



What is Rheumatoid Arthritis?

- Most common chronic inflammatory arthritis
- Systemic, progressive, autoimmune disease that affects synovial joints, tissues & organs
- Persistent inflammation causes damage to cartilage & bones
- Joint damage and deformity cannot be reversed



Pathophysiology

RA is immune mediated inflammatory disease

Synovium:

1. Synovial lining: Normal 1-3 cells thick
RA 8-10 cells thick
2. Subintimal area : Normal – few cells thick
RA-infiltrated with inflammatory cells (pannus)
(Waldburger & Firestein, 2008)



Pathophysiology

Cartilage: Normal- resilient
RA- integrity is impaired by cytokines

Bone: RA-cytokines influence activation of osteoclasts & causes bone destruction

Synovial cavity: Normal- 1-2 ml of fluid
RA- large collection of fluids

Pathophysiology

- **T-cell** activation proliferates and begins to secrete additional cytokines and produce enzymes that increase and perpetuate the inflammatory response
- **B-cell** become activated through interactions with T-cells and through soluble cytokines
- **Plasma cells** produce antibodies rheumatoid factor & anti-cyclic citrullinated peptide

(Waldburger & Firestein, 2008)



Prevalence

- The Centers for Disease Control and Prevention
CDC –March 2017
- Estimated 54.4 million U.S. adults have arthritis (25 % of the population)
- 1.3 million U.S. Adults estimated to have RA

American College of Rheumatology [ACR], 2017



Etiology

- Q Unknown
- Q Genetic predisposition
- Q Environment factors -infections, smoking
- Q Hormones -2-3 times higher in women
- Q Often begins between fourth & sixth decades

(Waldburger & Firestein, 2008)



Disease Burden

RA is an economic burden on patients, families, and society due to cost of medical care and disability, usually during working years (Greenapple, 2012).



Prevalence

The Centers for Disease Control and Prevention
CDC –March 2017

Estimated **54.4 million** U.S. adults have arthritis
(25 % of the population)

American College of Rheumatology [ACR], 2017



■ No Arthritis ■ Have Arthritis

Disease Burden

Estimates of RA's yearly health care costs are **\$8.4 billion** and total yearly societal costs are about **\$19.3 billion**.

Curtis, JR, et al., 2015



Signs and Symptoms

Early S&S:

- Insidious onset
- Fatigue
- Low grade fever
- Weight loss, decreased appetite
- Joint pain, muscle pain
- Numbness & tingling in the hands

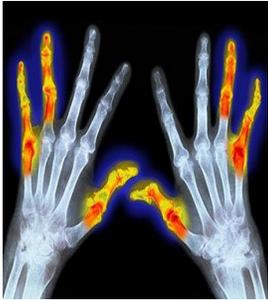


Organ Systems Involved in RA

Organ	Symptoms
Ophthalmologic	Sicca (10%-15%) Scleritis, Uveitis
Cardiac	Pericarditis, accelerated atherosclerotic disease
Pulmonary	Nodules, diffuse interstitial lung disease
Hematologic	Anemia (25%-30%), thrombocytopenia, thrombocytosis, lymphadenopathy
Neurologic	Peripheral entrapment neuropathy, cervical myelopathy
Felty's syndrome	Splenomegaly with neutropenia, thrombocytopenia
Vascular	Small & systemic vessel vasculitis

Signs and Symptoms

- Most commonly presents as symmetric polyarthritis (especially small joints of hand and feet)
- Joint pain, tenderness, stiffness, swelling, erythema, decreased movement joints
- Morning stiffness that last > 1 hour
- Rheumatoid nodules
- Dry eyes and mouth



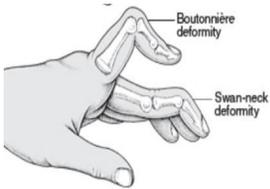
Organ Systems Involved in RA

Organ	Symptoms
Skin	Rheumatoid nodules over pressure areas (25-50%)
Renal	Low grade membranous glomerular nephrology
Muscles	Muscle atrophy
Hepatic	Nonspecific transaminitis (Tehlirian & Bathon, 2008)

Signs and Symptoms

Fixed deformities may develop quickly:

- Ulnar deviation
- Swan-neck deformities
- Boutonniere deformities

Laboratory Findings

- **CBC:** anemia of chronic disease & thrombocytosis (indicates active disease)
- **Chemistries:** normal hepatic, renal, and uric acid tests
- **ESR:** usually elevated, can be normal
- **CRP:** usually elevated
- **ANA (antinuclear antibodies):** positive in 30%



Laboratory Findings

- **RF (rheumatoid factor):** positive in 70%-80% with 86% specificity for RA
- **Anti-CCP (anti-cyclic citrullinated peptide antibodies):** positive in 57%-66% with high specificity 93%-97%

(West, 2015)



Diagnosis

“There is no one test to diagnose RA” (ACR, 2017)

Diagnosis is based on history, clinical exam of joints and organs, blood test results, x-rays & MRI.



Imaging

X-rays: hands, wrists and feet used to evaluate for erosions, symmetrical joint space narrowing (Earliest change on x-ray of small joints is periarticular osteopenia)



2010 ACR Classification Criteria for RA

Add scores A-D & a score of ≥6/10 is needed to be classified as definite RA

A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joint (with or without large joint involvement)	2
4-10 small joints (with or without large joint involvement)	3
> 10 joints (at least 1 small joint)	5

(Kontzias, 2018)

Imaging

Magnetic resonance imaging (MRI) & ultrasound are more sensitive scans to detect early joint erosions and inflammation.

(Tehirian & Bathon, 2008)



2010 ACR Classification Criteria for RA

B. Serology (at least 1 test result is needed)	
Negative RF and negative CCP	0
Low-positive RF or low positive CCP	2
High positive RF or high positive CCP	3

2010 ACR Classification Criteria for RA

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



- Differential Diagnosis**
- Viral polyarthritis – (parvovirus B19, hepatitis B virus)
 - Systemic lupus erythematosus (SLE)
 - Polymyalgia Rheumatica
 - Reactive Arthritis
 - Sarcoidosis
 - Psoriatic Arthritis
 - Crystal-induced arthritis-(gout, pseudogout)
 - Osteoarthritis
 - Lyme arthritis
- Kontzias, 2018



Treat to Target (T2T)

Studies of RA treatment show improved outcomes with early more aggressive therapy with the goal of tight disease control

(Early treatment = diagnosed within 6 months of symptoms)

Framework for RA management was presented in 2010 to rheumatology groups and updated in 2015.

(Jacobson, Fritz, Carter et al. , 2012)

Treat 2 Target Algorithm

1. Determine the Goal of Therapy
 Usually patients with early RA should aim for clinical remission and patients with advanced disease low disease activity is an appropriate goal to improve function.

Clinical remission: absence of S&S of significant inflammatory disease activity
This does not mean cured!



Treat 2 Target Algorithm

5. Maintain treatment goal
6. Modify treatment as needed
 (Jacobson, Kober et al., 2008)



Treat 2 Target Algorithm

2. Choose a composite measure to assess disease activity

- a. CDAI (Clinical Disease Activity Index)
- b. DAS28-CRP/DAS28-ESR (Disease Activity score using CRP or ESR)
- c. PAS/PAS II (Patient Activity Scale)
- d. RAPID3 (Routine Assessment of Patient index data)
- e. SDAI (Simple Disease Activity Index)



Treatment

Past treatment started with :
 Corticosteroids/non-steroidal anti-inflammatory drugs (NSAIDs)
 and then advanced to non-biologic disease-modifying anti-rheumatic drugs (DMARDs)
 (CDC, 2014)



Treat 2 Target Algorithm

3. Measure disease activity

- a. After starting RA treatment or changing to a new therapy
- b. Measure disease activity every 1-3months

4. Adjust treatment (if needed) every 3-6 months until goal is reached



Treatment

Treatment of RA includes:

- ✓ Drugs (NSAIDs, corticosteroids and DMARDs)
- ✓ Rest
- ✓ Exercise
- ✓ Nutrition
- ✓ Physical measures
- ✓ Surgery (as indicated)

(Kontzias, 2018)

NSAIDs

NSAIDs:

- Decrease Inflammation (do not prevent progression of disease)
- Inhibit production of prostaglandins (mediators of inflammation) by blocking cyclooxygenase (COX) enzymes
- In RA higher doses often required
- If ineffective after 4 week trial- try another

(Johns Hopkins Arthritis, 2018)

NSAIDs

Drug	Usual Dosage	Maximum Recommend Dose
Sulindac	150=200 mg bid	400 mg
Tolmetin	400 mg tid	1800 mg
Meloxicam	7.5 mg	15 mg
Celecoxib	200 mg 1/day or bid	400 mg
Combination Drugs Arthrotec Diclofenac/Misoprostole	50mg/200 mcg tid	150mg/800 mcg
Vimovo Naproxen/Esomeprazole	375 mg/500 mg bid 20 mg	
Duexis Ibuprofen/Famotidine	800 mg tid 26.6	

(Kontzias, 2018)

NSAIDs

Side effects:

1. GI upset (take with food & adjunctive medication with proton pump inhibitors)
2. Renal function impairment (salt retention, edema, increased blood pressure)
3. Increase cardiovascular risks

(Johns Hopkins Arthritis, 2018)




Corticosteroids

1. Anti-inflammatory agents
2. Useful early in RA disease as adjunctive therapy and chronic therapy for severe disease



NSAIDs

Drug	Usual Dose	Maximum Recommend Dose
Diclofenac	75 mg bid 50 mg tid 100 mg once/day SR	150 mg
Etodolac	300-500 mg bid	1200 mg
Nabumetone	1000-2000 mg/day in divided doses	2000 mg
Naproxen	200-500 mg bid	1500 mg
Ibuprofen	400-800 mg qid	3200 mg
Oxaprozin	1200 mg	1800 mg
Indomethacin	25 mg tid 75 mg bid SR	200 mg

Corticosteroids

Side effects:

1. Weight gain
2. Increased glucose and blood pressure
3. Accelerated osteoporosis
4. Increased risk cataracts and avascular necrosis of bones

(Johns Hopkins Arthritis, 2018)



Corticosteroids

- Prednisone 5-10 mg (usual dose)
- Once a day dosing is related with fewer side effects (usually given in the morning)
- Rayos (Prednisone)-Given at bedtime with delayed release in the mornings
- Methylprednisone (Medrol) 4 mg 1 daily

Intra-articular corticosteroids: used to control a local flare in a joint.



Traditional DMARDs

Drug	Adverse Effects	Information
Leflunomide 10-20 mg/day (Arava) MA: Not fully understood	Diarrhea Elevated LFT GI upset alopecia	Onset of action 4-8 weeks Labs: CBC, LFT Teratogen
Sulfasalazine 500 mg 2-3 grams per day in divided doses (Azulfadine) MA: Unknown	Rash Mild GI upset Mild cytopenia May increase LFT	Onset of action 6-12 weeks Labs: CBC, LFT, creatinine

(Kontzias, 2018)

Traditional DMARDs

- Are used first line to treat RA
- Slow progression of joint damage



DMARDs

Rarely used DMARDs

1. Gold (Myochrysin)
2. Minocycline
3. Azathioprine



Traditional DMARDs

Drug	Adverse Effects	Information
Methotrexate 2.5 mg (3-8) per week/ 25 mg injection (Rheumatrex, Otrexup, Rasuvo) Mechanism action (MA): Inhibits enzyme in metabolism of folic acid, dihydrofolate reductase	Hepatotoxicity Myelosuppression Stomatitis Nausea Hair loss Pneumonitis (rare)	First line DMARD Onset of action 4-6 weeks Take Folic acid 1 mg daily Labs: CBC, LFT, creatinine Avoid Etoh Bactrim can increase toxicity Teratogen
Hydroxychloroquine (Plaquenil) 200-400 mg day 5mg/kg once a day or in divided doses MA: Unknown	Corneal opacity or retinal degeneration (reversible) Mild dermatitis	Get eye exam every 6 months

Biologics

- Biologics are genetically engineered proteins
- Target specific areas of the immune system
- Biologic drugs have advanced RA treatment



Biologics

Prior to start of biologic drug:

1. Perform TB test (Quantiferon gold TB)
2. Obtain Hepatitis panel (Hepatitis B & C)
3. Inquire about fungal infections
4. Avoid live virus vaccinations



TNF-Inhibitors

Side Effects:

- Skin reactions
- Severe allergic reaction
- Infection
- Cancer risk (lymphoma, skin cancers)
- Neurologic complications (rare)
- Worsens heart failure
- Blood dyscrasias (may develop + ANA)
- New onset psoriasis

Biologics

Tumor necrosis factor (TNF) inhibitors

Mechanism of action: Blocks tumor necrosis factor. (TNF)-critical cytokine increases joint damage

Biologics entered market in 1999

(Johns Hopkins, 2018)



Others

T-Cell Costimulatory blockade:

Abatacept (Orencia)-Binds receptors on the antigen-presenting cell and prevents these receptors from binding to receptors on T cells
(decreases inflammation by downregulating T cell activation)

*Dose: IV weight based 500mg < 60 Kg, 1g 6 Kg/month
125 mg SQ once/week*

TNF-Inhibitors

1. Etanercept (Enbrel)
50 mg Subcutaneous (SQ) weekly
2. Infliximab (Remicade)
3mg-10mg/KG IV 0,2,6 weeks/Q 8 weeks
3. Adalimumab (Humira)
40mg every 2 weeks subcutaneous
4. Certolizumab pegol (Cimzia)
400mg SQ 0,2,4 weeks then 200mg every 2 week or 400 mg every 4 weeks
5. Golimumab (Simponi)
2mg/KG weeks 0,4,then Q 8 weeks or 50 mg SQ 1/month

Others

Side Effects (Abatacept):

- Use with caution in patients with COPD
- Respiratory & opportunistic infections
- Headache
- Nausea
- Malignancies (similar to patients with RA)
- Infusion reaction (usual mild)

Others

B-Cell Depletion:
Rituximab (Rituxan)-Monoclonal antibody binds to CD20 and results in B-cell depletion

Dose: 1 g IV at 0, 2 week and then every 4-6 months (Methylprednisolone 60-125 mg IV with each dose)

Others

Side Effects (IL-6):

- GI perforation risk (Avoid diverticulitis history)
- Infection risks
- Neutropenia, thrombocytopenia
- Anaphylaxis
- Demyelinating neurologic disorders

Others

Side Effects (Rituximab):

- Mild itching
- Rashes
- Back pain
- Hypertention/hypotension
- Fever
- Increased risk of infection
- Neutropenia

Others

Interleukin-1 (IL-1):
Anakinra (Kineret)
 Blocks the biologic activity of IL-1 which is a protein that is a major player in inflammation
Dose: 100 mg SQ daily (infrequently used)

Side effects:
 Immunosuppression
 Neutropenia
 Injection site reaction

Others

Interleukin-6 (IL-6):

Tocilizumab (Actemra)
Sarilumab (Kevzara)
 Binds to IL-6 receptors & inhibits IL-6 signally through these receptor
*Dose: Tocilizumab: IV 4mg or 8mg/Kg Q 4 weeks
 162mg SQ every 1-2 weeks
 Sarilumab: 150-200 mg SQ every 2 weeks*

Janus Kinase (JAK) Inhibitor

Tofacitinib (Xeljanz)
 Blocks body's production of Janus Kinase enzymes that play a role in joint inflammation
Dose: 5 mg bid or 11 mg/day

Side effects:
 Infections, elevated LFT, neutropenia, elevated lipids, malignancies, bowel perforation (rare)

Biosimilars

Biosimilars are biological products similar to an approved medication that *does not* have meaningful differences in efficacy, potency or safety.

(Jacobson, Grinnell-Merrick, 2017)



Goal

Early, aggressive treatment to target to prevent joint destruction and disability.



Biosimilars

Bioimilar Product	Reference Product	Side effects
Infliximab-dyyb	Infliximab	Infections Malignancy
Etanercept-szsz	Etanercept	Infections Malignancy
Adalimumab-atto	Adalimumab	Infections Malignancy
Infliximab-abda	Infliximab	Infections Malignancy

(Jacobson, Grinnell-Merrick, 2017)



Adjunctive Modalities

- Rest – when fatigued or joints inflamed
- Exercise-walking, swimming, biking
- Nutrition-fruits, vegetables, healthy grains
- Physical measures-canes, walkers, splints
- Surgery-synovectomy, total joint arthroplasties

(Arthritis Foundation, 2018)



Questions?





**“Preventing Destruction and Disability from
Rheumatoid Arthritis by Treating to Target”**

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