Rheumatoid Arthritis

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Objectives

- Recognize and diagnose rheumatoid arthritis (RA)
- Understand basic treatment approach in patients with RA
- Understand the risk associated with treatment of RA
- Identity common preventative health issues that arise in care of patient with RA in primary care

Epidemiology

- Incidence: 0.5 per 1000 persons per year
- Prevalence of RA is 1% to 2%
  - Steadily increases to 5% in women by age 70
- Risk factors:
  - Female are 2-3:1 compared to men
  - Genetic factors: HLA-DR and Shared epitope
  - Tobacco
  - Infections (bacterial, viral)
- Age at onset: can occur 20-30’s. Average age 66 years

Synovial pathology

- Synovium is the primary site of inflammation in RA.
- Normal synovium: usually discontinuous, about one to two layers thick
- RA synovium:
  - Hyperplasia, infiltrating T cells, macrophages, dendritic cells, B cells, mast cells
  - Inflammatory cytokines
  - Extensive new vessel formation
Normal vs RA joint

Pathogenesis of RA

Diagnosis of rheumatoid arthritis

Table 3. The IB21 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Score</th>
<th>Target population (Who should be tested?)</th>
<th>Relevant data (Yes or No)</th>
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<tbody>
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<td>Early in disease process (≤ 6 months)</td>
<td>Positive ANA</td>
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<tr>
<td>1</td>
<td>Early in disease process (≤ 6 months)</td>
<td>Negative ANA</td>
</tr>
<tr>
<td>2</td>
<td>Late in disease process (&gt; 6 months)</td>
<td>Positive ANA</td>
</tr>
<tr>
<td>3</td>
<td>Late in disease process (&gt; 6 months)</td>
<td>Negative ANA</td>
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<tr>
<td>4</td>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>All patients</td>
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</table>
Clinical features

- Vary from patient to patient
- Typically slow, insidious development of symptoms
  - Explosive, acute polyarticular onset can occur
  - Monoarticular acute onset very rare

Assessment of RA

- Assessment typically include clinical, functional, biochemical, and imaging parameters
- Morning stiffness: > 1 hour
- Location of affected joints
  - Polyarticular
  - Symmetrical
- Presence of tenderness and swelling
- Rheumatoid nodules

Synovitis

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Assessment of RA

- Serum electrolytes, liver function, and renal function are usually normal
- Depressed albumin and increased gamma globulin production
- 25% of RA patients will have a normocytic normochromic anemia (chronic inflammation)
- ESR and CRP are typically elevated

Radiological Findings in RA

- Hands, wrists, and feet
- Periarticular osteopenia
  - Non-specific or diagnostic
- Juxta-articular erosion (6-12 months)
- Symmetrical joint space narrowing (6-12 months)
- Late findings: subluxation and loss of joint alignment

RF and CCP

- Serology not used for screening
- Categorize inflammatory arthritis
- Seronegative RA

Differential diagnosis

- Connective tissue diseases presenting with polyarticular arthritis:
  - Lupus, systemic sclerosis, mixed connective tissue disease, and Sjogren's syndrome
- Psoriatic arthritis
  - Arthritis can precede rash
  - DIP involvement
- Other spondyloarthropathy
- Crystal arthropathy
**Differential diagnosis**

- Infectious (viral)
  - Parvovirus B19
  - Hepatitis C (can present with RF+)
- Non-inflammatory conditions:
  - Fibromyalgia
  - Overuse syndromes
  - Degenerative / osteoarthritis
- Malignancy

**Extra-articular manifestation of RA**

- Skin: rheumatoid nodules
- Felty's syndrome: splenomegaly with neutropenia, large granular lymphocytes, thrombocytopenia
- Pulmonary: pleural thickening, pleural effusion, ILD, nodules, BOOP, Caplan's syndrome, cricoarytenoid arthritis, PAH
- Cardiac: pericarditis, accelerated atherosclerotic disease

**Extra-articular manifestation of RA (continued)**

- Ophthalmologic: keratoconjunctivitis sicca, episcleritis, scleritis, uveitis
- Neurologic: peripheral entrapments neuropathy, cervical myelopathy
- Muscular: muscle atrophy, myositis
- Renal: low grade membranous glomerular nephropathy, reactive amyloid
- Vascular: small vessel vasculitis, systemic vasculitis

**Treatment of RA**

- Early treatment (rapid damage and disability)
- Disease severity must be determined
- Risk vs benefits
- Monitoring for drug toxicity
- Monitoring disease activity (DAS28 score, radiographs..etc)
Treatment options

- NSAIDs and COX-2 inhibitors:
  - Symptomatic relief (anti-inflammatory / analgesic effects)
  - No change in disease progression
  - Warning: CKD, CAD, gastritis
- Low dose prednisone:
  - 10-15 mg daily
  - No change in disease progression
  - Bridging therapy / early adjunct therapy
  - Warning: diabetes, osteoporosis, weight gain..etc.

DMARDs

- Initiation of DMARD therapy within the first 3-6 months
- Step up therapy method

Conventional DMARDs

- Hydroxychloroquine
  - Anti-malarial with unknown mechanism of action – lysosomes
  - Mild disease < 5 years
  - ? decrease rate of structural damage
  - 200-400 mg daily
  - Toxicity: generally safe, retinopathy / corneal deposits (yearly eye exams). G6PD testing.

Conventional DMARDs (continued)

- Sulfasalazine
  - Unknown mechanism
  - Reduces the development of joint damage
  - 2-3 g / day
  - Toxicity: generally safe. Sulfa allergy. GI intolerance, cytopenia and hepatotoxicity

http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/#new
Conventional DMARDs:

**Methotrexate**

- Dihydrofolate reductase inhibitor
- First line agent for most patient with RA
- Oral or subcutaneous (15-25 mg weekly)
- Very effective (monotherapy)
- Good efficacy, favorable toxicity profile, ease of administration, and relatively low cost
- Slows or halts radiographic damage

**Methotrexate (Toxicity)**

- Hepatotoxicity, pneumonitis, and severe myelosuppression are all very rare.
- Alcohol intake, hepatitis serologies. GI intolerance, alopecia, oral ulcers – can be eliminated folic acid or SQ injections.
- CBC, LFT’s and renal function every 2-3 months.
- No pregnancy!

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**Leflunomide**

- Dihydroorotate dehydrogenase inhibitor
- Alternative oral agent to methotrexate
- Does slow radiographic changes
- 10-20 mg daily (loading dose 100 mg x 3)
- Toxicity: GI intolerance, mild hair thinning, hepatotoxicity, myelosuppression. Alcohol intake and hepatitis panel. CBC, LFT’s, and renal function every 2-3 months.
- No pregnancy!

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**Double therapy**

- Methotrexate
- Leflunomide

**Triple therapy**

- Methotrexate
- Leflunomide
- Sulfasalazine
- Hydroxychloroquine

**Proportion with Good Response (%)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Methotrexate</th>
<th>Leflunomide</th>
<th>Sulfasalazine</th>
<th>Hydroxychloroquine</th>
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**Figure 1.** Patients with Good Response to the Assigned Study Treatment.


Klippel, Primer on the rheumatic diseases, 13th edition. 200, 138

http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/#new
## Biologic DMARDs

**Tumor necrosis factor (TNF) inhibitors:**
- Etanercept (Enbrel): soluble receptor fusion protein that binds to soluble TNF
- Adalimumab (Humira): human monoclonal antibody binds to soluble and membrane bound TNF
- Infliximab (Remicade): chimeric monoclonal antibody
- Others: golimumab (Simponi), certolizumab (Cimzia): human monoclonal

**TNF inhibitor toxicity:**
- Increase risk on infection (skin, URI, UTI, pneumonia)
- Opportunistic infection (reactivation of TB, fungal)
- ? lymphoma / malignancy
- Hepatitis B reactivation
- Heart failure
- Cytopenia
- Drug induced lupus
- New onset psoriasis

**T-cell costimulatory blockade**
- Abatacept: interferes with APC and T-cells by binding to CD80/CD86 which prevents it from binding to CD28
- Toxicity: similar to TNF. COPD.

**IL-1 inhibitors**
- Anakinra: human recombinant anti-IL-1 receptor antagonist
- Toxicity: infections less common compared to TNF. Malignancy similar to general population. Injection site reaction.

**B-cell depletion**
- Rituximab: chimeric monoclonal antibody that binds to CD20
- Toxicity: infusion reaction, reactivation of viral infection, PML

**IL-6 inhibitor**
- Tocilizumab: humanized anti-human IL-6 receptor antibody that binds to soluble and membrane-bound IL-6 receptor
- Toxicity: infection, malignancy, perforations, neutropenia, and hypercholesterolemia
### Biologic DMARDs

- **JAK-STAT pathway**
  - Toxicity: infection, malignancy, perforation, neutropenia, hypercholesterolemia.

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### Other treatment

- Intramuscular Gold
- Azathioprine
- Minocycline
- Cyclosporine

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### Comorbidities

- **Osteoporosis:**
  - Due to disease or use of steroids
  - Routinely advised to take calcium and vitamin D (vit D deficiency common)
  - Bone density scan early
  - 7.5 mg of prednisone > 3 months - bisphosphonate

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### Comorbidities

- **Cardiovascular disease**
  - Number one cause of death in RA
  - RA is a risk factor
  - Typically under assessed
  - Recommend using similar guidelines established for diabetes
### Other considerations for PCP

- **Pregnancy**
  - Typically improves symptoms of RA
  - Not recommended with some DMARDs (methotrexate and leflunomide). Half life can be months.
  - Biologics have not been studied but have been used in pregnancy


### Pre-op evaluation

- Atlantoaxial subluxation (long standing and uncontrolled disease)
- Infections
- Stop methotrexate 1-2 week prior to surgery
- TNF inhibitors should be held
- Bridge with low dose steroids
- Stress dose steroids

### Vaccination

- Annual influenza vaccine (inactivated not live attenuated)
- Pneumococcal vaccine every 5 years
- DO NOT recommend any live attenuated vaccines (measles, mumps, rubella, zoster...etc).


### Summary

- RA is a chronic, inflammatory arthritis that is symmetrical and polyarticular
- Diagnosed using the combination of physical exam and laboratory tests in the correct setting
- RF and CCP not screening tests
- Early diagnosis and treatment is key
- DMARDs carry significant risks and toxicities that need to be monitored
- Risk for other diseases that should be monitored