Diagnostic Tests in Rheumatic Disease: What’s Old, What’s New & What’s Useful?

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Diagnostic Tests in Rheumatic Disease: What's Old, What's New & What's Useful

1. Introduction
2. ESR & CRP
3. RF & anti-CCP
4. ANA
5. ANCA
6. Imaging Studies
Diagnostic tests rarely establish a diagnosis in rheumatic disease and frequently provide more prognostic than diagnostic information.

Sensitivity and specificity are a good start: they are available for many tests and are not dependent on prevalence of disease.

Predictive value is the most useful characteristic of a test but varies with disease prevalence (or pre-test probability) – it is highly dependent on judgment.

The rheumatic disease criteria help standardize studies but have limitations - milder disease may be excluded.
ERYTHROCYTE SEDIMENTATION RATE (ESR)

- Highly sensitive, but not specific
  - That includes the ESR > 100

- Rises with age (normal = age/2; see Ann Intern Med 1986;104:515), pregnancy, infection, malignancy

- Be prepared to deal with the results (SUO* versus false negative)

*Sed rate of unknown origin
The ESR: How it’s done
ERYTHROCYTE SEDIMENTATION RATE (ESR)

Rheumatic Disease
- Giant Cell Arteritis, Polymyalgia Rheumatica (PMR) - high sensitivity, useful as adjunct to monitor course
- Other diseases - variable, somewhat unreliable

Non-rheumatic Disease
- Subacute Bacterial Endocarditis - high sensitivity
- Other diseases - may be helpful in monitoring treatment of osteomyelitis, inflammatory bowel disease, abscess
C-REACTIVE PROTEIN (CRP)

• Discovered in human serum, able to precipitate with c-polysaccharide of the pneumococcus
• Conserved in evolution (chickens, horseshoe crab, etc.)
• Helpful to monitor inflammation/disease activity; less sluggish in its response (vs. ESR) - may change over hours
• Range of abnormal values for CRP is greater than for ESR
• CRP tends not to rise much in lupus unless infection present - CRP > 10 mg/dl, 80+% have bacterial infections
• Minor elevations in CRP may identify ↑cardiac risk

• Unknown: Is CRP better for assessing disease severity or predicting prognosis than ESR? What if they are discordant?
## ESR vs. CRP

<table>
<thead>
<tr>
<th></th>
<th>ESR</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>↑</td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td>↑</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>↑</td>
<td>X</td>
</tr>
<tr>
<td>Drugs (e.g., steroids, NSAIDs)</td>
<td>↓</td>
<td>X</td>
</tr>
<tr>
<td>Smoking</td>
<td>↑</td>
<td>X</td>
</tr>
</tbody>
</table>

Adapted from: Best Practice Advocacy Centre New Zealand  
• CRP more sensitive (98.9% vs. 91.5%) and predicted relapse better than ESR

• ESR reflected response to treatment better (ESR high in 13%, CRP in 42% after 4 weeks of treatment)

• IL-6 was even better: persistent elevation predicted relapse
### ESR vs. CRP for Temporal Arteritis

- 764 patients with ESR, CRP & temporal artery biopsy (23% of which were positive)
- Sensitivity of CRP = 87%
- Sensitivity of ESR = 84%
- Only 7 patients (4%) with a positive TAB for GCA had a normal ESR and CRP

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>84.2%</td>
<td>29.5%</td>
</tr>
<tr>
<td></td>
<td>149/177</td>
<td>173/592</td>
</tr>
<tr>
<td>CRP</td>
<td>86.4%</td>
<td>30.5%</td>
</tr>
<tr>
<td></td>
<td>153/177</td>
<td>179/587</td>
</tr>
<tr>
<td>ESR and CRP</td>
<td>80.8%</td>
<td>41.2%</td>
</tr>
<tr>
<td></td>
<td>143/177</td>
<td>242/587</td>
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</tbody>
</table>
Symmetric, persistent polyarthritis in “rheumatoid distribution”
RHEUMATOID FACTOR

• Considered helpful: sensitive and specific, reliable, inexpensive, included among criteria for RA, present in other rheumatic disease.

However,
• Sensitivity & specificity in RA are modest
• False positive test results are common & may outnumber true positive test results in many primary care settings.
• Prognostic information likely outweighs diagnostic information and results do not affect management.
Rheumatic diseases associated with a positive rheumatoid factor

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>50-90%</td>
</tr>
<tr>
<td>SLE</td>
<td>15-35%</td>
</tr>
<tr>
<td>Sjogren's syndrome</td>
<td>75-95%</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>20-30%</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>40-100%</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>50-60%</td>
</tr>
<tr>
<td>Condition</td>
<td>Percentage</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Aging (&gt;age 70)</strong></td>
<td>10-25%</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>25-50%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>15-40%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>10%</td>
</tr>
<tr>
<td>Syphilis</td>
<td>up to 10%</td>
</tr>
<tr>
<td>Parasitic disease</td>
<td>up to 90%</td>
</tr>
<tr>
<td>Leprosy</td>
<td>up to 60%</td>
</tr>
<tr>
<td>Viral infection</td>
<td>up to 60%</td>
</tr>
<tr>
<td><strong>Pulmonary Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>3-33%</td>
</tr>
<tr>
<td>Interstitial pulm. fibrosis</td>
<td>10-50%</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30-50%</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Miscellaneous Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>45-70%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5-25%</td>
</tr>
</tbody>
</table>
Pre-test probability makes all the difference

Based on Sens = 0.7 & Spec = 0.85 for RF in RA:

<table>
<thead>
<tr>
<th>Pre-test Probability</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>4%</td>
<td>99.6%</td>
</tr>
<tr>
<td>20%</td>
<td>54%</td>
<td>92%</td>
</tr>
<tr>
<td>30%</td>
<td>67%</td>
<td>87%</td>
</tr>
<tr>
<td>50%</td>
<td>82%</td>
<td>74%</td>
</tr>
<tr>
<td>75%</td>
<td>93%</td>
<td>49%</td>
</tr>
<tr>
<td>90%</td>
<td>98%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Rheumatoid Factor Summary

- Moderately sensitive and specific
- Higher titers have higher specificity and positive predictive value
- Positive predictive value is low in most non-specialty settings
- A negative test does not rule out disease (20-50% of RA patients are seronegative)
- High titer RF without rheumatic disease: think of cryoglobulinemia and SBE
Anti-cyclic citrullinated protein (anti-CCP)

- Anti-CCP antibodies - target citrulline, a modified form of arginine
- Sensitivity = 50-70%
- Specificity = 95-98%, correlates with erosive disease, can be present before symptoms
- May identify some RF-negative RA patients
- May identify some “false+ RF” patients (e.g., negative in patients with Hep. C)
- ?Pathogenic - modest sensitivity argues against

The bottom line: anti-CCP useful given its higher specificity but RA still cannot be diagnosed by a blood test.
Meta-analysis of 86 studies:
- Sensitivity was similar for the 2 tests (67% vs. 69%)
- Specificity of anti-CCP was higher than RF (95% vs. 85%)
- “... anti-CCP antibody positivity is more specific than IgM RF positivity for diagnosing rheumatoid arthritis and early rheumatoid arthritis.”
Criteria for RA

The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA

Criteria to apply to those who:
• have at least 1 joint with definite clinical synovitis
• synovitis not better explained by another disease

A score of 6 out of 10 is needed for classification of a patient as having definite RA

A. Joint involvement -
   1 large joint: 0
   2-10 large joints: 1
   1-3 small joints: 2
   4-10 small joints: 3
   >10 joints (at least 1 small joint): 5
Criteria for RA (continued)

B. Serology –
• RF and anti-CCP both negative: 0
• Low titer positive RF or anti-CCP: 2
• High titer RF or anti-CCP: 3

C. Acute-phase reactants
• CRP and ESR both normal: 0
• Either CRP or ESR elevated: 1

D. Duration of symptoms
  <6 weeks: 0
  > 6 weeks: 1
Something new: multiple biomarker testing

Patients & Caregivers

Patients: Sign up and connect with us
If you are a patient or family member, friend, or caregiver of a person living with RA, we invite you to connect with us.

Healthcare Professionals

Healthcare Professionals: View the latest video
Watch Dr. Philip Mease discuss **Measuring RA at the Molecular Level**

Vectra DA is validated for use in adults diagnosed with RA. Test results are intended to aid in the assessment of disease activity in RA patients when used in conjunction with standard clinical assessment. This test is not intended or validated to diagnose RA. Vectra DA is not available outside of the United States.
Vectra testing: disease activity measure

- 12 biomarkers, including CRP, IL-6, serum amyloid A (largest contributors to score)
- Vectra scores correlate with clinical measures of disease activity (e.g., DAS28), x-ray changes
- Not for diagnosis, only for disease activity
- Marginal benefit uncertain
Photosensitive, malar rash sparing nasolabial fold, alopecia
An Emailed case...

“...I sent an ANA on a young female patient with unexplained weight loss but not much else. Her ANA was 1:80, speckled. Would you make much of this in the absence of other symptoms?”
## ANA Sensitivity in Selected Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>ANA Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>95-99%</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>100%</td>
</tr>
<tr>
<td>Sjogren’s Syndrome</td>
<td>75%</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>50-90%</td>
</tr>
<tr>
<td>MCTD</td>
<td>99-100%</td>
</tr>
<tr>
<td>RA</td>
<td>20-40%</td>
</tr>
</tbody>
</table>

Other: autoimmune thyroid disease, hepatitis, PBC, infections
ANTINUCLEAR ANTIBODIES

Useful to know:
- The ANA is highly sensitive (95-99%) in SLE, low specificity, lab variability; also sensitive for Sjogren’s Syndrome, Scleroderma, Drug-Induced Lupus

Maybe helpful to know:
- The higher the ANA titer, the more likely the result is a true positive

Probably useless:
- The ANA pattern (diffuse, speckled, peripheral, nucleolar)
ANA SUBTYPES

Also called specific autoantibodies, extractable nuclear antigens (ENAs), ANA “panel”

- Anti-ds-DNA (peripheral) and anti-Sm (speckled) are highly specific, but not sensitive, for SLE
- Anti-Ro crosses placenta and mediates congenital CHB, neonatal lupus
- Any pattern/specificity may be noted in SLE
  - anti-Ro (speckled) also common in Sjogren’s, Scleroderma
  - anti-histone (diffuse) common in RA, aging, DILE
  - RNA staining (nucleolar) found in Scleroderma, RA, Sjogren’s
Antinuclear antibody (ANA) Patterns

Peripheral or Rim: anti-dsDNA
Diffuse: nonspecific

Speckled: anti-Ro or anti-Sm
Nucleolar: anti-RNA
Antineutrophilic cytoplasmic antibody (ANCA)

- c-ANCA (cytoplasmic)
  - Usually anti-proteinase-3 (PR-3)

- p-ANCA (peri-nuclear)
  - Often anti-myeloperoxidase (MPO)
# ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

<table>
<thead>
<tr>
<th>Rheumatic Disease</th>
<th>c-ANCA/PR3</th>
<th>p-ANCA/MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td>80%</td>
<td>10%</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>Eosinophilic Granulomatosis with polyangiitis (Churg-Strauss)</td>
<td>10%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Other vasculitides generally ANCA-negative: hypersensitivity, Henoch-Schönlein purpura (HSP), polyarteritis nodosa, GCA, Takayasu’s

**Note:** drug-induced vasculitis (especially PTU, hydralazine, minocycline) also associated with +p-ANCA/MPO; tainted cocaine may have both anti-MPO and anti-PR3

RA, SLE, Sjogren’s, other rheumatic disease may be associated with nonspecific p-ANCAs (not directed against MPO)
## ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

<table>
<thead>
<tr>
<th>ANCA in non-rheumatic disease:</th>
<th>cANCA/PR-3</th>
<th>pANCA/MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic crescentic glomerulonephritis</td>
<td>10-20%</td>
<td>65-75%</td>
</tr>
<tr>
<td>Anti-GBM Disease</td>
<td>10%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>

Nonspecific pANCA (that is, *not* directed against MPO) also observed in:
- Ulcerative colitis
- Primary sclerosing cholangitis
- Cystic Fibrosis
- Autoimmune hepatitis
- Infection: leprosy, malaria, SBE
- (Pre)eclampsia, diffuse alveolar hemorrhage, graft-versus-host disease
ANCA to predict relapse?

- The correlation between ANCA level and disease activity is variable
- Ability of ANCA level & relapse depends in part on:
  - Disease phenotype, e.g., renal involvement or alveolar hemorrhage
  - Treatment, e.g., rituximab vs. cyclophosphamide

<table>
<thead>
<tr>
<th>Rituximab (N = 50)</th>
<th>Rise</th>
<th>No rise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Relapse Concurrent</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No relapse</td>
<td>13†</td>
<td>6‡‡</td>
</tr>
</tbody>
</table>

ANCA: Summary

• It is not enough to know that the ANCA is positive

• Anti-PR3 and Anti-MPO are highly specific for crescentic GN, GPA (WG), related vasculitides

• Monitoring ANCA results in known ANCA-associated disease is of limited value

• In the proper clinical setting, ANCA results may be enough to warrant treatment without biopsy (but such settings are probably rare)

• A negative ANCA is the rule in largest and smallest vessel vasculitides

• Sensitivity and specificity are good but not perfect
The expanding role of ultrasound and MRI in Rheumatic Disease

**Ultrasound**
- examples:
  - temporal arteritis - halo surrounding inflamed artery
  - tendinitis - thickening of tendon with peritendinious fluid
  - rotator cuff disease, including rupture
  - erosions in rheumatoid arthritis

**MRI**
- early erosions in RA
- myositis
Ultrasound in joint and tendon disease

- Fluid
- Thickening

Tendonitis

Normal
Ultrasound and MRI: Sensitive for early erosions in inflammatory joint disease

Erosion by MRI & US, missed by radiograph

X-ray

MRI

Ultrasound
Ultrasound findings in gout & CPPD (pseudogout)
Ultrasound-guided joint aspiration
MRI
inflammatory muscle disease
(myositis)
Dual energy CT for diagnosis of gout

http://therheumatologypodcast.com/podcast/dual-energy-ct-for-diagnosis-of-gout
DIAGNOSTIC TESTS IN RHEUMATIC DISEASE

• Most “diagnostic tests” in rheumatic disease are not diagnostic and have significant limitations
• Selective testing, rather than ordering “panels,” tends to provide more useful information
  • Avoid the temptation to check ANA, RF, ESR in every patient with arthralgia, or ANCA for every patient with possible vasculitis
• Testing to “rule-out” disease in settings of low likelihood is often unhelpful—a negative test often does not exclude disease and a positive test may be confusing
• Anti-CCP is the first highly specific biomarker for RA
• Don’t avoid checking “non-exotic” labs, e.g., urinalysis, CBC renal function
• Consider time as a diagnostic test of choice
DIAGNOSTIC TESTS IN RHEUMATIC DISEASE (2)

- What’s old? ESR, RF, ANA, ANCA, radiographs

- What’s new(er)? CRP, anti-CCP, MSK US, MRI
  - Anti-CCP is the first highly specific biomarker for RA

- What’s useful? Each one of the above when ordered selectively and interpreted in light of known limitations

- Stand by:
  - CRP vs. ESR?
  - How best to assess RA disease activity?
  - Routine office use of musculoskeletal US?
  - Dual energy CT for gout?
Thanks for your attention!