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

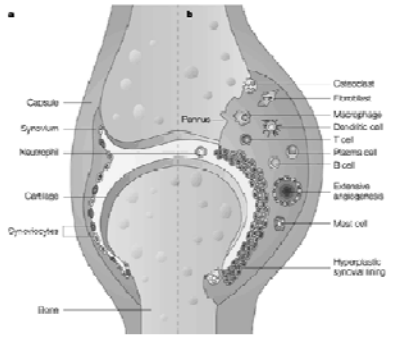
Epidemiology

- 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

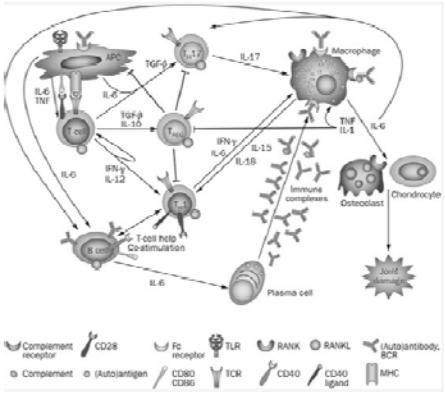
- Synovium is the primary site of inflammation in RA.
- Normal synovium: usually discontinuous, about one to two layers thick
- RA synovium:
  - Hyperplasia, infiltrating T cells, macrophages, dendritic cells, B cells, mast cells
  - Inflammatory cytokines
  - Extensive new vessel formation

Normal vs RA joint



Therapeutic strategies for rheumatoid arthritis. Josef S. Smolen & Günter Steiner. *Nature Reviews Drug Discovery* 2, 473-488 (June 2003)

Pathogenesis of RA



The pathogenesis of rheumatoid arthritis: new insights from old clinical data? Josef S. Smolen, Daniel Aletaha & Kurt Redlich. *Nature Reviews Rheumatology* 8, 235-243 (April 2012)

Diagnosis of rheumatoid arthritis

ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
DOI 10.1002/art.27584
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Arthritis & Rheumatism
An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

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Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

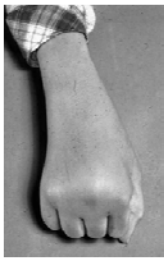
	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

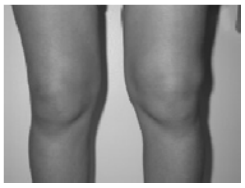
Figure 1. Tree algorithm for classifying definite rheumatoid arthritis (RA) (green circles) or for excluding its current presence (red circles) among those who are eligible to be assessed by the new criteria. APR = acute-phase response. Serology: + = low-positive for rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA); serology: ++ = high-positive for RF or ACPA; serology: +/++ = serology either + or ++. See footnotes to Table 3 for further explanation of categories.

Clinical features

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

Synovitis

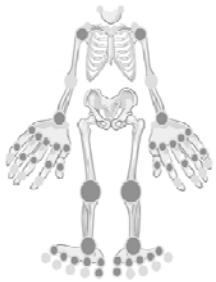




Unsal *et al. Pediatric Rheumatology* 2007 5:7 doi:10.1186/1546-0096-5-7

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



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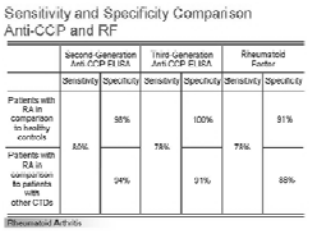
Assessment of RA

- 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

RF and CCP

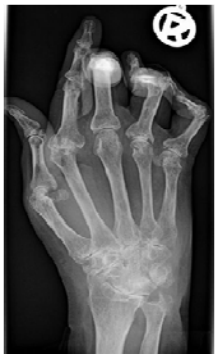


- Serology not used for screening
- Categorize inflammatory arthritis
- Seronegative RA

http://www.mayomedicallaboratories.com/images/articles/hottopics/2011/08-rheumatoid/slide15.jpg

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



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

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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.

Klipple. Primer on the rheumatic diseases, 13th edition. 200. 138
http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/#new

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

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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

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Conventional DMARDs: 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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Conventional DMARDs: 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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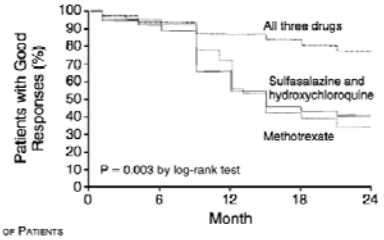
Triple therapy



No. of Patients					
Methotrexate	36	34	20	14	12
Sulfasalazine and hydroxychloroquine	35	31	19	15	14
All three drugs	31	29	27	25	24

Figure 1. Patients with Good Responses to the Assigned Study Treatment.

O'dell et al. Treatment of Rheumatoid Arthritis with Methotrexate Alone, Sulfasalazine and Hydroxychloroquine, or a Combination of All Three Medications. N Engl J Med 1996; 334:1287-1291

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

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Biologic DMARDs

- 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

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Biologic DMARDs

- 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.

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Biologic DMARDs

- 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

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Biologic DMARDs

- JAK-STAT pathway
  - Tofacitinib: JAK inhibitor. Oral biologic.
  - 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

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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

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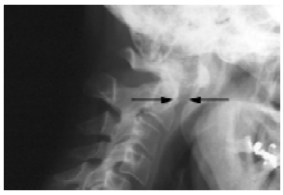
Pre-op evaluation

- 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).

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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