

## Rheumatoid Arthritis - RA

### Clinical Background

Rheumatoid arthritis (RA) is an autoimmune disorder and is the most common adult inflammatory arthritis worldwide.

#### Epidemiology

- Incidence
  - 25/100,000 men
  - 54/100,000 women
- Age – peaks in 30s-40s
- Sex – M<F

#### Etiology

- Genetics
  - 30% concordance for twins
  - 80% of Caucasians with RA express HLA-DR1 or DR4 subtypes

#### Risk Factors

- Family history
- Smoking
- Silicate exposure

#### Pathophysiology

- Joint damage begins with proliferation of synovial macrophages and fibroblasts
- Neovascularization follows
- Inflamed synovial tissue grows irregularly, forming pannus tissue
- Pannus invades cartilage and bone with joint destruction

#### Clinical Presentation

- Constitutional manifestations
  - Weakness
  - Fatigue
  - Anorexia
  - Low-grade fever
- Joints
  - Pain and stiffness in multiple joints
    - Wrist and proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints affected most commonly
    - Joints are puffy and warm
- Extra-articular involvement
  - Anemia
  - Joint and spine disease
    - Cervical spine disease due to instability of atlas on axis
    - Joint deformity (swan neck, boutonnière)
  - Ocular disease – episcleritis
  - Cardiopulmonary disease
    - Interstitial fibrosis

- Lung nodules that cavitate
- Pericarditis may occur in 1/3 of patients
- Rheumatoid nodules – may resolve
- Vasculitis – small and medium vessel disease
- Complications
  - Cancer
    - Often secondary to therapy
      - Lymphoma, leukemia most common
  - Cervical atlanto-axial dislocation
  - Appearance of early cardiovascular disease (average 10 years earlier than population statistics)
  - Serious infection rate increased
  - Pulmonary interstitial disease
- Juvenile idiopathic arthritis (JIA)
  - Compromised of heterogeneous group of arthritis of unknown origin
  - Begins before age 16
  - The International League of Associations for Rheumatology (ILAR) classifies JIA into 7 diseases
    - Differ in clinical presentation and in some cases genetic background
    - Polyarticular arthritis is most similar to RA in terms of clinical presentation and serologic testing

#### Treatment

- Aggressive use of disease-modifying antirheumatic drugs (DMARDs) to prevent damage in addition to NSAIDs

## Diagnosis

- Indications for testing – persistent joint pain with early morning stiffness
- American College of Rheumatology criteria – at least 4 required for diagnosis
  - Morning stiffness – for at least 1 hour over a period of at least 6 months
  - Arthritis of 3 or more joints – from wrist, PIP, MCP, elbow, knee, ankle, metatarsophalangeal (MTP)
  - Hand joint involvement – wrist, MCP, PIP
  - Symmetric arthritis – same joints as arthritis
  - Rheumatoid nodules – subcutaneous nodules around joints
  - Positive rheumatoid factor
  - Radiographic changes – erosions or loss of density of joints
- Laboratory testing
  - No single test confirms the diagnosis
  - Complete blood count with differential – may be helpful to rule out infection
  - Erythrocyte sedimentation rate (ESR) (often increased >30 mm/hr) or C-reactive protein (CRP)
  - Rheumatoid factor (RF) IgM
    - Negative in 30% in early onset RA
    - Present in 5-10% of healthy individuals, prevalence increases with age
    - Not specific for RA; however, present in systemic sclerosis, hepatitis C, cryoglobulinemia and systemic lupus erythematosus
  - Anti-cyclic citrullinated peptide (CCP) IgG antibody
    - More than 98% specific, positivity supports the diagnosis of RA
    - As a screening method for RA, the IgM-RF and the CCP assays are superior to other RF isotypes
    - CCP can be detected in up to 38.4% of IgM-RF negative sera

- The presence of anti-CCP and IgA-RF may predict the development of RA
- Anti-CCP antibodies are associated with RF positive polyarticular course of juvenile idiopathic arthritis (JIA)
- JIA – testing of this antibody frequently negative; serology most likely positive in polyarticular arthritis form
- Rheumatoid factor isotypes
  - RF IgA in combination with anti-CCP may predict radiological damage in RA
- Rarely, joint aspiration with synovial fluid analysis may be required to rule out crystalline arthritis
- Imaging studies
  - Plain x-ray of involved joints may be helpful if local destruction is discovered

#### Differential Diagnosis

- Infectious arthritis
- Reactive arthritis
- Seronegative spondyloarthropathies
- Connective tissue disease
- Fibromyalgia
- Polyarticular gout
- Thyroid disease
- Hemochromatosis
- Sarcoidosis
- Vasculitis
- Acute rheumatoid fever
- Polymyalgia rheumatica

#### Screening

- Thiopurine methyltransferase (TPMT) activity – used to detect individuals with low (abnormal) TPMT activity that may be at risk for excessive myelosuppression when exposed to standard doses of thiopurines such as azathioprine (Imuran) and 6-mercaptopurine (Purinethol)
- TPMT phenotype testing does not replace need for clinical monitoring of patients treated with thiopurine drugs
- Genotype for TPMT cannot be inferred from TPMT activity (phenotype)
  - Phenotype testing should not be requested for patients currently treated with thiopurine drugs; results will be falsely low
  - Current TPMT phenotype may not reflect future TPMT phenotype, particularly in patients who received blood transfusions within 30-60 days of testing

#### Monitoring

- ESR or CRP may be useful in monitoring disease progression

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
CBC with Platelet Count & Automated Differential <b>0040003</b> Method: Automated Cell Count with Flow Cell Differential	Helpful in initial evaluation to rule out infection		
C-Reactive Protein <b>0050180</b> Method: Immunoturbidimetric	Monitor inflammation in patient with RA Test is well-standardized		
Cyclic Citrullinated Peptide Antibody, IgG <b>0055256</b> Method: Enzyme-Linked Immunosorbent Assay	Diagnosis and prognosis of RA	The diagnostic value of antibodies to CCP in JIA has not been determined	
Rheumatoid Factor <b>0050465</b> Method: Immunoturbidimetric	Diagnose RA	Negative results do not rule out RA Results should be used in conjunction with clinical findings to make a diagnosis of RA	
Sedimentation Rate, Westergren (ESR) <b>0040325</b> Method: Westergren	Evaluate activity of disease		
Rheumatoid Factor, IgM, IgG, & IgA by EIA <b>0051298</b> Method: Enzyme Immunoassay	May be useful when combined with anti-CCP to predict radiological damage in RA	Negative results do not rule out RA RF in any isotype combination may be found in hepatitis C, Sjögren syndrome and other chronic infections	

### Additional Tests Available

Test Name and Number	Comments
Leflunomide, Serum or Plasma <b>0093302</b> Method: High Performance Liquid Chromatography/Mass Spectrometry	

<p>Leflunomide, Urine <b>0093306</b></p> <p>Method: High Performance Liquid Chromatography/Mass Spectrometry</p>	
<p>Gold, Serum or Plasma <b>0091265</b></p> <p>Method: Graphite Furnace Atomic Absorption Spectroscopy</p>	
<p>Methotrexate <b>0090311</b></p> <p>Method: Fluorescence Polarization Immunoassay</p>	
<p>Methotrexate Sensitivity by MTHFR Genotyping <b>0051286</b></p> <p>Method: Polymerase Chain Reaction/Fluorescence Monitoring</p>	
<p>Thiopurine Methyltransferase, RBC <b>0092066</b></p> <p>Method: Enzymatic/High Performance Liquid Chromatography</p>	<p>TPMT enzyme activity can be inhibited by several drugs including the following:</p> <ul style="list-style-type: none"> <li>• Naproxen</li> <li>• Ibuprofen</li> <li>• Ketoprofen</li> <li>• Furosemide</li> <li>• Sulfasalazine</li> <li>• Mesalamine</li> <li>• Olsalazine</li> <li>• Mefenamic acid</li> <li>• Thiazide diuretics</li> <li>• Benzoic acid</li> </ul> <p>Patients should abstain from these drugs for at least 48 hours prior to TPMT testing in order to avoid falsely low results</p> <p>TPMT activity for patients who have recently received a blood transfusion may not accurately reflect future TPMT phenotype</p>

**Additional Information**

Compliance monitoring for leflunomide, gold and other commonly used medications may be appropriate. Please contact the laboratory to discuss available test options

**Guidelines**

Guidelines for the management of rheumatoid arthritis: 2002 Update. American College of Rheumatology. Atlanta: Georgia [Accessed: 20 Apr 2009]

Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002; 46 (2) 328-346.

**General References**

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