Rheumatology Labs for Primary Care Providers

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Objectives

Review the Indications for and Interpretation of lab testing for the following diseases:

- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Gout
- Ankylosing Spondylitis
Rheumatoid Arthritis

• RA is a systemic inflammatory autoimmune disease.

• 2010 American College of Rheumatology criteria for diagnosis assign points for four different domains: number of joints involved, serologic abnormalities, elevated acute phase reactants, and symptom duration at least six weeks.
## 2010 ACR/EULAR Classification Criteria for RA

### JOINT DISTRIBUTION (0-5)

<table>
<thead>
<tr>
<th>Number of Joints</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<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 (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

### SEROLOGY (0-3)

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

### SYMPTOM DURATION (0-1)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

### ACUTE PHASE REACTANTS (0-1)

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</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
Tests for Rheumatoid Arthritis

1. Serologic Labs: Rheumatoid Factor (RF) and the Anti-Citrulline Antibody (CCP)
2. Acute Phase Reactants: ESR and CRP
3. X-rays: Typically hands and feet
PERIOSTEUM

SUBCHONDRAL BONE PLATE

JOINT CAPSULE

SYNOVIIUM

ARTICULAR CARTILAGE

TENDON

MUSCLE
Rheumatoid Factor

• First described in 1940, antibodies directed against the Fc portion of IgG.
• Appears to be an abnormal immune response to chronic inflammatory diseases.
• Can be detected in about 5% of healthy adults.
RF Associations

• Rheumatologic Diseases: rheumatoid arthritis, sjogren’s syndrome, MCTD, mixed cryoglobulinemia, systemic lupus erythematosus, PM/DM.

• Non-rheumatologic diseases: chronic infections (especially HCV: positive RF in 50-75% of patients), sarcoidosis, primary biliary cirrhosis, malignancy (esp. B-cell neoplasms).
RF Diagnostic Value

• RF can be detected many years before onset of disease.
• Most asymptomatic people with a positive RF do not progress to RA.
• Estimates of the sensitivity and specificity of the RF for RA vary considerably depending on the pre-test probability.
• Consensus seems to be that the sensitivity of the RF in patients who have RA is about 70%.
RF Summary

• No clear consensus for indications for ordering the RF.
• The RF has little or no value as a screening test in healthy populations or for patients with arthralgias.
• The negative predictive value of the RF is limited by the significant prevalence of RF-negative RA.
Antibodies

Anti-Citrullinated Peptide Antibodies

• In RA there is induction of the peptidyl arginine deiminase (PAD) enzyme which converts arginine to citrulline ("increased citrullination").

• Leads to immune reactivity with the production of anti-citrullinated protein antibodies.
Anti-CCP Antibodies in RA

• Sensitivity 50-75%, Specificity >90%
• Like the RF, can be present prior to the onset of RA symptoms.
• Can be present in other diseases (overlap syndromes, active tuberculosis), but generally not present with HCV.
• Associated with increased risk of aggressive disease.
Systemic Lupus Erythematosus

- SLE is a chronic inflammatory disease of unknown cause.
- Variable clinical features: fatigue, rashes, alopecia, arthritis, Raynauds, pleuritis/pericarditis, lymphanedopathy, oral/nasal ulcers.
- Also: Frequent hematologic disorders; anemia, leukopenia, thrombocytopenia.
- Nephritis
<table>
<thead>
<tr>
<th>Classification criteria for systemic lupus erythematosus</th>
<th>SLICC criteria for the classification of systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR criteria for the classification of systemic lupus erythematosus</strong>[^1][^2]</td>
<td><strong>SLICC criteria for the classification of systemic lupus erythematosus</strong>[^3]</td>
</tr>
<tr>
<td><strong>Criteria</strong></td>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Malar rash</td>
<td>Facial erythema, not raised, over the malar eminences, tending to spare the nasal bridge</td>
</tr>
<tr>
<td>Photo sensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, in patient history or clinicians observation</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratin scale and follicular plugging, atrophic scarring may occur in other lesions</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or oropharyngeal ulceration, usually painless, observed by a clinician</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis – Constricting history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria greater than 500 mg/24 hours or greater than 3 x elevation not performed OR Cellular casts – this is red cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Seizures OR psychosis – in the absence of offending drugs or known metabolic derangements (alcohol, drugs, infections, or electrolyte imbalance)</td>
</tr>
<tr>
<td>Lupus nephritis – with intravenous OR Leukopenia – Less than 4000/mm³ total on two or more occasions OR</td>
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</tr>
<tr>
<td>Thrombocytopenia – Less than 100,000/mm³ (in the absence of offending drugs)</td>
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</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>Positively identified assay for lupus anticoagulant using a standard method, or on a false positive screening test for lupus anticoagulant defined by the 1988 ACR criteria based on the laboratory reference range</td>
</tr>
<tr>
<td>ARA</td>
<td>ANA level above laboratory reference range</td>
</tr>
<tr>
<td>SLE cell test</td>
<td>Direct Coombs test</td>
</tr>
</tbody>
</table>

**ACR:** American College of Rheumatology; **SLICC:** Systemic Lupus International Collaborating Clinics; **SLE:** systemic lupus erythematosus; **ENA:** extractable nuclear antigens; **ANA:** antinuclear antibody; **Anti-DNA:** antibody to DNA; **Anti-Sm:** antibody to Sm antigen.

SLE Diagnosis

• Sometimes see “Definite” lupus, Probable lupus, and “Possible” lupus.
• Undifferentiated Connective Tissue Disease
• ANA Negative SLE?
• Rhupus? (erosive vs. nonerosive arthritis)
• MCTD
• Discoid Lupus
• Drug Induced Lupus
SLE Labs

- The ANA is positive in virtually all patients with SLE at some point in the course of their disease.
- Labs for suspected SLE: ANA, C3 and C4, ESR, CBC, Chemistry Panel, UA.
The Anti-Nuclear Antibody

• Several different techniques are commonly used: Indirect Immunofluorescence, also solid phase assays.
• The significance of ANA titers is very controversial: In healthy adults age 20-60 the ANA is detected at a titer of 1:40 in 30% of patients, and in 5% at a titer of 1:160.
• Prevalence of inflammatory connective tissue disease is 1% or less.
Four common ANA staining patterns

In the homogeneous pattern (A), the entire nucleus is diffusely stained. The chromosomes at the metaphase plate are also stained. In the speckled pattern (B), very small, uniform, fluorescent dots are seen throughout the nucleus. The centromere pattern (C) is characterized by the presence of 30 to 60 dots distributed throughout the nucleus in resting cells. The dots localize to chromosomes at the metaphase plate in dividing cells. The nucleolar staining pattern is shown in (D).

Courtesy of Donald B Bloch, MD.
The ANA Profile

- dsDNA: Specific for Systemic Lupus, titer goes up and down with disease activity
- SM: Specific for SLE
- SS-A, SS-B: Sjogrens, also SLE and others
- RNP: MCTD
- Anti-Histone Ab: Drug induced lupus
- Anti-Centromere Ab, Anti-Scl-70 Ab: Systemic Sclerosis
- Anti-Phospholipid antibodies
ANA Pre-Test Probability

- Sjogrens: dry mouth/dry eyes, parotid swelling: SS-A, SS-B, RF.
- Systemic Sclerosis: Raynaud’s, skin induration: Anti-centromere Ab, Anti-Scl-70.
- Drug-Induced lupus: rash, arthritis, serositis, on appropriate medication.
- Anti-phospholipid Antibody Syndrome: Miscarriage, rash, thrombotic event.
HLA-B27

• Present in at least 90% of patients with Ankylosing Spondylitis
• But—Only 5% of B27+ individuals develop a spondyloarthritis.
• Prevalence of B27+ gene is about 5-10% depending on the population.
• AS is highly heritable—at least 90% of the risk of developing AS is thought to be inherited.
HLA-B27 Subtypes

• At least 100 different subtypes
• B*2705: Highly associated with AS, most frequent subtype in Caucasians.
• B*2704: Also associated with AS, most frequent subtype in Chinese and Japanese
• Other subtypes are not associated with AS (B82706 and B*2709).
• Possible AS pathogenesis theories depending on different subtypes.
AS Pathophysiology

• Pathologic changes occur mainly at the articulations of the axial skeleton, IE the SI joints, spine, hips, and shoulders.

• The main pathologic changes that occur are inflammation, bone destruction and new bone formation.

• The classic finding in AS is new bone formation leading to ankylosis of the SI joints.

• The main way to diagnose AS is with imaging.
**ASAS modification of the Berlin algorithm**

Chronic low back pain*

- **X-rays**
  - Positive
  - Negative
    - Presence of other SpA-features: IBP, heel pain (enthesitis), dactyritis, uveitis, positive family history, IBD, alternating buttck pain, psoriasis, asymmetrical arthritis, positive response to NSAIDs, acute phase reactants (raised ESR/CRP)

- ≥4 SpA-features
  - SpA
- 2-3 SpA-features
  - HLA-B27
    - Positive
      - SpA
    - Negative
      - Consider other diagnosis
- 0-1 SpA-features
  - HLA-B27
    - Positive
      - MRI
      - Consider other diagnosis
    - Negative
      - SpA

IBP is deleted as obligatory entry criterion and implemented as an additional SpA feature.
Starting point is the presence of chronic back pain longer than three months with an onset of back pain before the age of 45.

SpA: spondyloarthitis; AS: ankylosing spondylitis; x-rays: plain radiographs of the pelvis graded according to the modified New York criteria; IBP: inflammatory back pain; IBD: inflammatory bowel disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HLA: human leukocyte antigen; MRI: magnetic resonance imaging.
* >three months, onset <45.

Gout

• Characterized by uric acid saturation.
• Occurs earlier in life in men than women (after menopause uric acid levels in women rise to levels comparable to men).
• Thought to be an average of 10 years of asymptomatic hyperuricemia prior to clinical expression of gout.
• Estimated prevalence of gout of about 3% in the U.S.
Gout Diagnosis: Arthrocentesis

• Best way to diagnose gout is by seeing the crystals!
• Synovial Fluid Tests: cell count, crystals ID, gram stain and culture.
• Can very often see crystals even in between attacks.
Serum Uric Acid

- During an acute gout attack the serum uric acid may be high, normal, or low.
- Asymptomatic hyperuricemia generally defined as uric acid level >8.
- For patients taking medication for chronic gout the treatment goal is uric acid <6.
Gout Diagnosis

• Biopsy Tophi
• Imaging: ultrasound