What is Rheumatoid Arthritis?

- Chronic, progressive, and disabling inflammatory disease
  - Affects the synovial tissue of joints, especially of the hands/feet, although any joint can be involved
  - Affects extra-articular sites, such as the heart
- Most common type of inflammatory arthritis

Pathogenesis: Overview

- Balance of pro- and anti-inflammatory mediators skewed when external factors trigger an autoimmune reaction
  - Known mediators include:
    - Cytokines: IL-1, IL-6, IL-8, TNF-alpha
    - Lymphocytes: T cells (CD4+), B cells
  - Results in:
    - Chronic inflammation and destruction of joint bone and cartilage
    - Extra-articular manifestations

Pathogenesis: Joint Inflammation

Risk Factors for RA

- Genetic factors\(^1,2\)
  - 3-5x more common in first-degree relatives
  - May account for up to 60% of RA risk
- Infectious agents\(^3\)
- Hormones\(^3\)
- Miscellaneous factors: smoking, periodontitis\(^4\)
- Interaction between risk factors\(^4\)
  - More severe RA disease in smokers with periodontal disease

Who is Affected by RA?

- Most commonly presents between the ages of 35 and 45 years\(^1\)
- Overall lifetime risk of RA\(^2\)
  - 3.6% for women
  - 1.7% for men
- For women with a first-degree relative with RA, lifetime risk of RA approaches 18%\(^2\)
Commonly Affected Joints

- Symmetrical and polyarticular
  - Typically involves MCP, PIP, MTP joints
  - Typically spares certain joints
    - Thoracolumbar spine, DIPs of the fingers, IPs of the toes

Extra-articular Complications

<table>
<thead>
<tr>
<th>Affected tissue</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Association with RA due to disease, medications; important implications for vaccination</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pericarditis, endocarditis, myocarditis, MI; association due to underlying inflammatory disease, medications, reduced exercise, genetics</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Depression; PML (rare but often fatal in immunosuppressed; more common with biologics such as rituximab)</td>
</tr>
<tr>
<td>Skin</td>
<td>Subcutaneous nodules</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary nodules; interstitial lung disease</td>
</tr>
<tr>
<td>Eyes</td>
<td>Scleritis, episcleritis, retinal vasculitis</td>
</tr>
<tr>
<td>Other</td>
<td>Vasculitis, diabetes, GI bleeding, cancer (e.g., lymphoma)</td>
</tr>
</tbody>
</table>

What About Long-Term Prognosis?

- 50% risk of permanent work disability within 4.5 to 22 years of RA diagnosis¹
  - Associated with decreased quality of life and high healthcare costs
- Mortality in patients with RA²
  - Compared with the general population:
    - 50% increased risk of premature mortality
    - Life expectancy decreased by 3 to 10 years
  - Mortality risk increases with disease severity (e.g., RF-positive RA), number of comorbidities, and duration of disease

Patient Case

- Ms. Nelson is a 32 year old new mom (4 months postpartum) presenting to your primary care clinic complaining of 4 weeks of bilateral hand/wrist pain and swelling
  - She reports significant fatigue
  - She works as a nanny and is having a hard time lifting and caring for the children
- Other history
  - Several colds over the last 3 months, but no rash
  - She currently has rhinitis, resolving non-productive cough
  - No GU symptoms
  - No new sexual partners

Physical Exam

- Skin warm and dry without rash or lesions, and no nail changes
- Lungs: CTA bilaterally; cardiac: S1-S2 without murmur or extra heart sounds, RRR
- No lymphadenopathy
- Musculoskeletal exam
  - Bilateral MCPs 1-3 swollen and tender
  - Bilateral wrists swollen and tender
  - Right knee tender
  - Hands warm with mild erythema over MCPs
  - Full active ROM spine, shoulders, hips, knees, and ankles

Laboratory Findings

- Parvovirus studies: negative
- Hepatitis panel and HIV negative when tested 1 year prior (during pregnancy)
  - ESR: 45 mm/hr
  - CRP: 12 mg/L
  - Rheumatoid factor: 28 IU/mL
  - Anti-CCP: negative
  - ANA: negative

Autoantibodies in RA

- Rheumatoid factor (RF)
  - Not highly sensitive or specific for RA
  - 40% of patients positive in first 6 months
  - 85% of patients positive with established disease
  - Frequently negative at diagnosis
  - May be elevated in other autoimmune conditions such as PsA, SLE, etc; frequently elevated in hepatitis C

- Anti-CCP
  - More specific for rheumatoid arthritis than RF
  - Not elevated in hepatitis C
  - Predictive of more aggressive disease
  - May be positive up to 5 years before onset of disease


ACR RA Classification Criteria

- Classification criteria NOT diagnostic criteria
  - Instead, developed to study early RA

- 2 requirements for applying classification criteria to patients
  - Patient has at least 1 joint with definite clinical synovitis (swelling)
    - Does not include DIPs, 1st MTP, or 1st CMC
  - Synovitis is not better explained by "another disease"
  - Differential diagnosis varies on clinical presentation


2010 ACR/EULAR Classification Criteria for RA

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>VALUE</th>
<th>POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOINT DISTRIBUTION (0-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 large joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 large joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small joint (large joints not counted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 small joint (large joints not counted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 small joint (large joints not counted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEROLOGY (0-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative RF AND negative ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low positive RF OR low positive ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High positive RF OR high positive ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYMPTOM DURATION (0-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACUTE PHASE REACTANTS (0-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal CRP AND normal ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td></td>
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</tr>
</tbody>
</table>

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ Prospectively over time (cumulatively)

→ Retrospectively if data on all four domains have been adequately recorded in the past

Large joints are shoulders, elbows, hips, knees, and ankles. Small joints refer to the MCP joints, PIP joints, second through fifth MTP joints, thumb IP joints, and wrists.

Classification Criteria in Practice

When are Radiographs Needed?

- In general:
  - Radiographs not required for RA classification
  - Should not be taken for classification only

- Exceptions:
  - To rule out RA in someone with longstanding symptoms of unknown origin
  - In someone with longstanding disease symptoms, if radiographs do not show erosions or RA changes, then the diagnosis is less likely

Radiographic Features of RA

- Soft-tissue swelling
- Joint space narrowing
- Erosions
  - Presence of typical erosions allows for the classification of RA even without fulfillment of the scoring system

Algorithm to Classification of RA Including Radiographs

Referral to Rheumatology

- Utilizing the classification criteria for RA may help get the patient in faster to rheumatology
  - Classification criteria are not intended to help referral. However, scoring the patient and providing rheumatology with your assessment and labs may help to demonstrate the need for the patient to be seen by rheumatology
- Call your rheumatology provider if you are concerned about a patient
  - Unclear diagnosis, poor treatment response, disease flare, difficult-to-manage side effects, etc.
- Early recognition and treatment of RA is important to help prevent joint damage and ultimately lead to better outcomes in the long-term

Treatment Goals for RA

- Eliminate pain
- Prevent joint damage
- Prevent loss of function
- Prevent comorbidities/increased mortality

  Effective disease control may be possible if treated early and aggressively.

Before Starting Therapy

- Obtain CBC, LFTs, creatinine level, and hepatitis B and C status
  - Repeat at regular intervals depending on the therapy
- Influenza vaccination
- Ophthalmologic exam for hydroxychloroquine
- TB screening for biologic DMARDs

ABC, complete blood count; DMARD, disease-modifying antirheumatic drug; LFT, liver function test; TB, tuberculosis.

Approach to RA Treatment

- Treatment choice based on disease activity, severity, prognosis, comorbidities, and likelihood of compliance
  - Consider patient preferences related to cost, convenience, monitoring requirements, potential adverse reactions, etc.
- The earlier the start, the better
  - Should start at diagnosis
  - Can start with nonbiologic or biologic DMARDs
- Follow evidence-based guidelines
  - 2008 ACR guidelines
  - Updated ACR RA guidelines: 2012

2008 ACR RA Guideline

- Guideline focus:
  - Use of nonbiologic and biologic therapies for the treatment of RA
  - Concomitant use of antiflammatory drugs and interarticular and oral glucocorticoids
  - Background of optimal and appropriate use of nonmedical therapies (e.g., physical and occupational therapies)
- Recommendations based on disease duration, disease activity, and prognostic features

ACR, American College of Rheumatology; RA, rheumatoid arthritis.

ACR Updated Guidelines for Use Of DMARDs and Biologic Drugs

- 2012 update concentrated on 4 updated sections
  - Indications for use and switching of DMARDs and biologics
  - Use of biologic agents in high-risk RA patients with hepatitis, cancer, or congestive heart failure, qualifying for more aggressive treatment
  - Screening for TB in RA patients starting or receiving biologic drugs
  - Vaccination in patients starting or receiving DMARDs or biologics

ACR Updated Guidelines for Use Of DMARDs and Biologic Drugs

- Low disease activity or remission remains the goal for each patient
- Each therapy must be specific to each patient’s health needs
- Recommends change to more intensive earlier therapy to potentially provide better outcomes

Medical Management of RA

- Non-biologic DMARDs
  - Single agent
    - Methotrexate
    - Leflunomide
    - Hydroxychloroquine
    - Minocycline
    - Sulfasalazine
  - Dual DMARDs
  - Triple DMARDs

- Biologic DMARDs
  - Not recommended in patients with early RA and only low or moderate disease activity
  - Combination with methotrexate
  - Monotherapy

Potential Contraindications to DMARD Treatment

- Infectious disease: bacterial infection, TB, shingles, serious fungal infection, or pneumonitis (ILD)
- Hematologic and oncologic
- Cardiac: class III-IV heart failure
- Liver: abnormal LFTs, hepatitis B or C
- Renal
- Neurologic: MS
- Pregnancy and breastfeeding
- Perioperative infectious risk

DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.
Methotrexate: Gold Standard for RA

**Mechanism of action:** Interferes with DNA replication, inhibits lymphocyte proliferation (folate antagonist), and has anti-inflammatory effects (adenosine accumulation)

**Dose:**
- Initial: 7.5-10 mg/week
- Increase every 4-8 wk by 2.5-5 mg
- Max: 20-25 mg/week

**Contraindications:**
- Pregnancy category X; liver and renal failure, platelet count <50,000/mm³

**Prescreening:**
- CBC, LFT, creatinine, hepatitis B and C

**Monitoring:**
- Hepatic, pulmonary, blood toxicity; CBC, LFT, creatinine every 2-4 weeks for 3 months, then every 8-12 weeks

**Adverse reactions:**
- Mouth ulcers, nausea, fatigue, alopecia, diarrhea, achines, arthralgia
- Other: Consider folic acid supplementation; no alcohol; >180 mg/day caffeine reduces efficacy; high alert for incorrect dosing

Sulfasalazine

**Mechanism of action:** Potent antiinflammatory effects

**Dose:**
- 1000 mg bid-tid

**Contraindications:**
- Liver disease, platelet count <50,000/mm³

**Prescreening:**
- CBC, LFT, creatinine

**Monitoring:**
- CBC, LFT, creatinine every 2-4 weeks for 3 months, then every 8-12 weeks

**Adverse reactions:**
- Blood toxicity
- Other: Slightly inferior to MTX; pregnancy category B

Hydroxychloroquine

**Mechanism of action:** Antimalarial drug

**Dose:**
- 200 mg bid or 400 mg qd

**Contraindications:**
- In patients with retinal or visual field changes

**Prescreening:**
- CBC, LFT, creatinine, ophthalmologic exam

**Monitoring:**
- Yearly ophthalmologic exams

**Adverse reactions:**
- Risk of ocular reactions; otherwise well-tolerated
- Other: Reduces signs and symptoms of RA, but does not slow radiographic progression as monotherapy; reduces the risk of new-onset diabetes. Pregnancy Category C

Leflunomide

**Mechanism of action:** Decreases T lymphocytes

**Dose:**
- 10-20 mg/day

**Contraindications:**
- Pregnancy category X; liver disease, platelet count <50,000/mm³

**Prescreening:**
- CBC, LFT, creatinine, hepatitis B and C

**Monitoring:**
- CBC, LFT, creatinine every 2-4 weeks for 3 months, then every 8-12 weeks

**Adverse reactions:**
- Diarrhea, weight loss, elevated blood pressure, potential for abnormal LFTs
- Other: Newer nonbiologic DMARD

Biologic DMARDs: Overview

- **Considerations for injectable agents:**
  - Rotate injection sites
  - Some needle covers made from latex; caution in latex allergy
- **Adverse reactions:**
  - Injection-site or infusion reactions
  - Infections: TB, hepatitis, fungal, and bacterial (sepsis)
  - Rare: lupus and MS
- **Contraindications:**
  - Active or recurrent cancer
  - Untreated infection, active or latent TB
  - Cannot receive live virus vaccinations
  - Severe heart failure (class III-IV)

Anti-TNF Agents in RA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Dosing and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Fully human anti-TNF antibody</td>
<td>40 mg SC every other week, with or without MTX</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Pegylated anti-TNF antibody</td>
<td>400 mg SC at week 0, 2, and 4, then 200 mg every other week (or 400 mg monthly)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF receptor-IgG fusion protein</td>
<td>50 mg SC weekly with or without MTX via single-dose, prefilled syringes or autoinjectors</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Fully human anti-TNF antibody</td>
<td>50 mg SC monthly via single-dose, prefilled syringes or autoinjectors</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Mouse-human chimeric anti-TNF antibody</td>
<td>In conjunction with MTX, 3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks; titration to 8 mg/kg IV or every 4 weeks as needed</td>
</tr>
</tbody>
</table>

*SC, subcutaneous; MTX, methotrexate; TNF, tumor necrosis factor*
### Other Biologic DMARDs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Dosing and administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>T-cell modulator</td>
<td>500-1000 mg (weight-based) IV week 0, 2, and 4, then every 5 weeks or IV day 1, 125 mg SC day 2, then 125 mg SC weekly</td>
<td>Use in patients with &gt; 6m of disease; monitor respiratory status closely in COPD patients and discontinue if problems occur</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1 receptor antagonist</td>
<td>100 mg/day SC, 100 mg qod in patients with severe renal disease</td>
<td>Less effective than anti-TNF agents used in &lt;5% of RA patients; contraindicated in patients with history of asthma; latex needle cover</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Anti-CD20 antibody</td>
<td>2 x 1,000 mg IV infusions separated by 2 weeks</td>
<td>Used in combination with MTX, may decrease vaccine effectiveness; used when anti-TNF agents fail; rare but often fatal PML</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor blocker</td>
<td>4 mg/kg IV over 60 minutes every 4 weeks; titrated to 8 mg/kg as needed</td>
<td>Used alone or in combination with MTX or other DMARDs in patients with inadequate response to anti-TNF therapy</td>
</tr>
</tbody>
</table>

IL, interleukin; IV, intravenous; PML, progressive multifocal leukoencephalopathy; SC, subcutaneous; TNF, tumor necrosis factor.


### Other Agents: NSAIDs

- Help with inflammation & pain
- No disease-modifying capability
- Contraindicated in patients with renal disease
- Caution in patients with heart disease & peptic ulcer disease
- Increased incidence of heart attack, stroke, GI disease, renal disease

IL, interleukin; IV, intravenous; PML, progressive multifocal leukoencephalopathy; SC, subcutaneous; TNF, tumor necrosis factor.


### Other Agents: Corticosteroids

**Pros**
- Helps with pain and inflammation
- Some disease-modifying capability, so can help while other agents take effect (3-6 months or more)
- When used with a DMARD, additive disease-modifying activity is noted

**Cons**
- Can mask severity of disease through anti-inflammatory action
- Long- and short term risks include:
  - Immune suppression
  - Osteoporosis
  - Glucose intolerance/diabetes
  - Weight gain
  - Hyperlipidemia
  - Hypertension
  - Cataracts
  - Skin atrophy
  - Acne
  - Steroid psychosis

DMARD, disease-modifying antirheumatic drug.


### Drugs No Longer Considered Appropriate for RA Treatment

- Gold, oral & injectable
- Azathioprine
- Chlorambucil
- Cyclophosphamide
- Cyclosporin
- Minocycline
- Mycophenolate mofetil


### Additional Interventions

- Exercise recommended for all RA patients to:
  - Keep joints loose, support affected joints
  - Maintain/improve balance and strength
  - Ward off depression/improve mood
- Smoking cessation
- Stress management
- Foot health
- Vaccination
  - Yearly influenza vaccine
  - Pneumococcal vaccine when indicated

### Emerging Therapies in RA

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Target(s)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib (CP-690,550)</td>
<td>Jak3</td>
<td>III</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>Syk</td>
<td>III</td>
</tr>
<tr>
<td>LY2127399</td>
<td>BAFF</td>
<td>III</td>
</tr>
<tr>
<td>Secukinumab (AIN457), LY2439821</td>
<td>IL-17</td>
<td>I-I</td>
</tr>
<tr>
<td>LY3009104 (INCB28050)</td>
<td>Jak1/2</td>
<td>II</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov, 07/2011

### Patient Case

- **Treatment considerations**
  - Patient is breastfeeding and not on birth control
  - Options:
    - Hydroxychloroquine
    - Biologic DMARD

### Monitoring for Safety and Therapeutic Response

- **Assess disease activity**
  - Labs: ESR, CRP, PLT, etc.
  - Joint examination: 28-joint count
  - Disease flares
- **Monitor treatment-specific side effects**
- **Monitor comorbidities**
  - CV: lipid profile, tobacco use, etc
  - Osteoporosis: DXA, calcium, vitamin D, exercise, FRAX
  - Mental health

### Ongoing Monitoring

- **Assess disease activity**
  - Labs: ESR, CRP, PLT, etc.
  - Joint examination: 28-joint count
  - Disease flares
- **Monitor treatment-specific side effects**
- **Monitor comorbidities**
  - CV: lipid profile, tobacco use, etc
  - Osteoporosis: DXA, calcium, vitamin D, exercise, FRAX
  - Mental health

### 3-Month Follow-Up

- Started on etanercept 2 weeks after first visit by rheumatologist
- Feeling much better, able to work
- Laboratory findings:
  - RF 112 IU/mL, ESR 12 mm/hr, CRP 0.8 mg/L
- Physical examination:
  - Right wrist still painful and swollen, otherwise no joint complaints
- Requesting influenza vaccine

### Patient Education

- **Appropriate use of medications**
  - Medication adherence
- **Expectations regarding treatment efficacy and potential side effects**
- **Need to monitor and report adverse events**
  - Frequent lab monitoring may be needed, particularly with non-biologic DMARDs
- **Implications of being immunocompromised**
  - Importance of vaccinations
  - But avoidance of live vaccines
Summary

• New ACR RA classification criteria facilitate:
  – Earlier recognition of RA
  – Earlier referral to rheumatology
• Early treatment initiation provides best protection against joint damage and functional impairment
• Ongoing monitoring critical for ensuring safe treatment, managing side effects, and improving patient adherence

ACR, American College of Rheumatology; RA, rheumatoid arthritis