characteristics of Joint Involvement
- pain, swelling, loss of function of joint
- inflammatory characteristics
  - morning stiffness (> 1 hour)
  - aggravated by rest, ameliorated by activity
  - signs of acute inflammation: rubor, tumour, calor, dolor
- non-inflammatory/degenerative characteristics
  - no or minimal morning stiffness (< 30 minutes)
  - aggravated by use, ameliorated by activity

Pattern of Joint Involvement (see Table 4)
- symmetrical vs. asymmetrical
- small vs. large
- mono-, oligo- vs. polyarticular
- axial vs. peripheral

| Table 4. Patterns of Joint Involvement (most common or serious to least common) |
|---|---|
| **Monoarticular** | **Polyarticular** | **Non-articular** |
| Infection | Infectious | Musculoskeletal |
| Bacterial | Lyme disease | Tendonitis |
| Mycobacterial | Bacterial endocarditis | Bursitis |
| Fungal | Gonococcus | Strain |
| Viral | Viral (EBV, parvovirus) | Fibromyalgia |
| Spirochetes | Post-infectious | Neurologic disease (see Neurosurgery Chapter) |
| Crystal-induced | Rheumatic fever | Spinal stenosis/degenerative disc disease |
| Gout | Reactive arthritis | Spondylolisthesis |
| CPPD | Enteric infections | Cauda equina syndrome |
| Hydroxypatite | Inflammatory disease | Tumour |
| Hemarthrosis | Seropositive | Thoracic outlet syndrome |
| Trauma/fracture | Seronegative | Vascular |
| Anticoagulants | | Intermittent claudication |
| Bleeding diatheses | | |
| Tumour | | |
| Inflammatory disease | | |
| Seropositive | | |
| Seronegative | | |
| Degenerative | | |

* Red Flag: Acute monoarthritis is INFECTIOUS until proven otherwise. Synovial fluid analysis, with cell counts, stat Gram stain and G&S, is mandatory.

Extra-Articular Features (Colour Atlas and Table 1)
- consider skin and appendages, eyes, lungs, cardiac, pulmonary, GI, GU, neurologic, psychiatric

Activities of Daily Living and Limitations
- gross motor - walking, stairs, toileting
- fine motor - dressing (buttons, zippers), grooming, eating, grip

General Health
- infections, constitutional symptoms, sexual history, and past medical history

Treatments
- medications and dosages
- physiotherapy, occupational therapy
- alternative therapies
- surgical - reconstructive vs. total joint replacement
- ask about the effectiveness of each
PHYSICAL EXAMINATION

1. Approach to Peripheral Joints

**Inspection “Look”**
- note involved/active joints
- mnemonic: **SEADS**
  - assess for Swelling, Erythema, Atrophy of muscles, Deformities and Skin changes
- nodes, nodules, other changes

**Palpation “Feel”**
- warmth, joint line and other (bone, tendon, cartilage) tenderness, effusion
- crepitus, laxity/instability

**Range of Motion “Move”**
- assess active, passive range of motion
- stress pain

2. Approach to the Axial Skeleton

**Inspection “Look”**
- posture
- alignment: kyphosis, lordosis, scoliosis

**Palpation “Feel”**
- muscle spasm
- bony and soft tissue tenderness

**Range of Motion**
- lateral flexion (normal person can reach fibular head)
- forward flexion
- extension
- rotation (have patient seated to fix pelvis)

**Mechanical Back Pain**
- signs of nerve root irritation: straight leg raise, Lasegue manoeuvre, bowstring test, femoral stretch test
- neurological examination: bulk, tone, power, sensation, reflexes

**Special Manoeuvres for Assessing Inflammatory Back Pain**
- occiput-to-wall distance (normal is 0 cm)
- forward finger-to-floor distance
- modified Schröeber test
  - position patient in full flexion
  - measure three vertical 10 cm segments in midline starting at the level PSIS (S2 level)
  - reposition patient in full extension
  - normal reduction in segments is to 8 cm (upper segment), 7 cm, and 6 cm (lowest segment)
- forward finger-to-floor distance
- change in chest expansion between maximal inspiration and expiration (normal > 5 cm)

INVESTIGATIONS

**Bloodwork and Urinalysis**
- general - CBC, BUN, creatinine (these will affect therapeutic decisions)
- acute phase reactants - ESR, complement (C3 and C4), fibrinogen, serum proteins, alpha-2, gamma globulin, CRP, albumin
- ESR is important in diagnosing GCA

**Clinical Pearl**
- **ESR > 100 is found in GCA, CTD, SBE, osteomyelitis, TB, renal cell carcinoma, multiple myeloma, and paraproteinemia.**

- urinalysis to detect disease complications (proteinuria, active sediment)
- serology - autoantibodies (Table 5)
Table 5. Autoantibodies and Their Prevalence in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Normals</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>RA 80%</td>
<td>&lt; 5%</td>
<td>Levels correlate with disease severity in RA</td>
</tr>
<tr>
<td></td>
<td>Sjögren's 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>SLE 95%</td>
<td>&lt; 5%</td>
<td>Sensitive but not specific for SLE</td>
</tr>
<tr>
<td></td>
<td>other CTDs (e.g. RA, PSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>SLE 30-70%</td>
<td>0%</td>
<td>Levels correlate with disease activity</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>SLE &lt; 30%</td>
<td>0%</td>
<td>Specific but not sensitive for SLE</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>Sjögren's 40-95%</td>
<td>0.5%</td>
<td>Subacute cutaneous LE and mothers of babies with neonatal lupus</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>Sjögren's 40%</td>
<td>0%</td>
<td>Usually occurs with anti-Ro</td>
</tr>
<tr>
<td>Antiphospholipid antibodies (LAC, ACLA)</td>
<td>APS SLE 31-40%</td>
<td>&lt; 5%</td>
<td>By definition present in APS Only small subset of SLE patients develop clinical syndrome of APS</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Drug-induced SLE &gt; 90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>idiopathic SLE &gt; 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>MCTD</td>
<td>0%</td>
<td>By definition present in MCTD</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>CREST &gt; 80%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Anti-topoisomerase 70</td>
<td>PSS 26-76%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active Wegener's &gt; 90%</td>
<td>0%</td>
<td>Specific and sensitive</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>Wegener's 10%, other vasculitis</td>
<td>0%</td>
<td>Nonspecific and poor sensitivity</td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Polymyositis 10-30%</td>
<td>0%</td>
<td>Specific but not sensitive</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Dermatomyositis 15-20%</td>
<td>0%</td>
<td>Specific but not sensitive</td>
</tr>
</tbody>
</table>

Rheumatoid Factor (RF)

- autoantibodies (IgM > IgG > IgA) directed against Fc domain of IgG
- not specific for RA, 5% of healthy people are positive, and 10-20% of people over age 65 are positive
- increased in most seropositive diseases, SBE, bacterial and viral infections, (i.e. hepatitis C), and many other conditions
- methods of detection
  1. nephelometry
  2. latex fixation
  3. sheep red cell agglutination
     • reported as dilution at which patient's serum has no remaining activity (1:80 suspicious, 1:160 is positive)

Antinuclear Antibodies (ANA)

- antibodies directed against nuclear components (DNA, RNA, histones, centromere, Sm)
- LE cell prep - indirect test of ANA
  • LE cells are PMNs that have phagocytosed extruded nuclei of other cells
  • nucleus extrusion is due to ANAs
  • typical of SLE, seen in RA, PSS, DMY, infections
- fluorescent ANA test
  • fluorescent markers bind ANA
    • SLE shows rim or homogeneous pattern; PSS, Sjögren's, RA, and MCTD shows speckled pattern
- antiDNA Ab test
  • Abs are directed against single stranded (ss) or double stranded (ds) DNA
  • lupus characterized by anti-dsDNA Ab
  • crithidia test is specific for dsDNA
  • Elisa or Farr (radioimmunoassay) are both specific to disease and sensitive to change in disease activity
ANTIBODIES AGAINST CLOTTING FACTORS
- present in SLE
- tested by anticoagulant activities; PTT
- confirmed by 50:50 test and serology

ANTIBODIES AGAINST ERYTHROCYTES
- tested by hemoglobin level, direct Coombs' test, reticulocyte count, leukocyte count, and platelet count

ANTIGEN-ANTIBODY (Ag-Ab) COMPLEXES
- can detect them with the following tests
  1. low serum C3 and C4 level
  2. lupus band test on tissue biopsy
     - immunofluorescent Ab against IgG and C3 at the dermal-epidermal junction
  3. light microscopy for ragocytes, which are PMNs that have engulfed Ag-Ab complexes

SYNOVIAL FLUID ANALYSIS
- synovial fluid is an ultrafiltrate of plasma plus hyaluronate; it lubricates joint surfaces and nourishes articular cartilage
- analysis provides definitive diagnosis for infectious, inflammatory, and crystalline disease
- normal synovial fluid is colourless or straw-coloured and has <200 WBC/mm³

THREE MOST IMPORTANT TESTS OF SYNOVIAL FLUID (The Three Cs)
- cell count and differential
- crystal examination
- culture and Gram stain

GROSS APPEARANCE
- volume, colour, clarity, viscosity

MICROSCOPY (see Colour Atlas RH6)
- total and differential leukocyte count
- cytology exam, Gram and special stains
- crystal exam is diagnostic for gout vs. pseudogout
  - gout (monosodium urate)
    - needle-shaped
    - negatively birefringent = yellow when parallel to axis of red compensator (by definition)
  - pseudogout (calcium pyrophosphate dehydrogenase)
    - rhomboid-shaped
    - positively birefringent = blue when parallel to axis of red compensator (by definition)

MICROBIOLOGY
- bacterial, mycobacterial, and fungal C+S

CHEMICAL TESTS
- protein, glucose, LDH (less helpful than cell count)

IMMUNOLOGY
- complement levels (C₃, C₄, CH₅₀)
- Ig concentration
- RF, ANA, immune complexes, bacterial antigens, and cryoglobulins
### Table 6. Synovial Fluid Analysis

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Non-Inflammatory</th>
<th>Inflammatory</th>
<th>Infectious</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colour</strong></td>
<td>Clear</td>
<td>Clear</td>
<td>Opaque</td>
<td>Opaque</td>
<td>Sanguinous</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High (due to hyaluronate)</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>WBC / mm³</strong></td>
<td>&lt; 200</td>
<td>&lt; 2,000</td>
<td>&gt; 2,000</td>
<td>&gt; 50,000</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>% PMN</strong></td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
<td>&gt; 25%</td>
<td>&gt; 50%</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Trauma</td>
<td>Osteoarthritis</td>
<td>Seropositives</td>
<td>Septic arthritis</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathy</td>
<td>Seronegatives</td>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertrophic arthropathy</td>
<td>Crystal arthropathies</td>
<td></td>
<td>CPPD</td>
</tr>
</tbody>
</table>

### RADIOLOGY

- **inflammatory**
  - periarticular osteopenia, erosions, uniform decrease in joint space
- **non-inflammatory**
  - local cartilage loss, irregularly decreased joint space, bony overgrowth, cyst formation

### Table 7. Imaging Modalities in Musculoskeletal Disease

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain Film</td>
<td>High resolution; inexpensive</td>
<td>Inadequate soft tissue images; radiation exposure</td>
<td>Bone pathology</td>
</tr>
<tr>
<td>CT</td>
<td>Superior to plain film in complex joints</td>
<td>Radiation exposure; suboptimal for detecting soft tissue pathology; cost</td>
<td>Sacroiliac joints, ankle joints, spinal canal, chest</td>
</tr>
<tr>
<td>MRI</td>
<td>No radiation exposure; optimal for detecting soft tissue pathology, effusions, abscesses, avascular necrosis</td>
<td>Cost; potential for patient injury from metallic objects; potential for contrast allergy</td>
<td>Evaluation of tendons, bursae, effusions, ligament, muscle, spinal canal; increased signal in T2 weighted image in AVN</td>
</tr>
<tr>
<td>U/S</td>
<td>No radiation exposure; inexpensive</td>
<td>Resolution decreases with deeper structures; high variation in quality between centres</td>
<td>Evaluation of rotator cuff injury, tendons, bursae, effusions</td>
</tr>
<tr>
<td>Bone Densitometry</td>
<td>Relatively low radiation exposure</td>
<td></td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Angiography</td>
<td>Ideal for vascular pathology</td>
<td>Radiation exposure; contrast allergy; risk of emboli, arterial dissection</td>
<td>Inflammatory disorders with vascular components</td>
</tr>
<tr>
<td>Scintillography (Bone Scan)</td>
<td>Sensitive for metabolic processes</td>
<td>Low resolution, non-specific</td>
<td>Septic joints, fractures</td>
</tr>
</tbody>
</table>

### DEGENERATIVE ARTHRITIS: OSTEOARTHRITIS (OA)

#### Epidemiology

- most common arthropathy
- increased prevalence with increasing age
  - (35% of 30 year olds, 85% of 80 year olds)

#### Pathogenesis

- genetic predisposition
- abnormal physical forces leading to altered joint function and damage
DEGENERATIVE ARTHRITIS: OSTEOARTHRITIS (OA) … CONT.

Pathology
- primary event is deterioration of articular cartilage due to local biomechanical factors and release of proteolytic and collagenolytic enzymes
  - OA develops when cartilage catabolism > synthesis
  - loss of proteoglycans and water exposes underlying bone
- abnormal local bone metabolism further damages joint (see Colour Atlas RH9)
  - subchondral sclerosis
  - osteonecrosis and cyst formation
  - bone grows beyond joint margin = osteophytes (spurs)
- synovitis is secondary to cartilage damage

Classification
- primary (idiopathic)
  - most common
  - etiology unknown; likely genetic predisposition
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - neuropathic (also known as Charcot joints)
    - atypical joint trauma due to loss of proprioceptive senses (e.g. diabetes, syphilis)
  - avascular necrosis (e.g. fracture, steroids, alcohol, gout, sickle cell)
  - other (e.g. congenital malformation)

Clinical Features
- over age 40
- signs and symptoms localized to affected joints (not a systemic disease)
- pain is often insidious and gradually progresses over years
- flare-ups and remissions may occur

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>joint pain with motion; relieved with rest</td>
<td>joint line tenderness; stress pain</td>
</tr>
<tr>
<td>short duration of stiffness (&lt; 1/2 hr) after immobility</td>
<td>bony enlargement at affected joints</td>
</tr>
<tr>
<td>joint instability/buckling</td>
<td>malalignment/deformity (angulation)</td>
</tr>
<tr>
<td>loss of function</td>
<td>limited ROM</td>
</tr>
<tr>
<td>joint locking due to &quot;joint mouse&quot; (loose piece of bone in joint)</td>
<td>periarticular muscle atrophy</td>
</tr>
<tr>
<td></td>
<td>crepitus on passive ROM</td>
</tr>
</tbody>
</table>

Joint Involvement
- any joint can be affected (especially knee, hip, hand, spine)
- shoulder, elbow, wrist and ankle are less common sites
- hand
  - DIP (Heberden's nodes = osteophytes —> enlargement of joints) (see Colour Atlas RH10)
  - PIP (Bouchard's nodes)
  - CMC (usually thumb)
  - MCP is often spared

Clinical Pearl
- OA of MCP joints can be seen in hemochromatosis or chondrocalcinosis.
- hip
  - dull or sharp pain in trochanter, groin, anterior thigh, or knee
  - internal rotation and abduction are lost first
- knee
  - narrowing of one compartment of the knee is the rule, medial > lateral
  - standing x-rays must be done (not supine)
- foot
  - common in first MTP
- lumbar spine
  - very common especially L4-L5, L5-S1
  - degeneration of fibrocartilaginous intervertebral discs possibly with disc hemiation or listhesis (slippage) and facet joint degeneration
  - reactive bone growth can contribute to neurological impingement
  - sciatica (disc protrusion or posterior osteophytes)
  - neurological claudication (spinal stenosis)
- cervical spine
  - common, especially in lower cervical area
  - neck pain
Laboratory Results
- Lab results are normal in OA, whereas they are abnormal in inflammatory conditions
  - Blood
    - Normal CBC and ESR
    - Negative RF and ANA
  - Synovial fluid
    - Viscous
    - Cell count > normal, but < 2,000
    - Normal glucose and protein levels
    - Rarely acute inflammation with crystals
  - Radiology (4 classic findings)
    - Narrowing of joint space (uni-compartmental)
    - Geode formation (intraosseous cysts)
    - Subchondral sclerosis: "seagull sign" = whiter than normal area on each side of bone
    - Osteophytes

Management
- Presently no treatment alters the natural history of OA
- Non-pharmacologic therapy
  - Weight loss
  - Rest/low-impact exercise
  - Physiotherapy-heat/massage/exercise programs/ultrasound; strengthening to afterload the joint
  - Occupational therapy-aids, splints, cane
- Medical therapy (see Table 8)
- Surgical treatment
  - Joint debridement, osteotomy, total/partial joint replacement, fusion

<table>
<thead>
<tr>
<th>Table 8. Medical Therapeutic Options for Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Acetaminophen high dose</td>
</tr>
<tr>
<td>4 g/d ($0.05-0.12)</td>
</tr>
<tr>
<td>NSAID non-selective</td>
</tr>
<tr>
<td>($0.10-2.83)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
</tr>
<tr>
<td>($1.25-2.50)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Other Treatments</td>
</tr>
<tr>
<td>Combination analgesic</td>
</tr>
<tr>
<td>(ASA + codeine) ($0.17-0.23)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intra-articular corticosteroid injection ($0.07-0.38)</td>
</tr>
<tr>
<td>Intra-articular hyaluronan qimith ($240-385 for 3 injections)</td>
</tr>
<tr>
<td>Capsaicin cream ($26-30)</td>
</tr>
<tr>
<td>Glucosamine sulfate</td>
</tr>
</tbody>
</table>
SEROPositive Rheumatic Diseases: Connective Tissue Disorders

Table 9: Features of Seropositive Arthropathies

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Rheumatoid Arthritis</th>
<th>Systemic Lupus Erythematosus</th>
<th>Scleroderma</th>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Symmetrical</td>
<td>Multisystemic disease</td>
<td>Raynaud's, stiffness of fingers, skin tightness, heartburn/dysphagia</td>
<td>Heliotrope rash (eye lids), Gottron's papules, macular erythema and poikilodermatosis (shoulders, neck and chest), proximal muscle weakness +/- pain</td>
</tr>
<tr>
<td></td>
<td>Polyarthritis (small joint involvement)</td>
<td>- rash, photosensitivity, Raynaud's, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AM stiffness (&gt;1hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>Effusive joints</td>
<td>Confirm historical findings (typically small joints)</td>
<td>Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effusive joint</td>
<td>Rash, proximal muscle weakness</td>
</tr>
<tr>
<td></td>
<td>Tenosynovitis</td>
<td>+/- effusive joints (can be minimal, look for soft tissue swelling)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone-on-bone crepitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-specific</td>
<td>Increased ESR in 50-60%</td>
<td>Increased ESR</td>
<td>Increased ESR</td>
<td>Increased ESR</td>
</tr>
<tr>
<td></td>
<td>Increased platelets</td>
<td>Decreased platelets</td>
<td>Increased platelets</td>
<td>Normal platelets</td>
</tr>
<tr>
<td></td>
<td>Decreased Hb</td>
<td>Decreased Hb (autoimmune)</td>
<td>Decreased Hb</td>
<td>Decreased Hb</td>
</tr>
<tr>
<td></td>
<td>Decreased WBC (Felty's)</td>
<td>Decreased WBC (leukopenia, lymphopenia)</td>
<td>Normal WBC</td>
<td>Normal WBC</td>
</tr>
<tr>
<td>Specific</td>
<td>RF + in ~80%</td>
<td>ANA + in 95%</td>
<td>ANA + in &gt;90%</td>
<td>CPK elevated in 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-SM + in 30%</td>
<td>Anti-topoisomerase 1 (diffuse)</td>
<td>ANA + in 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-dsDNA + in 50-60%</td>
<td>Anti-centromere (usually in CREST)</td>
<td>Anti-Jo-1, anti-Mi-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased C3, C4, total hemolytic complement</td>
<td></td>
<td>Muscle biopsy-key for diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>False positive VDRL (in lupus subtypes)</td>
<td></td>
<td>EMG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased PTT (in lupus subtypes; eg. antiphospholipid Ab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial Fluid</td>
<td>Inflammation</td>
<td>Mild inflammation with + ANA</td>
<td>Not specific</td>
<td>Not specific</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis (&gt;10,000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographs</td>
<td>Demineralization</td>
<td>Generally nondestructive/nonerosive</td>
<td>+/- pulmonary fibrosis</td>
<td>+/- esophageal dysmotility</td>
</tr>
<tr>
<td></td>
<td>Joint space narrowing</td>
<td>+/- osteoporosis</td>
<td>+/- esophageal dysmotility</td>
<td>+/- interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Erosions of subchondral bone</td>
<td>+/- soft tissue swelling</td>
<td>+/- calcinosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence of bone repair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rheumatoid Arthritis (RA)
- chronic, symmetric, erosive synovitis of peripheral joints (i.e. wrists, MCP joints, and MTP joints)
- characterized by a number of extra-articular features

Epidemiology
- incidence 0.6-2.9 per 1,000 population
- F:M = 3:1
- age of onset 20-40
- genetic predisposition: HLA DR4/DR1 association

Pathogenesis (see Figure 2)
- hallmark of RA is hypertrophy of the synovial membrane
  - outgrowth of granulation tissue (pannus) into and over the articular surface results in destruction of articular cartilage and subchondral bone
- initiating event unknown, but appears to involve antigenic stimulation of susceptible T cells
- stimulation of T cells results in
  - B and T cell proliferation
  - angiogenesis
  - accumulation of inflammatory cells in the synovium
  - synovial cell proliferation
  - development of rapidly growing pannus
- all pathways lead to destructive erosions with IL-1, IL-6, and TNF playing major roles
two theories which attempt to explain chronic remissions and exacerbations seen in RA
1. sequestered Ag
   - during inflammation, ICs are deposited at cartilage-bone junction, which is an avascular area → ICs remain free of reticulo-endothelial system but are released as further cartilage breaks down → triggering cascade
2. molecular mimicry
   - cartilage damage → altered configuration of cartilage resembles the offending agent → triggering cascade

Unknown Ag(s)

Antigen presenting cell

Activated CD4 Cell

B-cell activation

IgG production including RF

Immune complex formation in joint

Activation of complement cascade

B and T-cell accumulation in synovium

Release of inflammatory mediators

Degradation of peptidoglycan of cartilage

Cartilage and bone destruction

Figure 2. Pathogenesis in RA

Diagnostic Criteria (American Rheumatism Association, 1987)
(4 or more of the following)
1. morning stiffness (> 1 hour) for > 6 weeks
2. arthritis of three or more joint areas (commonly involved joints include PIP, MCP, wrist, elbow, knee, ankle, MTP) for > 6 weeks
3. arthritis in at least 1 of: MCP, PIP, wrist for > 6 weeks (see Colour Atlas RH12)
4. symmetric arthritis for > 6 weeks
5. rheumatoid nodules (see Colour Atlas RH13 and RH14)
6. serum RF - found in 60-70% of RA patients
7. x-ray changes: erosions or periarticular osteopenia, most likely to see earliest changes at the ulnar styloid, at the 1st and 2nd MCP joints, and at the 1st and 2nd PIP joints (see Colour Atlas RH11)
Table 10. Clinical Manifestations

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Radiographic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>usually none</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>malaise, mild joint stiffness, and swelling</td>
<td>swelling of small joints of hands or wrists or pain in hands, wrists, knees, and feet</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>joint pain and swelling AM stiffness, malaise and weakness</td>
<td>warm, swollen joints, effusion, soft tissue proliferation within joints, pain and limitation of motion, rheumatoid nodules</td>
<td>soft tissue swelling</td>
</tr>
<tr>
<td>4</td>
<td>same as Stage 3</td>
<td>Stage 3 but more pronounced swelling</td>
<td>MRI - proliferative pannus x-ray - periarticular osteopenia</td>
</tr>
<tr>
<td>5</td>
<td>Stage 3 and loss of function and early deformity (eg. ulnar deviation at MCP joint)</td>
<td>Stage 3 and joint instability, flexion contractures, decreased ROM, extra-articular complications</td>
<td>early erosions, joint space narrowing</td>
</tr>
</tbody>
</table>

Note: clinical course highly variable —> sporadic, insidious, aggressive or severe polyarticular synovitis with extra-articular organ involvement

Complications of Chronic Synovitis

- joint deformities
  - swan neck: hyperextension of PIP, flexion of DIP
  - boutonnière: fixed flexion contracture of PIP, extended DIP
  - ulnar deviation of MCP; radial deviation of wrist joint
  - hammer toes: subluxation of heads of MTP; foreshortening of extensor tendons
  - flexion contractures
- atlanto-axial and subaxial subluxation
- limited shoulder mobility, dislocation, spontaneous tears of the rotator cuff leading to chronic spasm
- tendon sheath involvement
  - tenosynovitis —> may cause rupture of tendons
- compression of carpal tunnel: thenar atrophy, tingling of thumb, index finger, and middle finger
- ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute thrombophlebitis
- anemia of chronic disease
- high ESR, hypergammaglobulinemia
- early mortality

Extra-Articular Features (EAF)

- can be classified in terms of the underlying process which is either a vasculitis or a lymphocytic infiltrate

**Vasculitis**
- episcleritis
- nodules
- periungual infarction
- skin ulcers
- neuropathy

**Lymphocytic Infiltration**
- Sjögren's Syndrome
- pulmonary fibrosis (see Colour Atlas RH15)
- Hashimoto's thyroiditis
- pleural effusion/pleurisy/lung nodules
- pericarditis/myocarditis/valvular disease
- hepatosplenomegaly (Felty's syndrome: neutropenia, RA, splenomegaly)

Figure 3. Classification of EAF of RA
**Functional Capacity Classification**
- Class I: no restrictions
- Class II: moderate restriction; able to perform normal activities
- Class III: marked restriction; can't perform activities of usual occupation/self-care
- Class IV: incapacitation, confinement to wheelchair

**Management**
1. control inflammation
2. relieve pain and stiffness
3. maintain function and lifestyle
4. prevent joint damage

**A. Education, counselling, occupational therapy, dietary therapy**
(e.g. selenium)

**B. Medical Therapy**

1. **Disease Modifying Antirheumatic Drugs (DMARDs)**
   - decrease erosions
   - associated with better long-term disability index
   - early intervention has the greatest impact on disease progression
     (Grade A recommendation, Ontario Treatment Guidelines, Fall 2000)
   - delayed onset of action (8-12 weeks)
   - commonly used DMARDs = antimalarials (e.g. hydroxychloroquine), gold, methotrexate, sulfasalazine
   - less frequently used DMARD = azathioprine (Imuran)
   - rarely used DMARDs = penicillamine, cyclophosphamide
   - mild and early stages: hydroxychloroquine and sulfasalazine preferred;
     if suboptimal after 6 months —> other DMARDs
   - moderate to severe disease (especially if RF+)
     • single regimen with methotrexate
     • combination therapy
       • methotrexate, sulfasalazine, and chloroquine
       • methotrexate and cyclosporine
   - new drugs: TNF inhibitors +/- methotrexate, leflunomide (Arava)

2. **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**
   - provide symptom control such as decreasing joint pain, tenderness, and morning stiffness
   - do not alter natural history of RA

3. **Corticosteroids**
   - useful short-term adjuvants
   - do not alter natural course of RA
   - local use
     • intra-articular injections for control of inflammation in specific joints
     • eye drops for scleritis or episcleritis
   - systemic use
     • high doses for vasculitis
     • low doses while awaiting onset of second-line drugs
     • supplement action of NSAIDs in elderly
     • cardiopulmonary involvement
     • severe refractory disease
     • function needed for employment
   - for doses > 7.5 mg/day, prophylactic bisphosphonate, calcium, vitamin D treatment to reduce osteoporosis

4. **Experimental Therapy**
   - three lines of research
     1. neutralization of cytokines (i.e. soluble TNF receptors)
     2. receptor blockade (i.e. IL-1 receptor antagonist)
     3. activation of anti-inflammatory pathways (i.e. IL-4, IL-10)
### Table 11. Drugs Used in the Treatment of Rheumatic Diseases

#### First Line Treatments: DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Cautions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold (injectible)</td>
<td>Rash, mouth soreness/ulcers</td>
<td>IBD</td>
</tr>
<tr>
<td>$1.53-2.43</td>
<td>proteinuria, marrow suppression</td>
<td>Kidney/liver disease</td>
</tr>
<tr>
<td>Gold (oral)</td>
<td>Diarrhea, rash, stomatitis</td>
<td>Same as above</td>
</tr>
<tr>
<td>$1.26-2.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>GI symptoms, retinopathy, neutromopathy, skin rash</td>
<td>Retinal disease, G6PD deficiency</td>
</tr>
<tr>
<td>$0.52-1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Rash, loss of taste/appetite, neuropathy, nephrotic syndrome</td>
<td>Penicillin allergy</td>
</tr>
<tr>
<td>$0.49-3.92</td>
<td></td>
<td>Hematologic/kidney disease</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>GI symptoms, headache, low blood count, rash</td>
<td>Allergy to sulfa drugs/ASA</td>
</tr>
<tr>
<td>$0.11-2.58</td>
<td></td>
<td>Kidney disease, G6PD deficiency</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Pancytopenia, biliary stasis, rash, hair loss, vomiting, diarrhea</td>
<td>Kidney/liver disease</td>
</tr>
<tr>
<td>$0.60-1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Urticaria, N/V/D, tubular necrosis, leukopenia, thrombocytopenia, cirrhosis, pneumonitis, oral ulcers</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>$0.43-1.14</td>
<td></td>
<td>Liver disease</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cardiotoxicity, N/V/D, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility</td>
<td>Kidney/liver disease</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Bleeding, hypertension, decreased renal function, hair growth, tremors/shaking</td>
<td>Kidney/liver disease</td>
</tr>
<tr>
<td>$9.95-19.90</td>
<td></td>
<td>Infection, hypertension</td>
</tr>
<tr>
<td>limited use form</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### First Line Treatments: New Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action and Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entanercept</td>
<td>Fusion protein of TNF receptor and Fc portion of IgG</td>
</tr>
<tr>
<td>(Enbrel)</td>
<td>Biweekly SC injections decrease number of active joints by 50% from baseline after six months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>IgG Ab against TNFα</td>
</tr>
<tr>
<td>(Remicaid)</td>
<td>IV dose rapidly reduces number of swollen joints</td>
</tr>
</tbody>
</table>

#### Second Line Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Cautions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>(see Table 8 for side effects and precautions)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 Inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Other Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Cautions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Osteoporosis, avascular necrosis, Hypertension, Cataracts, glaucoma, Peptic ulcer, Psychosis, Susceptibility to infection, Hypokalemia, hyperglycemia, Hyperlipidemia</td>
<td>Active infections, Osteoporosis, Hypertension, Gastric ulcer, Diabetes</td>
</tr>
<tr>
<td>$0.01-0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### C. Surgical Therapy

1. **Synovectomy**
   - local destruction or removal of inflamed synovium from individual joints (surgical or radioactive)
   - produces long-term effect

2. **Joint Replacement**
   - hip, shoulder, knee

3. **Joint Fusion**
   - wrist, thumb, C-spine

4. **Reconstruction**
   - tendon repair
SEROPOSITIVE RHEUMATIC DISEASES: CONNECTIVE TISSUE DISORDERS... CONT.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
- disorder characterized by inflammation in several organ systems and the production of autoantibodies that participate in immunologically-mediated tissue injury
- peripheral polyarthritis with symmetric involvement of small and large joints WITHOUT joint erosion

Epidemiology
- incidence F:M = 10:1
- age of onset in reproductive years, 13-40
- more common in Blacks and Asians
- bimodal mortality pattern
  - early (within 2 years)
    - active SLE
    - active nephritis
    - infection secondary to steroid use
  - late (> 10 years)
    - inactive SLE
    - inactive nephritis
    - atherosclerosis possibly secondary to long-term steroid use

Proposed Etiology
- altered immunity
  - too many autoAbs causing damage by cytotoxic effects or Ag-Ab complexes
  - altered regulating mechanism e.g. decreased T-suppressors or defective function
- heredity
  - common HLA B8, DR3 (approximately 10% have positive family history)
- role of estrogen
  - prepubertal and postmenopausal women have similar incidence to men
  - men who develop lupus have a higher concentration of estrogenic metabolites
- infection
  - virus (nonspecific stimulant of immune response)
- drugs
  - anticonvulsants (dilantin, phenobarbital)
  - methyldopa
  - antihypertensives (hydralazine)
  - antiarrhythmics (procainamide)
  - anti-histone antibodies are commonly seen in drug-induced lupus
  - oral contraceptive pills associated with exacerbation

Diagnostic Criteria
- person is diagnosed with SLE if any 4 or more of the 11 criteria are present serially or simultaneously
- “4,7,11” rule
  - 4 out of 11 criteria (4 lab, 7 clinical) for diagnosis
- many have constitutional symptoms (fatigue, weight loss, fever) at the time of presentation
- clinical criteria
  1. malar rash: classic “butterfly rash”; no scarring involved since basement membrane intact (see Colour Atlas RH1)
  2. discoid rash: may cause scarring (see Colour Atlas RH3)
  3. photosensitivity
  4. oral/nasal ulcers: usually painless
  5. arthritis: non-erosive, symmetric; involving 2 or more small or large peripheral joints
  6. serositis
    - pleurisy, pericarditis, peritonitis
  7. neurologic disorder
    - headache, seizures, psychosis, neuropathy
    - cytoid body = cotton wool exudates on fundoscopy = CNS involvement of lupus with infarction of nerve cell layer of the retina
- laboratory criteria
  8. renal disorder (see Nephrology Chapter) (see Colour Atlas RH16)
    - proteinuria, cellular casts (RBC, Hb, granular, tubular or mixed)
    - > 0.5 g/day or 3+
9. hematologic disorder
   - hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
10. immunologic disorder
   - positive LE cell preparation, anti-dsDNA Ab, anti-Sm Ab,
      false positive VDRL
11. antinuclear antibody (ANA) - most sensitive test
   - other associated features
     - skin manifestations: urticaria, livedo reticularis, bullae,
       panniculitis, alopecia
     - vasculitic lesions: periungual telangiectasia, Raynaud's
     - eye manifestations: conjunctivitis, episcleritis, keratoconjunctivitis
     - neuropsychiatric: personality disorders, depression, psychoses
   - neonatal lupus erythematosus (NLE) (rare)
     - due to transfer of maternal anti-Ro and/or anti-La antibodies through placenta
     - shortly after birth, infants develop typical discoid lesions with exposure to UV light
     - very rare to develop SLE later in life
     - anti-Ro positive mothers with SLE - 1-5% risk of developing NLE
     - transient complications: fetal thrombocytopenia, rash, and rarely congenital heart block
     - neonates may require pacemaker
   - late-onset SLE
     - presents at age > 50
     - higher incidence of interstitial lung disease
     - less neuropsychiatric and renal involvement
   - subacute cutaneous SLE
     - photosensitive rash
     - Ro positive, ANA negative
   - discoid SLE (see Colour Atlas RH17)

Clinical Pearl
- Drug-induced SLE often presents atypically with systemic features and serositis; usually associated with anti-histone antibodies.

Clinical Pearl
- Consider septic arthritis and AVN in patients with SLE and joint pain.

lab investigations:
   - serologic hallmark is high titre ANA (homogeneous/rim pattern)
     - positive in 98% patients with SLE
   - ANA has high sensitivity and therefore is a useful screening test
   - anti-dsDNA Ab and anti-Sm Ab are specific for SLE (low sensitivity)
   - anti-dsDNA, C3, C4 may be useful in following disease activity if serology is clinically concordant
   - lupus anticoagulant may cause clotting abnormalities and increased PTT

Management Principles
- treat early using the mildest form possible, then slowly withdraw therapy
- if higher doses of steroids necessary for long-term control of disease
  - use steroid sparing agents as well, then taper steroids if possible
- bisphosphonates, Ca, vitamin D if steroids used

Treatment
- symptomatic treatment tailored to organ system involved and severity of disease
- patient education - sunblock, avoid UV light and estrogens
- NSAIDs - arthritis, pleurisy, pericarditis
- antimalarials - dermatologic and MSK manifestations, constitutional symptoms (fever, weight loss, etc.)
- topical steroids for rash
- systemic corticosteroids - prevent end organ damage secondary to inflammation (decreasing doses + slow taper)
cytotoxic agents (steroid sparing): azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil
hydroxychloroquine if SLE w/o serious internal organ involvement - improves disease control, prevents flares, improves long-term outcomes
immunosuppressant drugs for serious internal organ involvement (eg. cerebritis or glomerulonephritis)

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)
- multisystem vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- circulating autoantibodies (antiphospholipid antibody and lupus anticoagulant) interfere with coagulation cascade
- primary vs. secondary
  - secondary APS develops in: SLE, other connective tissue diseases, malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), infections (HIV, hepatitis C, TB, infectious mononucleosis)
- catastrophic APS
  - fatal condition with sepsis, respiratory distress syndrome, malignant hypertension, multiorgan infarction and transfusion dependent thrombotic thrombocytopenic purpura

Clinical Features
- primary manifestation is venous or arterial occlusion
  - venous occlusion - DVT, PE, renal and retinal vein thrombosis
  - arterial occlusion - stroke, TIA, multi-infarct dementia, chorea, myocardial infarction, valvular incompetence, limb ischemia
- recurrent spontaneous abortions
- hematologic abnormalities
  - thrombocytopenia, hemolytic anemia, neutropenia
- skin
  - livedo reticularis (classical lesion), purpura, leg ulcers, and gangrene
- serology
  - lupus anticoagulant or anticardiolipin antibody positive on 2 occasions, at least 8 weeks apart

Treatment
- thrombosis
  - lifelong anticoagulation with warfarin
  - target INR 2.5-3.5
- recurrent fatal loss: aspirin, heparin, +/- steroids
- catastrophic APS: high-dose steroids, anticoagulation, cyclophosphamide, plasmapheresis

SCLERODERMA/PROGRESSIVE SYSTEMIC SCLEROSIS (PSS)
generalized disorder of connective tissue characterized by fibrosis and degenerative changes in blood vessels, visceral organs and skin
- no inflammation
- clinical hallmarks of PSS are tight skin and Raynaud's phenomenon
diagnosis made on clinical grounds

Epidemiology
- F:M = 3-4:1
- incidence peaks in fifth and sixth decade
- associated with HLA DR1, DR3, DR5
- associated environmental factors
  - PSS: silica exposure, epoxy resins, aromatic hydrocarbons
  - PSS-like: polyvinyl chloride, toxic oil syndrome, contaminated L-tryptophan (eosinophilia myalgia syndrome)
Scleroderma

Pathogenesis

- vasculopathy (not vasculitis)
  - decreased vascular luminal size
  - intimal proliferation and medial mucinous degeneration \(\rightarrow\) progressive obliteration of vessel lumen \(\rightarrow\) secondary fibrosis of tissues
  - resembles malignant hypertension
  - no inflammation: atrophy and fibrosis

Clinical Features

- skin
  - bilateral symmetrical swelling of fingers, hands and feet leading to skin tightening (see Colour Atlas RH8)
  - initial phase characterized by painless pitting edema, which on resolution leaves thick, tight skin
  - characteristic face: mask-like facies, beak nose, radial perioral furrows (see Colour Atlas RH18)
  - other skin changes
    - atrophy, ulcerations, hypo- and hyperpigmentation, matt telangiectasias, calcinosis, periungual erythema, pruritus

- Raynaud's phenomenon
  - clinically presents as episodes (minutes to hours) of blanching and/or cyanosis of digits followed by erythema, tingling and pain
  - due to vasospasm and structural disease of blood vessels following cold exposure or emotional stress
  - if severe, can result in infarction of tissue at fingertips \(\rightarrow\) digital pitting scars, frank gangrene or autoamputation of the fingers or toes
  - scleroderma is the most common cause of secondary Raynaud's phenomenon

- GI tract (~90%)
  - becomes a rigid tube leading to decreased motility
  - distal esophageal hypomotility \(\rightarrow\) dysphagia in substernal region
  - loss of lower esophageal sphincter function \(\rightarrow\) gastric reflux, ulcerations and strictures
  - small bowel hypomotility \(\rightarrow\) bacterial overgrowth, diarrhea, bloating, cramping, malabsorption, weight loss
  - large bowel hypomotility \(\rightarrow\) infrequent cause of constipation
    - pathognomonic radiographic finding on barium contrast studies are large bowel wide mouth diverticula

- kidneys
  - "scleroderma renal crisis" (10-15%) may lead to malignant arterial hypertension, oliguria and microangiopathic hemolytic anemia
  - mild proteinuria, creatinine elevation and/or hypertension are more common

- lungs
  - interstitial fibrosis, pulmonary HTN, pleurisy, and pleural effusions

- heart
  - left ventricular dysfunction, pericarditis, arrhythmias, pericardial effusion

- musculoskeletal
  - polynarthalgias and sometimes frank polyarthritis affecting both small and large joints
  - bones resorbed with subcutaneous calcifications (calcinosis)
  - "resorption of distal tufts" (radiological finding)
  - proximal weakness secondary to disuse/atrophy/low grade inflammatory myopathy

- endocrine
  - may have hypothyroidism
**SEROPOSITIVE RHEUMATIC DISEASES: CONNECTIVE TISSUE DISORDERS... CONT.**

**Diagnosis**
- diagnostic criteria: 1 major or 2 or more minor of the following
  - major criterion: proximal scleroderma
  - minor criteria: sclerodactyly, digital pitting scars or loss of substance from the finger pad, bibasilar pulmonary fibrosis
- serology
  - anti-topoisomerase 1: specific but not sensitive for systemic sclerosis
  - anti-centromere favours diagnosis of CREST

**Treatment**
- education about precautionary measures (e.g. avoid cold)
- penicillamine for scleroderma of little value; expectant treatment with methotrexate/cyclosporine
- symptomatic treatment
  - GERD: proton pump inhibitors are first line, then H₂ receptor antagonists
  - small bowel bacterial overgrowth: broad-spectrum antibiotics (tetracycline, metronidazole)
  - Raynaud’s: calcium channel blockers, peripheral vasodilators, local nitroglycerin cream, systemic PGE₂ inhibitors
  - renal disease, HTN: ACE inhibitors
  - myositis, pericarditis: steroids

**IDIOPATHIC INFLAMMATORY MYOPATHY**
- characterized by proximal limb and neck weakness, sometimes associated with muscle pain
- early symptom is difficulty lifting head off pillow
- autoantibodies: ANA, anti-Jo-1, anti-Mi-2, other myositis-specific antibodies
- classification
  - polymyositis (PMY) / dermatomyositis (DMY)
  - juvenile DMY (usually with vasculitis)
  - PMY/DMY associated with malignancy
  - PMY/DMY associated with connective tissue disease
  - amyopathic DMY
  - inclusion body myositis (IBM)

**Polymyositis (PMY)/Dermatomyositis (DMY)**
- PMY is CD8 cell-mediated muscle necrosis
- DMY is B cell and CD4 immune complex-mediated perifascicular vasculitis
- DMY has characteristic dermatological features, found in children and adults, F>M
- PMY found in adults

**DMY/PMY Associated with Malignancy**
- increased risk of malignancy in females, age > 50, DMY > PMY, normal CK, refractory disease
- 2.4-6.5 fold increased risk of underlying malignancy usually in internal organ (ovarian, stomach, prostate, nonmelanoma skin cancer), cancers typical to that population

**Inclusion Body Myositis**
- age > 40, slowly progressive, vacuoles in cells on biopsy, M > F
- suspect when patient unresponsive to treatment

**Clinical Features**
- progressive symmetrical proximal muscle weakness (shoulder and hip) that develops over weeks to months with an increase in muscle enzyme levels
- dermatological involvement (mainly seen in DMY)
  - Gottron’s papules and Gottron’s sign are pathognomonic of dermatomyositis (occurs in 70% of patients) *(see Colour Atlas RH4)*
  - Gottron’s papules
    - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
  - Gottron’s sign
    - erythematous smooth or scaly patches over the dorsal interphalangeal or metacarpophalangeal joints, elbows, knees, or medial malleoli
    - heliotrope (purple) rash over the eyelids; usually with edema *(see Colour Atlas RH2)*
    - “shawl sign”
      - erythematous rash over neck, upper chest, and shoulders
cardiac involvement
- dysrhythmias, congestive heart failure, conduction defect, ventricular hypertrophy, pericarditis

GI involvement
- oropharyngeal and lower esophageal dysphagia, reflux

pulmonary involvement
- weakness of respiratory muscles, intrinsic lung pathology, aspiration

Diagnosis
1. progressive symmetric proximal muscle weakness
2. muscle enzyme levels: increased CK, aldolase, LDH, transaminases (AST, ALT)
3. EMG: short polyphasic motor units, high frequency repetitive discharge, insertional irritability
4. muscle biopsy: segmental fibre necrosis, basophilic regeneration, perivascular inflammation and atrophy
5. cutaneous eruption typical of dermatomyositis (required for diagnosis of DMY)
   - Definite PMY/DMY: fulfill 4 criteria
   - Probable PMY/DMY: fulfill 3 criteria
   - Possible PMY/DMY: fulfill 2 criteria

MRI is used to determine location for biopsy, and to follow disease progression

Treatment
- physical therapy
- assessment of organ involvement (ECG, PFT's, CXR, swallowing study)
- high dose corticosteroid (1-2 mg/kg/day) and slow taper
- immunosuppressive agents
  - azathioprine, methotrexate, cyclophosphamide, cyclosporine
- intravenous immunoglobulin (DMY)
- malignancy surveillance
  - detailed history and physical (breast, pelvic and rectal exam)
  - CXR, abdominal and pelvic ultrasound, stool occult blood, pap smear, mammogram

MIXED CONNECTIVE TISSUE DISEASE (MCTD)/OVERLAP SYNDROME
- combination of RA, SLE, scleroderma, and polymyositis with high titres of anti-ribonucleoprotein Ab (anti-RNP)
- anti-RNP, “speckled ANA fluorescence,” but absence of Ab to dsDNA, Sm and histones
- patient may have rash, RA, mouth and face of PSS
- “a disease in evolution” or an undifferentiated connective tissue disease
  - 50-60% will evolve into SLE
  - 40% will evolve into scleroderma
  - only 10% will remain as MCTD for the rest of their lives

SJÖGREN’S SYNDROME
- chronic, inflammatory disorder, likely autoimmune, characterized by CD4/CD8 cell-mediated infiltration and destruction of salivary and lacrimal glands
- primary form and secondary form (ie. associated with RA, SLE, dermatomyositis, and HIV)
- results in “sicca complex”: dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia)
SEROPOSITIVE RHEUMATIC DISEASES: CONNECTIVE TISSUE DISORDERS... CONT.

Table 12. Signs and Symptoms of Sicca

<table>
<thead>
<tr>
<th>Manifestations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular</strong></td>
<td>• burning/dry/painful eye relieved by tears</td>
</tr>
<tr>
<td></td>
<td>• foreign body sensation (worse in evening)</td>
</tr>
<tr>
<td></td>
<td>• blepharitis</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td>• dry mouth—difficulty swallowing food without drinking</td>
</tr>
<tr>
<td></td>
<td>• rapidly progressive caries (secondary to decreased saliva volume and its antibacterial factors)</td>
</tr>
<tr>
<td></td>
<td>• erythema of hard palate and oral mucosa</td>
</tr>
<tr>
<td></td>
<td>• oral candidiasis, angular cheilitis</td>
</tr>
</tbody>
</table>

- may evolve from an organ-specific to systemic disorder
- systemic manifestations include arthralgias/arthritis, subclinical diffuse interstitial lung disease, renal disease, palpable purpura, systemic vasculitis, lymphoma, Waldenström’s macroglobulinemia
- antibodies commonly seen in Sjögren’s include anti-La, anti-Ro, RF, ANA

**Clinical Pearl**

- Patients with Sjögren’s syndrome are at higher risk of non-Hodgkin’s lymphoma.

**Diagnosis (SSASSS)**

- S: Schirmer test (assess tear flow)
- S: Slit lamp exam with Rose-Bengal stain
- A: Autoantibodies (anti-Ro and –La)
- S: Salivary flow measurements
- S: Sialography
- S: Salivary gland biopsy: gold standard
- diagnosis by two of the following
  - characteristic labial salivary biopsy
  - keratoconjunctivitis sicca
  - associated connective tissue or lymphoproliferative disorder

**Treatment**

- good dental hygiene
- artificial tears or surgical punctal occlusion for xerophthalmia
- adequate hydration for xerostomia
- hydroxychloroquine, corticosteroids, immunosuppressive agents for severe systemic involvement
- topical nystatin/clotrimazole x 4-6 weeks for oral candidiasis
- most common complication: staphylococcal blepharitis

SEROPOSITIVE RHEUMATIC DISEASES: VASCULITIDES

**Vasculitis (see Colour Atlas RH7)**

- inflammation and necrosis of blood vessels with resulting tissue ischemia/infarction
- any organ system can be involved
- keys to diagnosis
  - clinical suspicion (presentation is non-specific)
  - labs non-specific: anemia, increased WBC and ESR, abnormal urinalysis
  - biopsy if tissue accessible
  - angiography if tissue inaccessible
- treatment generally entails corticosteroids and/or immunosuppressives
SEROPOSITIVE RHEUMATIC DISEASES: VASCUITIDES \ldots CONT.

<table>
<thead>
<tr>
<th>Table 13. Classification of Vasculitis and Postulated Mechanism of Vascular Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small vessel</strong></td>
</tr>
<tr>
<td>• NON-ANCA-ASSOCIATED</td>
</tr>
<tr>
<td>• Predominantly cutaneous vasculitis</td>
</tr>
<tr>
<td>• Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>• Essential cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>• ANCA-ASSOCIATED</td>
</tr>
<tr>
<td>• Wegener's granulomatosis</td>
</tr>
<tr>
<td>• Churg-Strauss vasculitis</td>
</tr>
<tr>
<td>• Microscopic polyangiitis</td>
</tr>
<tr>
<td><strong>Medium-sized vessel</strong></td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
</tr>
<tr>
<td>• Kawasaki's</td>
</tr>
<tr>
<td><strong>Large vessel</strong></td>
</tr>
<tr>
<td>• Giant Cell Arteritis (Temporal Arteritis)</td>
</tr>
<tr>
<td>• Takayasu's</td>
</tr>
<tr>
<td><strong>Immune complexes</strong></td>
</tr>
<tr>
<td><strong>ANCA</strong></td>
</tr>
<tr>
<td><strong>Immune complexes and granuloma formation</strong></td>
</tr>
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</table>

**PREDOMINANTLY CUTANEOUS VASCULITIS**
- also known as hypersensitivity/ cutaneous leukocytoclastic vasculitis
- caused by an immune reaction to either an endogenous or exogenous antigen
- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases

**Etiology**
- predominantly skin involvement; cutaneous vasculitis following
  - drug exposure
  - viral or bacterial infection
  - idiopathic causes
- drugs associated with this disease include allopurinol, gold, sulfonamides, penicillin, phenytoin
- other organ systems may be involved to varying degrees

**Pathology**
- small vessels involved (post-capillary vessels most frequently)
- usually causes a leukocytoclastic vasculitis = debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

**Clinical Features**
- skin
  - palpable purpura +/- vesicle formation and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules

**Diagnosis**
- vascular involvement established by biopsy

**Treatment**
- stop possible offending drug
- usually self-limiting
- corticosteroids +/- immunosuppressive agents

**HENOCH-SCHÖNLEIN PURPURA** (see Pediatrics Chapter)
- vascular deposition of IgA causing systemic vasculitis (skin, GI, renal)
- most frequently seen in childhood
- usually self-limiting condition

**WEGENER'S GRANULOMATOSIS**
- granulomatous inflammation of small- and medium-sized arteries and veins of respiratory tract and kidneys
- most common in middle age
- most present initially with symptoms of URTI
- transformation from inflammatory prodrome (serous otitis media and sinusitis) to full blown vasculitic syndrome
SEROPOSITIVE RHEUMATIC DISEASES: VASCULITIDES . . . CONT.

Clinical Features
- systemic
  - malaise, fever, weakness, weight loss
- respiratory
  - upper tract: sinusitis or rhinitis, nasoseptal perforation, saddle nose deformity, otitis media, and extension into the orbit with proptosis
  - lower tract: cough, hemoptysis, tracheobronchial erosion, pneumonitis, cavity formation
- kidney
  - segmental necrotizing glomerulonephritis (vasculitis rarely seen)
- other
  - joint, skin, eye complaints

Diagnosis
- American College of Rheumatology 1990 criteria include 2 of the following
  1. nasal or oral inflammation
  2. abnormal findings on CXR, including nodules, cavitations (see Colour Atlas R5)
  3. urinary sediment (protein, RBC casts)
  4. biopsy of involved tissue: lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis
- other tests include
  - specific: ANCA (c-ANCA > p-ANCA)
  - general: anemia, leukocytosis, elevated ESR

Treatment
- prednisone 1 mg/kg for 6 to 12 months +/- cyclophosphamide 2 mg/kg/day PO
- 3-6 months followed by high dose methotrexate (20-25 mg PO/SC weekly)

CHURG-STRAUSS SYNDROME
- granulomatous inflammation of small- and medium-sized vessels with hypereosinophilia and eosinophilic tissue infiltration
- triad of allergic rhinitis, asthma, systemic vasculitis
- 70% are associated with p-ANCA
- other manifestations include coronary arteritis, myocarditis, and neuropathy

MICROSCOPIC POLYANGIITIS
- pauci-immune necrotizing small vessel vasculitis
- affects kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin
- strongly associated with ANCA (p-ANCA > c-ANCA)
- absence of granulomatous inflammation and asthma

POLYARTERITIS NODOSA (PAN)

Epidemiology
- any age (average 40's-50's)

Etiology
- unknown in most cases

Pathology
- focal panmural necrotizing inflammatory lesions in small- and medium-sized arteries
- thrombosis, aneurysm or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion
- may involve one or many organ systems: most commonly affects joints, kidneys, peripheral nerves, GI, skin

Clinical Features
- joints
  - arthralgia and arthritis usually early in course
- kidneys
  - aneurysmal dilatation (not glomerulonephritis)
  - hypertension (25% of patients)
- peripheral nervous system
  - peripheral neuropathy with sudden pain, paresthesia, motor deficit, and mononeuritis multiplex
- GI
  - abdominal pain, hematemesis, melena, ischemic bowel, transaminase elevation
- skin
  - palpable purpura, ulceration, livedo reticularis, and digital tip infarct
- heart
  - myocardial infarction
  - coronary arteritis leading to congestive heart failure
**SEROPOSITIVE RHEUMATIC DISEASES: VASCULITIDES . . . CONT.**

**Diagnosis**
- vascular involvement established by biopsy or angiography

**Treatment**
- prednisone 1 mg/kg/day; cyclophosphamide 2 mg/kg/day PO

**GIANT CELL ARTERITIS (TEMPORAL ARTERITIS)**
- **RED FLAG** - untreated can lead to blindness (20-25%)
- inflammation of medium- and large-sized arteries, predominantly those originating from the aortic arch and the aorta itself
- ophthalmic posterior ciliary arteries most common

**Clinical Features**
- over 50 years of age, more common in women
- temporal headaches and scalp tenderness due to inflammation of the involved portion of the temporal or occipital arteries
- sudden, painless loss of vision, diplopia and/or permanent visual loss due to narrowing of the ophthalmic or posterior ciliary arteries
- tongue and jaw claudication (pain in muscles of mastication on chewing)
- polymyalgia rheumatica (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome; involvement of subclavian, brachial branches of aorta result in pulseless disease, aortic aneurysm +/- rupture

**Diagnosis**
- clinical suspicion, increased ESR, increased CRP, temporal artery biopsy, angiography

**Treatment**
- high dose prednisone 1 mg/kg in divided doses until symptoms resolve
- azathioprine or methotrexate if refractory (not proven)
- highly effective in the treatment of giant cell arteritis and in the prevention of blindness and other vascular complications

**TAKAYASU’S ARTERITIS**
- chronic inflammation of larger arteries, most often affecting the aorta and its branches
- usually young adults of Asian descent
- F>M

**OTHER VASCULITIDES**
- Buerger's disease
  - also known as thromboangitis obliterans
  - inflammation is secondary to pathological clotting
  - affects small- and medium-sized arteries and veins of the distal extremities
  - most important etiological factor is cigarette smoking, most common in Asian males
  - may lead to distal claudication, gangrene
  - therapy requires smoking cessation
- Behçet's disease
  - multisystem disorder presenting with ocular involvement, recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement
  - pathology: leukocytoclastic venulitis
- vasculitis mimicry
  - cholesterol emboli
  - atrial myxoma
### Table 14. Features of Seronegative Disease

<table>
<thead>
<tr>
<th></th>
<th>Sacro-iliac Joint</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
<th>Iritis</th>
<th>Aortitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>+</td>
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<tr>
<td>IBD</td>
<td>++</td>
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<td>+</td>
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</tr>
<tr>
<td>Reactive</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Psoriatic</td>
<td>+</td>
<td>+</td>
<td>++++</td>
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</table>

### ANKYLOSING SPONDYLITIS (AS)
- Prototype of the spondyloarthropathies
- Characterized by
  - Enthesitis, sacroilitis, spondylitis
  - Inflammatory ocular diseases
  - Asymmetric oligoarthritis, mostly large joints (shoulder, hips)
  - Genitourinary disease: prostatitis
  - HLA B27 association

### Epidemiology
- Incidence 0.2% of general population
- M:F = 3:1; females have milder disease
- Age of onset is usually late teens or early twenties
- 90% of patients with AS have HLA B27 vs. 9% of the general population

### Pathophysiology
- Enthesitis
  - Inflammation of ligament where it attaches to bone
  - Inflammation leads to osteopenia, then erosion, then ossification

### Clinical Features
- Axial
  - Mid- and low back stiffness, pain at rest
  - Persistent buttock pain
  - Postural changes: increased dorsal kyphosis, decreased lumbar lordosis, forward protrusion of cervical spine (see Colour Atlas RH21)
  - Spinal restriction: lumbar/thoracic/cervical spine in flexion/extension/rotation
  - Decreased chest wall expansion (normal > 5 cm at T4)
- Appendicular
  - Asymmetrical large joint peripheral arthritis, most often involving lower limb
- Extra-articular manifestations
  - Acute anterior uveitis (25-30% patients)
  - Heart: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - Kidney: amyloidosis and IgA nephropathy
  - Pulmonary: apical fibrosis (rare)
  - Cauda equina syndrome (rare)

### Diagnosis
- Physical exam: increased occiput-to-wall distance, decreased chest expansion, loss of normal lumbar lordosis and increased thoracic kyphosis, painful sacroiliac joint, decreased modified Schröber (i.e. detection of decreased forward flexion of lumbar spine)
- X-ray of SI joint: radiographic “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late) (see Colour Atlas RH19)
- X-ray of spine: radiographic appearance of “squaring of edges” from erosion and sclerosis on corners of vertebral bodies leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes), producing a bamboo spine radiographically (see Colour Atlas RH20)
Treatment
- heat
- prevent fusion in poor posture and disability
  - exercise (e.g. swimming)
  - postural and deep breathing exercises
- medication
  - NSAIDs: do not alter natural history
  - DMARDs for peripheral arthritis (sulfasalazine, methotrexate)
  - infliximab for axial involvement
- manage extra-articular manifestations
- surgery: hip replacement, vertebral osteotomy for marked deformity

Prognosis
- spontaneous remissions and relapses are common and can occur at any age
- despite spinal deformity, function may be excellent
- good if female and onset after age 40
- early onset with hip disease may lead to severe disability; may require arthroplasty

Reactive Arthritis
- a generic term for arthritis following an infection (e.g. rheumatic fever, Reiter's)

Epidemiology
- 90% of patients are male, aged 20-40, and positive for HLA B27
- in HLA B27 patients, axial > appendicular involvement

Etiology
- onset following an infectious episode either involving the GI or GU tract
  - GI: Shigella, Salmonella, Campylobacter, Yersinia species
  - GU: Chlamydia, Mycoplasma species
- acute pattern of clinical course
  - 1-4 weeks post-infection
  - lasts weeks to years with 1/3 chronic
  - often recurring
  - spinal involvement persists

Clinical Features
- peripheral arthritis, asymmetric pattern
- iritis, plantar fasciitis, Achilles tendonitis, oral ulcers, spondylitis (thick and skipped syndesmophytes), diarrhea
- keratoderma blenorrhagica (hyperkeratotic skin lesions on palms and soles) and balanitis cincta (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- sausage digits (“dactylitis”) are characteristic of reactive and psoriatic arthritis

Diagnosis
- clinical
- lab findings: normocytic, normochromic anemia and leukocytosis
- cultures are sterile

Treatment
- appropriate antibiotics if there is documented infection
- NSAIDs, physical therapy, home exercise
- local therapy
  - joint protection
  - intra-articular steroid injection
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids, sulfasalazine, methotrexate (for peripheral joints only)
- manage ophthalmic and other manifestations

Psoriatic Arthritis
- psoriasis affects 1% of population
- arthropathy in 10% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

Etiology
- unclear but many genetic, immunologic and some environmental factors involved
  - (e.g. psoriatic plaque flora, particularly Group A Streptococci, and trauma)
SERONEGATIVE RHEUMATIC DISEASES . . . CONT.

Clinical Features
- skin and nail changes are typical findings
  - well-demarcated erythematous plaques with silvery scale (see Colour Atlas RH23)
  - nail involvement includes pitting, transverse or longitudinal ridging, discolouration, subungual hyperkeratosis, onycholysis, and oil drops

Clinical Pearl
- Check “hidden” areas for psoriatic lesions (ears, hair line, umbilicus, anal cleft, nails).

joints - 5 general patterns
- arthritis of DIP joints with nail changes
- destructive (mutilans) arthritis (5%)
- symmetric polyarthritis (similar to RA)
- sacroiliitis and spondylitis (usually older, male patients)
- asymmetric oligoarthritis (most common)

eye
- conjunctivitis, iritis

heart and lung (late findings)
- aortic insufficiency
- apical lung fibrosis

peripheral nervous system
- cauda equina claudication

radiology (see Colour Atlas RH22)
- floating syndesmophytes
- pencil and cup appearance at IP joints
- osteolysis, periostitis

Treatment
- treat skin disease (e.g. steroid cream, salicylic/retinoic acid, tar)
- NSAIDs
- intra-articular steroids if NSAIDs fail to reduce synovitis and pain
- severe disease with erosive arthritis
  - DMARDS: methotrexate, sulfasalazine, cyclosporine, gold, hydroxychloroquine, azathioprine, and TNF inhibitors
    - infliximab and etanercept

INFLAMMATORY BOWEL DISEASE (IBD)
(see Gastroenterology Chapter)
- particular manifestations of ulcerative colitis and Crohn's disease include peripheral arthritis (large joint, asymmetrical), spondylitis and hypertrophic osteoarthropathy
- arthralgia, myalgia, osteoporosis and aseptic necrosis of bone secondary to glucocorticoid treatment of the bowel inflammation

Table 15. Comparing Features of Spondylitis vs. Peripheral Arthritis in IBD

<table>
<thead>
<tr>
<th>HLA-B27 association</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td>M &gt; F</td>
<td>M = F</td>
</tr>
<tr>
<td>onset before IBD</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>parallels IBD course</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>type of IBD</td>
<td>UC = Crohn's</td>
<td>Crohn's</td>
</tr>
</tbody>
</table>

RH28 – Rheumatology          MCCQE 2002 Review Notes
CRYSTAL-INDUCED ARTHROPATHIES

GOUT
- derangement in purine metabolism resulting in hyperuricemia, monosodium urate crystal deposits in tissues (tophi), synovium (microtophi)
- recurrent episodes of acute arthritis

Epidemiology
- most common in males > 45 years old
- extremely rare in premenopausal female

Mechanism of Uric Acid Production
- sources of uric acid: diet and endogenous
- synthesis
  - hypoxanthine → xanthine → uric acid
  - both steps catalyzed by xanthine oxidase

Hyperuricemia
- due to dietary excess, overproduction of urate (< 10% of cases), or relative undersecretion of urate (> 90% of cases)
- primary or genetic
  - mostly due to idiopathic renal undersecretion (90%)
  - also idiopathic overproduction or abnormal enzyme production/function
- secondary
  - undersecretion
    - renal failure
    - drugs: diuretics, ASA, ethanol, cyclosporine, levodopa, ethambutol, vitamin B12, nicotinic acid
    - conditions: sarcoidosis, hypothyroidism, hyperparathyroidism, trisomy 21, preeclampsia/eclampsia
  - overproduction
    - increased nucleic acid turnover: hemolysis, myeloproliferative disease, lymphoproliferative disease, psoriasis, rhabdomyolysis, exercise, ethanol, obesity
- majority of people with hyperuricemia do not have gout, and normal or low uric acid levels do not rule out gout
- sudden changes in uric acid levels, temperature and pH are more important than actual levels
- common precipitants: alcohol use, dietary excess, dehydration (e.g. thiazide and loop diuretics), trauma, illness, surgery, tumour lysis syndrome
- other associated conditions: hypertension, obesity, diabetes, starvation

Clinical Presentation
- acute gouty arthritis (see Colour Atlas RH5)
  - painful, usually involving lower extremities (e.g. first MTP joint)
  - precipitation of urate crystals in the joint space
  - involvement of big toe = “podagra”
  - may progress to mimic cellulitis, but in cellulitis will be able to move joint
  - attack will subside on its own within several days to weeks and may or may not recur
- tophi
  - urate deposits in cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions, pressure points
  - painless, but may limit joint mobility
- kidney
  - gouty nephropathy
  - uric acid calculi

Diagnosis (see Colour Atlas RH6)
- need to demonstrate crystals of monosodium urate in joint aspirate
- negatively birefringent, needle-shaped crystals within the WBC of synovial fluid under polarizing lens present in > 90% of aspirates
- differential diagnosis includes pseudogout, trauma, sepsis, OA
CRYSTAL-INDUCED ARTHROPATHIES . . . CONT.

**Treatment**

- **treatment of acute gout**
  - NSAIDs and COX-2 inhibitors: high dose, then taper as symptoms improve (polyarticular gout)
  - corticosteroids - intra-articular, oral or intra-muscular (if renal or GI disease)
  - colchicine within first 24 hours but effectiveness limited by low therapeutic/toxic ratio
  - allopurinol can worsen an acute attack (therefore do not start during acute flare)

- **treatment of chronic gout**
  - not the same as treatment of acute gout
  - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
  - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  - antihyperuricemic drugs
    - drugs that decrease uric acid production (allopurinol inhibits xanthine oxidase)
    - uricosuric drugs (probencid, sulfinpyrazone) if failure on allopurinol or intolerant to allopurinol; do not use in renal failure
  - note that initiating any antihyperuricemic therapy may precipitate an acute gouty attack due to a rapid change in serum urate concentration
  - prophylaxis prior to starting antihyperuricemic drugs: colchicine/NSAID
  - in renal disease secondary to hyperuricemia, use low dose allopurinol and monitor creatinine

**PSEUDOGOUT (CHONDROCALCINOSIS)**

- acute inflammatory arthritis due to phagocytosis of IgG-coated calcium pyrophosphate dihydrate (CPPD) crystals by neutrophils and subsequent release of inflammatory mediators

**Epidemiology**

- elderly
- slower onset and lasts up to 3 weeks but self-limited
- more frequently polyarticular compared to gout
- risk factors: old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), diabetes, hemochromatosis

**Clinical Features**

- pain may be as severe as gout
- may present as chronic arthritis with acute exacerbations
- affects knee, wrist, hand, foot and big toe
- may be triggered by dehydration, acute illness, surgery, trauma
- 5% will be pseudorheumatoid (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- half of the patients will develop degenerative joint changes

**Diagnosis**

- x-rays show chondrocalcinosis: punctate radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radio densities in hyaline articular cartilage (see Colour Atlas RH25)
- chondrocalcinosis seen in 75% of pseudogout
- must aspirate joint to rule out septic arthritis, gout
- positive birefringence, rhomboid-shaped crystals in the synovial fluid and within neutrophils under polarizing light (present in 60% of patients and often only a few crystals) (see Colour Atlas RH24)
- differential diagnosis includes gout, trauma, sepsis, RA

**Treatment**

- aspiration of joint, rest and joint protection
- NSAIDs
  - also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- intra-articular steroids to relieve inflammation
CRYSTAL-INDUCED ARTHROPATHIES . . . CONT.

Table 16. Gout vs. Pseudogout

<table>
<thead>
<tr>
<th></th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td>M &gt; F</td>
<td>M = F</td>
</tr>
<tr>
<td>age</td>
<td>middle-aged males</td>
<td>older</td>
</tr>
<tr>
<td>onset of disease</td>
<td>acute</td>
<td>acute/insidious</td>
</tr>
<tr>
<td>crystal</td>
<td>negative birefringence, needle-shaped</td>
<td>positive birefringence, rhomboid-shaped</td>
</tr>
<tr>
<td>distribution</td>
<td>first MTP, foot</td>
<td>knee, hand, polyarticular</td>
</tr>
<tr>
<td>radiology</td>
<td>“holes in bones”</td>
<td>chondrocalcinosis</td>
</tr>
<tr>
<td>treatment</td>
<td>Indomethacin, Colchicine, COX-2 inhibitors</td>
<td>OA (knee, wrist, 2nd and 3rd MCP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAIDs</td>
</tr>
</tbody>
</table>

SEPTIC ARTHRITIS

- RED FLAG – permanent joint damage can occur in < 2 weeks rapidly
- an acute monoarthritis, rarely an oligoarthritis

**Etiology**
- hematogenous (adults)
- osteomyelitis (children)
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

**Common Organisms**
- *N. gonorrhoeae*: accounts for 75% of septic arthritis in young sexually active adults
- *S. aureus*: affects all ages - rapidly destructive, most nongonococcal cases of septic arthritis in adults
- Gram negatives: affects debilitated patients - rapidly destructive
- *S. pneumoniae*: affects children
- *H. influenzae*: affects infants (especially if incomplete immunization)
- *Salmonella* spp.: characteristic of sickle cell

**Predisposing Factors**
- extra-articular infection (e.g. GU tract, skin, lung)
- chronic illness (e.g. RA, DM, malignancy)
- prior drug use (e.g. antibiotics, immunosuppressives)
- prior joint damage (e.g. OA, RA, prosthetic joints)
- suppressed immune status (e.g. SLE, HIV)

**Clinical Features**
- preceding bacteremia with skin lesions and migrating polyarthritis settling to monoarthritis often of a large joint (most often the knee)
- systemic symptoms of sepsis: fever and malaise
- local symptoms in involved joint: swelling, warmth, pain, inability to weight-bear, marked decrease in range of movement
- gonococcal triad: migratory arthritis, tenosynovitis next to inflamed joint (see Colour Atlas RH26), maculopapulovesicular skin changes

**Diagnosis**
- high index of suspicion
- culture and sensitivity
  - gonococcal: in addition to blood and urine cultures, endocervical, urethral, rectal and oropharyngeal cultures
  - nongonococcal: blood and urine
  - arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, culture, examine for crystals
- infectious = opaque, 1WBC count (inflammatory), PMNs > 85%, culture positive
- growth of GC from synovial fluid is successful in < 50% of cases; therefore, Gram stain is more useful
- synovial biopsy if diagnosis is unclear
- +/- plain X-ray: used to rule out osteomyelitis; provides baseline to monitor treatment
Figure 5. The Diagnosis and Management of Acute Monoarthritis


Treatment (see Figure 5)
- surgical drainage if
  - > 72 hours of persistent infection
  - hip joint involvement
- start IV antibiotics empirically (delay may result in joint destruction)
  - use third generation cephalosporin + penicillinase resistant synthetic penicillin (e.g. ceftriaxone + cloxacillin) before culture results come back;
- Gram stain guides subsequent treatment:
  - Gonococcal: ceftriaxone 1g/d, IM or IV; if penicillin-sensitive- ampicillin (1g q6h IV) or penicillin G (10 million U/d) usually 2-4 days IV then 7 days PO
  - Nongonococcal: antibiotics against S. aureus, Strept X ≥ 2 wk IV then 2-4 wk PO
- no need to give intra-articular antibiotics, but do daily joint aspirations until culture sterile
- physiotherapy
- intra-articular steroids are contraindicated in septic arthritis
NON-ARTICULAR RHEUMATISM

- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendonitis, tenosynovitis, and fibromyalgia (fibrositis)

FIBROMYALGIA
- chronic, diffuse pain with characteristic tender points

Epidemiology
- F:M ≥ 3:1
- primarily ages 25 to 45, some adolescents
- prevalence of 2-5% in general population, higher in rheumatology patients
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

Pathology
- laboratory investigations typically normal unless underlying illnesses present

Clinical Features
- widespread aching, stiffness and reproducible tender points (see Figure 6)
- fatigue
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- non-restorative sleep, difficulty falling asleep, and frequent wakening
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel syndrome, migraines, tension headaches, obesity, depression, and anxiety

Diagnosis
- 3 month history of widespread pain
- pain in 11 of 18 tender points with approximate force of 4 kg
- must rule out numerous other causes, e.g. polymyositis, polymyalgia rheumatica, thyroid disorders, sleep apnea

Treatment
- education - disease is benign, non-deforming, does not progress
- exercise program (walking, aquatic exercises)
- support back and neck: neck support while sleeping, abdominal muscle strengthening exercises
- stress reduction
- psychiatric treatment when necessary
- medical therapy
  - tricyclic antidepressants
  - for sleep restoration
  - select those with lower anticholinergic side effects
  - NSAIDs if pain interferes with sleep
- biofeedback, meditation, acupuncture, physiotherapy may be helpful
POLYMYALGIA RHEUMATICA
- characterized by profound pain and stiffness of the proximal extremities
- closely related to giant cell arteritis

Epidemiology
- incidence 50 per 100,000 per year in those over age 50
- age of onset typically > 50
- F:M = 2:1

Clinical Features
- constitutional symptoms prominent (fever, weight loss, malaise)
- AM stiffness of proximal muscles and joints (neck, hip and shoulder girdles, thighs)
- physical examination reveals tender muscles but no weakness or atrophy
- laboratory investigations often reveal anemia, elevated ESR, CRP and platelets, normal CK
- diagnosis requires
  - age > 50 years
  - more than two affected muscle groups
  - at least a 2 week duration
  - increased ESR
  - rapid and lasting response to corticosteroids
  - must rule out infection, RA, SLE, PAN, malignancy, and giant cell arteritis

Treatment
- relieves symptoms
- start with steroid dose of 15-20 mg PO daily
- taper slowly over 2 year period monitoring ESR and symptoms closely
- treat relapses aggressively (50% relapse rate)
**Degenerative Arthritis:**  
**Osteoarthritis**  
- hand (DIP, PIP, 1st CMC)  
- hip  
- knee  
- 1st MTP  
- L-spine (L4-L5, L5-S1)  
- C-spine  
- uncommon: ankle, shoulder, elbow, MCP, rest of wrist

**Seropositive Rheumatic Diseases: Rheumatoid Arthritis**  
- PIP  
- MCP  
- wrist, not 1st CMC  
- elbow  
- shoulder  
- knee  
- ankle  
- MTP

**Seronegative Rheumatic Diseases: Ankylosing Spondylitis**  
- SI  
- spondylitis  
- hip  
- shoulder

**Crystal-Induced Arthropathies:**  
**Gout**  
- 1st MTP  
- ankle  
- knee

**Crystal-Induced Arthropathies:**  
**Pseudogout**  
- knee  
- polyarticular wrist  
- hand (MCP)  
- foot (1st MTP)
REFERENCES


CMAJ Clinical Basics Rheumatology Series


