Management of Rheumatoid Arthritis

*Early detection to ensure appropriate care*

**Learning objectives**

- Recognize the signs and symptoms of Rheumatoid Arthritis (RA)
- Assess the patient in order to provide a provisional diagnosis
- Understand the importance of an early and accurate diagnosis
- Recognize the importance of referring patients to a rheumatologist for co-management care
- Understanding the morbidity and risks associated with the disease
Rheumatoid Arthritis (RA)

What is RA and who does it affect?¹

- A chronic, systemic, inflammatory autoimmune disease
- Most common form of inflammatory disease that affects diarthrodial joints
- As disease progresses, it can lead to irreversible joint damage and disability

<table>
<thead>
<tr>
<th>Epidemiology</th>
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</thead>
<tbody>
<tr>
<td>Female:male</td>
</tr>
<tr>
<td>Age of onset</td>
</tr>
<tr>
<td>Prevalence</td>
</tr>
<tr>
<td>Incidence</td>
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</tbody>
</table>

How does RA present?

- Polyarticular (>4 joints), often symmetric
  - Swelling and tenderness of small peripheral joints [metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the fingers, interphalangeal joints of the thumbs, metatarsophalangeal (MTP) joints, and wrists]
  - As disease progresses, larger peripheral joints may become affected (ankles, knees, elbows, and shoulders)
- Systemic
  - Fever, weight loss, or fatigue
  - Morning stiffness ≥1 hour
  - Limited range of motion


Radiographic damage can occur early in RA

- Researchers studying RA now believe that joint damage can begin in the first year or 2 of the disease
  - Structural damage continues to progress throughout the course of the disease
- A key reason RA patients are seen late by rheumatologists is that patients delay talking about symptoms with their PCP


Did you know?

In a survey of 168 RA patients, there was a median delay of 12 weeks before a patient was assessed in primary care.
- May be driven by a lack of awareness of RA

Serial radiographs taken at 4-year intervals show progressive joint damage as evidenced by worsening carpal bone ankylosis, joint space loss, and metacarpophalangeal (MCP) erosions.
The case for early identification and referral to a rheumatologist

- Early identification of RA and referral to a rheumatologist can improve the long-term outcome of the disease

*Did you know?*

In a recent survey of 138 PCPs, 96% made a correct provisional RA diagnosis. Many RA cases were targeted for rheumatology referral, but 22% of cases were not.

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Primary Caregivers and RA
Primary caregivers and RA: Recognize, Assess, and Advocate1-3

Recognize

- Identify the signs and symptoms of RA
- Order baseline and diagnostic lab/imaging tests

Assess

- Perform a clinical examination
- Provide a provisional diagnosis

Advocate

- Direct the patient to the appropriate specialist
- Relay important patient assessment information

Joints of the hands and feet commonly affected by RA

- The physical examination is a critical component in making a diagnosis1
- The condition of the hands and wrists often indicates the patient’s overall disease status2
  - Symmetric swelling and tenderness upon palpation are usually first noted at wrist, MCP joints, PIP joints of the fingers, and MTP joints3
  - Rheumatoid joints are normally boggy and warm, but they typically are not erythematous

Extra-articular manifestations of RA

- Clinical evaluations should be done periodically as a response to new symptoms
- It is important to monitor patients for the conditions in the table below
- A referral to a specialist should be made if any co-morbidities arise that would require a specialist’s attention
- Prevalence: 40% at any time during course of disease

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Gastrointestinal</th>
<th>Ocular</th>
<th>Pulmonary</th>
<th>Cardiac</th>
<th>Renal</th>
<th>Rheumatologic</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid nodules</td>
<td></td>
<td></td>
<td>Pulmonary nodules</td>
<td>Pericarditis (5%)</td>
<td></td>
<td>Rheumatoid vasculitis</td>
<td>Rheumatoid vasculitis</td>
</tr>
<tr>
<td>Non-specific tenosynovitis</td>
<td></td>
<td></td>
<td>Interstitial lung disease</td>
<td></td>
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<tr>
<td>Episcleritis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pulmonary nodules</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vasculitis of the fingers</td>
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</tr>
</tbody>
</table>

Rheumatoid nodules
PsA, RA, OA, and AS: differential diagnoses

<table>
<thead>
<tr>
<th>PsA</th>
<th>RA</th>
<th>OA</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric</td>
<td>Symmetric</td>
<td>Asymmetric</td>
<td>No</td>
</tr>
<tr>
<td>Asymmetric</td>
<td>No</td>
<td>No</td>
<td>Symmetric</td>
</tr>
<tr>
<td>In morning and/or with immobility</td>
<td>In morning and/or with immobility</td>
<td>With activity</td>
<td>Yes</td>
</tr>
<tr>
<td>1:1</td>
<td>3:1</td>
<td>Hand/Foot more common in females</td>
<td>1:3</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CWA, B27</td>
<td>DR4</td>
<td>No</td>
<td>B27</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

PsA=Psoriatic Arthritis; OA=Osteoarthritis; AS=Ankylosing Spondylitis.
Differential diagnosis (continued)\textsuperscript{1,2}

- Systemic connective tissue disorders
  - Systemic lupus erythematosus (SLE)
  - Mixed connective tissue disease (MCTD)
  - Sjögren’s syndrome
- Seronegative spondyloarthropathies
  - Psoriatic arthritis (PsA)
  - Ankylosing spondylitis (AS)
  - Reactive arthritis
  - Arthritis associated with inflammatory bowel disease (IBD)
- Infectious arthritis
  - Lyme-associated arthritis
  - Hepatitis C-associated arthritis
  - Parvovirus B19-associated arthritis

\textsuperscript{1} Rindfleisch JA, Muller D. \textit{Am Fam Physician.} 2005;72(6):1037-1047.
\textsuperscript{2} Tehlirian CV, Bathon JM. In: Kippel JH, et al., eds. \textit{Primer on the Rheumatic Diseases;} 2008:114–121.

Swelling of the DIP joints, skin, and nail changes are common in PsA.

Malar or “butterfly” rash is often seen in SLE.

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Raynaud’s disease is common in MCTD.

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Lyme-associated arthritis can occur weeks after the acute infection, which is characterized by a bullseye rash.

Raynaud’s disease is common in MCTD.

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Lyme-associated arthritis can occur weeks after the acute infection, which is characterized by a bullseye rash.

Criteria for early referral\textsuperscript{1}

- Prompt referral is advised when RA is suspected based on supportive clinical criteria:

  1. ≥3 swollen joints
  2. MCP/MTP involvement: positive “squeeze test,” pain following hand or foot compression
  3. Morning stiffness ≥30 min

“Definite” RA is defined as:
Patients who:
• Have at least 1 joint with definite clinical synovitis (swelling)
• With the synovitis not better explained by another disease

Achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains:
• Number and site of involved joints
• Serologic abnormality
• Elevated acute-phase response
• Symptom duration

The new 2010 classification system, a score-based algorithm of 4 domains, redefines the current RA paradigm by focusing on the features at earlier disease stages that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features.

ACR/EULAR 2010 classification criteria for RA (continued)

<table>
<thead>
<tr>
<th>Classification criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint involvement</td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td>Acute-phase reactants</td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

RF=rheumatoid factor; ACPA=anti-citrullinated protein antibody; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein.
Laboratory markers

- Based on the ACR/EULAR 2010 RA classification criteria, in order to classify a patient with definite RA, physicians must obtain:
  - A history of symptom duration
  - A thorough joint evaluation
  - At least 1 serologic test (RF or Anti-CCP [ACPA])
  - At least 1 acute-phase response measure (ESR or CRP)

- Baseline complete blood count, urinalysis, and liver function tests are recommended and help to guide medication choices.

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Laboratory markers cont’d

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Clinical utility</th>
<th>Clinical limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>• Autoantibody test that is negative in 30% of early RA patients</td>
<td>• Can be positive in other chronic processes and inflammatory diseases (e.g., lupus, Sjögren’s syndrome)</td>
</tr>
<tr>
<td></td>
<td>• Not an accurate measure of disease progression</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP antibody test</td>
<td>• Directed against the citrullinated residues of protein</td>
<td>• May not be readily available in many laboratories</td>
</tr>
<tr>
<td></td>
<td>• Correlates well with disease progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sensitivity is 70%, specificity is 95%</td>
<td></td>
</tr>
<tr>
<td>ESR and CRP</td>
<td>• High levels at onset of disease are predictive of more aggressive disease and potentially worse prognosis</td>
<td>• Nonspecific for RA</td>
</tr>
<tr>
<td></td>
<td>• Used to monitor disease course and response to treatment</td>
<td></td>
</tr>
</tbody>
</table>

Serological factors in RA: anti-CCP and RF

- RF and anti-CCP are serum parameters strongly associated with an aggressive disease course
  - High levels of both correlate with erosive joint disease, functional disability, and extra-articular disease
- Diagnostic yield is enhanced by measuring both RF and anti-CCP in a patient suspected of having RA

<table>
<thead>
<tr>
<th>Serologic</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>70%</td>
<td>95%</td>
</tr>
<tr>
<td>RF</td>
<td>60%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Radiographic imaging in RA

- In early stages, radiographs of the small joints of the hands and feet will show periarticular osteopenia. This is variable and nondiagnostic.
- With disease progression, loss of cartilage causes symmetric joint space narrowing.
- Bony erosions generally appear on the margin of joints, both medially and laterally, and on both opposing bones.
The value of triage information in the referral process\textsuperscript{1-3}

- Priority-setting tools can help improve the referral process

Primary caregivers\textsuperscript{1,4,5}
- Recognize RA and provide a provisional diagnosis based on the criteria for early referral
- Referral to specialist to ensure early intervention
- Optional: order baseline testing/imaging

Rheumatologist\textsuperscript{4}
- Confirm diagnosis and prescribe appropriate therapy
- Jointly monitor patient progress, RA complications, and/or possible drug AEs with primary caregiver

Patient assessment and referral form\textsuperscript{1}
- Important information includes:
  - Basic details of patient’s history, including symptom duration
  - Physical examination results
  - Documentation of swollen joints
  - Inflammatory and serologic lab data

\textsuperscript{1} Thompson AE. Rheumatol Natl Grand Rounds. 2010;1(2):1-6.
\textsuperscript{5} Weinblatt ME, Kuritzky L. J Fam Pract. 2007;56(4 suppl):S1-8.

Referral form provided by Dr. Robin Dore.
RA Case Study

Case study

- MP, a 50-year-old woman noted bilateral hand discomfort for 3 months, followed 1 month later by bilateral foot pain when walking
- Self-medicated with OTC ibuprofen, 400 mg tid with minimal benefit; visits her family physician
  - Complains of stiffness after awakening (1 or 2 hours), which improves gradually in the course of the day
  - Remarks that she sometimes has difficulty turning faucets and firmly holding a toothbrush
  - Sleep is sometimes disturbed by pain; feels tired throughout the day

Case study1-3

• Physical examination normal, except for:
  – 4 swollen proximal interphalangeal (PIP) joints on the right hand and 4 on the left
  – Compression of metacarpophalangeal (MCP) joints indicate symmetric tenderness and pain (positive squeeze test)
  – Feet tender to palpation without obvious synovitis
  – Compression of metatarsophalangeal (MTP) joints causes pain (positive squeeze test)


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Lab values1

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>Elevated</td>
</tr>
<tr>
<td>CCP</td>
<td>Normal</td>
</tr>
<tr>
<td>RF</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Positive</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>Normal</td>
</tr>
</tbody>
</table>

• X-ray of hands, feet, and wrists
  – Soft tissue swelling most apparent around PIP and MCP joints in the index and middle fingers

Provisional diagnosis: rheumatoid arthritis

– Prescribe naproxen 500 mg bid and prednisone 7.5 mg qd
– Refer to rheumatologist for an early appointment
Co-morbidities in RA

- Clinical evaluations should be done periodically as a response to new symptoms\(^1\)\(^2\)
- It is important to monitor patients for any potential co-morbidities
- A referral to a specialist should be made if any co-morbidities arise that would require a specialist’s attention

**Cardiovascular disease\(^3\)\(^4\)**

- Patients with RA have a higher incidence of fatal and nonfatal cardiovascular events (MI and stroke) than the general population

**Infectious diseases\(^3\)**

- RA patients are at an increased risk for infections

**Malignancies**

- There is an increased risk of certain types of cancer in RA patients. The link between RA and cancer is unclear.

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Therapeutic management of RA\(^1\)\(^2\)

**Goals of treatment**

- Decrease pain
- Prevent or control joint damage
- Prevent loss of function

**Pharmacologic treatments**

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>To help relieve joint pain and swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonbiologic DMARDs</th>
<th>To help reduce joint pain, swelling and may slow progression of joint damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (MTX)</td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
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</table>

<table>
<thead>
<tr>
<th>Biologic DMARDs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TNF-α antagonists</td>
<td></td>
</tr>
<tr>
<td>IL-1 and IL-6 antagonists</td>
<td></td>
</tr>
<tr>
<td>Selective T-cell costimulation modulator</td>
<td></td>
</tr>
<tr>
<td>B-cell targeting</td>
<td></td>
</tr>
</tbody>
</table>

| JAK Inhibitors |                           |

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Conclusion

- Joint damage occurs early in most RA patients
- Early diagnosis and referral to a rheumatologist can make a difference in outcomes and patient benefit
- The quality of communication between providers can help to improve the efficiency of the referral process