Rheumatology Labs for the General Internist

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Disclosures

- No disclosures relevant to the topic.
Objectives

• Understand how specificity and sensitivity of rheumatologic labs affect likelihood underlying of rheumatic disease.

• Understand what constitutes an initial workup in clinical settings of suspected inflammatory arthritis, systemic lupus, myositis, scleroderma and vasculitis.

• Understand which labs may constitute the need for more urgent referral.
So How Diagnostic are Rheumatologic Labs?
Rheumatology Labs – General Concepts

• In Short – Rarely

• Theme of the day:

  *** NOT SCREENING TESTS ***

• In nearly all clinical settings serology is confirmatory to index of suspicion of disease rather than diagnostic by its own right

• In most clinical settings non-serology play a greater role in acuity of care than any of the labs do (i.e. RF vs K)
Inflammatory Arthritis

- What Constitutes Features of Inflammatory Arthritis?
  - Prolonged Morning Stiffness
  - Swelling or Tenderness of Joints
  - Abrupt or Unexpected loss of function………
Inflammatory Arthritis – Serologic Workup

- Rheumatoid Factor
- Cyclic Citrullinated Peptide (CCP) Antibody
- 14.3.3 eta Protein (?)
- Antinuclear Antibody (ANA)
- Uric Acid
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive Protein (CRP)

- Other things based on clinical setting:
  - ACE Levels
  - ANCA
  - HBsAg
  - HCV Antibodies
  - Cryoglobulins
  - Other ANAs
  - CBC
  - CMP
  - Urinalysis
  - SPEP
Erythrocyte sedimentation rate (ESR)

- The “pulse” of a Rheumatologist or our Achilles Heel???
- Was originally developed as a marker to follow pregnancy
- Tested in a vertically aligned tube of anticoagulated blood and measured by distance RBCs fall over time
- Age and Gender play a role in test reliability in addition to comorbidities
  - Typical rule of thumb for adjustment\(^1\)
    - Men: age / 2
    - Women: age+10 / 2

1: BMJ 1983;286:266
# Erythrocyte sedimentation rate (ESR)

<table>
<thead>
<tr>
<th>Falsely increases it</th>
<th>Falsely decreases it</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inflammatory disorders</td>
<td>• Increased plasma viscosity</td>
</tr>
<tr>
<td>• Hypergammaglobulinemia</td>
<td>• Increased number of RBCs</td>
</tr>
<tr>
<td>• Hypoalbuminemia</td>
<td>• Change in shape of RBCs</td>
</tr>
<tr>
<td>• Tissue Necrosis</td>
<td>• Decreased plasma proteins</td>
</tr>
<tr>
<td>• Pregnancy</td>
<td>•</td>
</tr>
<tr>
<td>• Anemia</td>
<td>•</td>
</tr>
<tr>
<td>• Age</td>
<td>•</td>
</tr>
<tr>
<td>• Heparinized Blood</td>
<td>•</td>
</tr>
<tr>
<td>• Cold Agglutinins</td>
<td>•</td>
</tr>
<tr>
<td>• Morbid Obesity</td>
<td>•</td>
</tr>
</tbody>
</table>
C-reactive protein (CRP)

- Member of the pentraxin family of proteins
- It is an acute phase reactant produced by the liver under the influence of IL-6 & IL-1
- Useful as it is very **acute**
  - Increases within 6 hours of stimulus
  - Peaks within 50 hours
  - Falls rapidly after removal of stimulus (T1/2 = 8 hours)
C-reactive protein (CRP)

- A decompensated liver can impair production of CRP as this marker is synthesized in the liver

- Age and Gender adjustment\(^2\)
  - Men: Upper limit of normal CRP (mg/L) = age / 50
  - Women: Upper limit of normal CRP (mg/L) = age / 50 + 0.6 (AA♀ + 1.0)

\(^2\): J. Rheum. 2000;27:2351-9
ESR / CRP – Summary

• Acute phase reactants → potential for false positive results are significant

• Most practical use is for confirmation of inflammatory disease or monitoring inflammation is some clinical settings

• Tests are less reliable as measures of rheumatic disease activity as not specific enough to illness and affected by comorbidities

  • Exceptions:
    • Systemic Vasculitis
    • Giant Cell Arteritis
      • As high as 90-100% sensitive for activity
# Likelihood of Rheumatic Disease with Abnormal Labs

<table>
<thead>
<tr>
<th>Suspected Disease</th>
<th>RF</th>
<th>ANA</th>
<th>HLA-B27</th>
<th>&gt; Uric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>SLE</td>
<td>AS</td>
<td>Gout</td>
<td></td>
</tr>
<tr>
<td>Patients with positive test (%)</td>
<td>80</td>
<td>99</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Prevalence positive test in normal individuals</td>
<td>2/100</td>
<td>1/100</td>
<td>6/100</td>
<td>5/100</td>
</tr>
<tr>
<td>Disease Prevalence</td>
<td>1/100</td>
<td>1/2000</td>
<td>1/300</td>
<td>1/200</td>
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<tr>
<td>Likelihood of disease if test is positive</td>
<td>1/2</td>
<td>1/20</td>
<td>1/18</td>
<td>1/10</td>
</tr>
<tr>
<td>Likelihood of disease if test positive and joint pain</td>
<td>1/1.5</td>
<td>1/5</td>
<td>1/4.8</td>
<td>1/2.5</td>
</tr>
</tbody>
</table>
Rheumatoid Factor

• What is a RF?
  • Auto-antibody directed against the Fc portion of an IgG
  • Can be of any isotype but IgG / IgM are routinely tested (some do IgA)
  • IgM is the most common

• How accurate is it?
  • Sensitivity: 60-80%
  • Specificity: as high as 78%
  • Healthy adults with a 5% incidence (>20% in those over 65 years of age)
Rheumatoid Factor

- Overall present in 70-85% of cases of Rheumatoid Arthritis
  - Incidence of disease increases with titer
- Frequency of positives increases with age in normal individuals
  - 20-60 years: 2-4%
  - 60-70 years: 5-10%
  - >70 years: 10-25%
Rheumatoid Factor - Associations

- **Rheumatic Conditions**
  - RA (50-85%)
  - SLE (15-35%)
  - Sjögrens Syndrome (up to 95%)
  - MCTD (30-60%)
  - Cryoglobulinemia (up to 100% if HCV+)
  - Myositis (5-10%)
  - Sarcoidosis (15%)
  - Systemic Sclerosis (20-30%)
  - Ankylosing Spondylitis (5-10%)
  - Psoriatic Arthritis (5-10%)

- **Non-rheumatic Conditions**
  - HBV
  - HCV
  - HIV
  - SBE
  - TB
  - IPF
  - PBC
  - Crohn’s Disease
  - IgA Nephropathy (~25%)
Rheumatoid Factor – Associations

- Felty’s (>95%)
- Hepatitis A
- Infectious Mononucleosis
- JIA
- Syphilis
- Influenza (A&B)
- Leukemia
- Lymphoma
- Gout (yep that’s right as many as 10%?!?!)
- Leprosy (as high as 50%!!!)
- Osteoarthritis (5-10%)
- Rheumatic Fever (5-10%)
- Polyarteritis Nodosa
- ANCA Associated Vasculitis
- Viral illnesses….
- Hosts of other malignancies…..
Rheumatoid Factor – Why is it Important?

• Helpful in confirming diagnosis
• Helps to identify subgroups of patients with rheumatic disease
• Can help predict therapeutic response to therapies
• Greater titers can be prognostic indicating more severe and persistent disease
• IgA RF are more tightly associated with rheumatoid vasculitis or erosive disease

• Where they can’t help:
  • Not helpful in monitoring disease activity in RA
  • No indicative of a treatment response in RA

*** Outside of SBE cases RF is ordered diagnostically and nearly never followed
Anti-cyclic Citrullinated Peptide (CCP) Antibodies

• What are they?
  • An antibody to filaggrin that has undergone post-translational modification of the amino acid arginine to citrulline
  • These peptides on fillaggrin (present in epidermal matrix) are recognized in early RA patients

• So CCP has gotta be better right?
  • Sensitivity: 33-67%
  • Specificity: 95%

• What else are they reported in?
  • Lupus, HCV, Psoriasis, Graves, Sjögrens, Tuberculosis
CCPs and their importance

• Can be diagnostic in “RF negative” RA

• Are often present in early RA and can predate development of RFs

• Can antedate synovitis in RA well prior to clinical onset of RA helping treat polyarthritis patients earlier

• Better predictor of erosive disease than RFs
  • (+) CCP and IgM RF is most likely patient for radiographic progression

• Where are they not helpful:
  • Monitoring disease activity (once positive always positive)
  • Correlate poorly with potential for extra-articular manifestations (unlike RF)
14.3.3 eta Protein

• An isoform of the 14-3-3 family of intracellular chaperonin proteins
  • Chaperonins are molecular chaperones that assist in protein folding powered by ATP

• Sensitivity 77% and Specificity 93%
  • Very similar to citrullinated peptide antibodies

• Has been associated with worse disease

• In a few cohort study looking at polyarthralgia patients adding it to workup did not increase likelihood of diagnosis of RA

• Assay is currently readily available
  • further study is needed to justify a role for the assay in routine clinical practice
The Dreadful Antinuclear Antibody

• The “Lupus Test” that more often means something other than Lupus

• An antibody directed against nuclear antigens screened for best by indirect immunofluorescence using hep-2 cells as a substrate

• The nuclear antigenic target determines the “sub”-antibody
  • Following up testing (i.e. anti-dsDNA and other ENA)

• Methodology greatly affects false (+) and false (-) rates

• Seen in 5-30% of normal individuals and affected significantly by age
  • $\geq 1:40$ 20-30% (some studies above 50% in those over 65)
  • $\geq 1:80$ 10-12%
  • $\geq 1:160$ 5%
  • $\geq 1:320$ 3%
Conditions Commonly Associated with ANAs

- Rheumatic Diseases
  - SLE
  - Polymyositis
  - Sjögren Syndrome
  - Scleroderma
  - Vasculitis
  - Rheumatoid Arthritis
- Normal Health Individuals
  - Elderly
  - Women (especially pregnant)
- Hematologic Disorders
  - AIHA
  - ITP
- Hepatic Diseases
  - Chronic Active Hepatitis
  - Primary Biliary Cirrhosis
  - Alcoholic Liver Disease
- Malignancies
  - Lymphoma
  - Leukemia
  - Melanoma
  - Solid Tumors
- Pulmonary Diseases
  - IPF
  - Asbestosis-induced Fibrosis
  - Primary Pulmonary HTN

***Also noted in Hashimotos, Graves, DM, MS, ESRD and organ transplantation patients***
Drugs Associated With Production of ANAs

- PAS
- Tegretol
- Thorazine
- Zarontin
- Apresoline
- Isoniazid
- Mesantoin
- Aldomet
- Metformin
- Sulfonylureas
- Statins
- Dilantin (and derivatives)
- Beta Blockers
- PTU
- Mysoline
- Procainamide
- Trimethadine
- Thiazides
- Tetracylines
- Oral Contraceptives
Infections Associated With Production of ANAs

- HBV
- HCV
- HIV
- Mononucleosis
- SBE
- Tuberculosis
- Lyme Disease
- Rickettsial infections
- Parasitic infections

- And the list goes on,
  - and on,
  - and on,
  - and………………………..
## Antinuclear Antibody Sensitivity

<table>
<thead>
<tr>
<th>Disease</th>
<th>% with Positive ANAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Lupus Erythematous</td>
<td>99%</td>
</tr>
<tr>
<td>Drug Induced Lupus</td>
<td>100%</td>
</tr>
<tr>
<td>Mixed Connective Tissue Disease</td>
<td>93%</td>
</tr>
<tr>
<td>Sjögren Syndrome</td>
<td>48%</td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td>85%</td>
</tr>
<tr>
<td>CREST Syndrome</td>
<td>45%</td>
</tr>
<tr>
<td>Polymyositis / Dermatomyositis</td>
<td>61%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>41%</td>
</tr>
</tbody>
</table>
## Sensitivity ≠ Specificity

<table>
<thead>
<tr>
<th></th>
<th>dsDNA</th>
<th>RNP</th>
<th>Smith</th>
<th>SSA</th>
<th>SSB</th>
<th>Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>60%</td>
<td>30-45%</td>
<td>30%</td>
<td>30%</td>
<td>15%</td>
<td>Rare</td>
</tr>
<tr>
<td>RA</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>Rare</td>
<td>Rare</td>
<td>(-)</td>
</tr>
<tr>
<td>MCTD</td>
<td>(-)</td>
<td>&gt;95%</td>
<td>(-)</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>PSS</td>
<td>(-)</td>
<td>&gt;95%</td>
<td>(-)</td>
<td>Rare</td>
<td>Rare</td>
<td>10-15%</td>
</tr>
<tr>
<td>CREST</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>60-90%</td>
</tr>
<tr>
<td>SjS</td>
<td>(-)</td>
<td>rare</td>
<td>(-)</td>
<td>70%</td>
<td>60%</td>
<td>(-)</td>
</tr>
</tbody>
</table>
### Significance of Pattern

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Nature of Antigens</th>
<th>Function of Antigens</th>
<th>Autoantibody</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenous / Diffuse</td>
<td>Histone Classes (i.e. H1 H2A…)</td>
<td>Linkage of nucleosomal DNA</td>
<td>Histone</td>
<td>SLE, DIL</td>
</tr>
<tr>
<td>Rim / Peripheral / Shaggy</td>
<td>Double or Single stranded DNA</td>
<td>DNA replication and repair</td>
<td>dsDNA</td>
<td>SLE</td>
</tr>
<tr>
<td>Speckled</td>
<td>Proteins A-G, snRNAs, U1-6, Nucleoproteins</td>
<td>Splicing of pre-mRNA, processing RNA polymerase</td>
<td>ENA – RNP &amp; Smith SS-A, SS-B</td>
<td>SLE, MCTD, Sjogrens</td>
</tr>
<tr>
<td>Centromere</td>
<td>Kinetochore</td>
<td>Cell division</td>
<td>Centromere</td>
<td>CREST</td>
</tr>
<tr>
<td>Nucleolar</td>
<td>nRNA</td>
<td>Transcription promotion</td>
<td>Jo-1</td>
<td>Myositis</td>
</tr>
<tr>
<td>Antibody Specificity</td>
<td>ACTIVE SLE</td>
<td>MCTD</td>
<td>PSS</td>
<td>CREST</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>------</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>ANA</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>70-90%</td>
<td>60-90%</td>
</tr>
<tr>
<td>Anti-ds-DNA</td>
<td>60%</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>30%</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>30%</td>
<td>&gt;95% (high titer)</td>
<td>Common (low titer)</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Centromere</td>
<td>Rare</td>
<td>Rare</td>
<td>10-15%</td>
<td>60-90%</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>30%</td>
<td>Rare</td>
<td>Rare</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>15%</td>
<td>Rare</td>
<td>Rare</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Nucleolar</td>
<td>Occasional</td>
<td>Negative</td>
<td>Common</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Scl-70</td>
<td>Rare</td>
<td>Negative</td>
<td>10-20%</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Histone</td>
<td>24-95%</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
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<tr>
<td>Anti-Chromatin</td>
<td>70%</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
</tbody>
</table>
ANAs – take homes

- They represent a diverse group of autoantibodies reacting to intranuclear, intranucleolar or intracytoplasmic antigens

- They are an unreliable definitive diagnostic test
  - Have a suspicion for underlying CTD and order specific ANAs accordingly but don’t be discouraged by a negative result if index of suspicion remains high

- Size Does Matter!!!! (*Watch for the significance of titer and pattern*)

- Always think of alternate non-rheumatic causes if clinical picture does not fit

- Titer of antibody rarely correlates to severity of disease or response to treatment
  - *Exceptions: dsDNA and C’*

- The clinically relevant internal manifestation of disease always matters more than the ANA
Myopathies

• Myalgia ≠ Myopathy
  • Must clinically separate muscle pain from weakness
  • Both have a host of causes: Neuropathic, Inflammatory, Infectious, Toxic……..

• >50% of patient > 50 with a ESR over 50 have polymyalgia
  • Those with signs of TA with highly elevated ESR very likely have GCA (90%)

• Creatine Kinase
  • Elevations are not really specific for any particular disorder
  • The more elevated it is the more likely a myopathy is present
  • Elevations in autoantibodies or acute phase reactants in addition can help narrow cause
Creatine Kinase Normals

- Most labs have a CK 0-200 as the reference range
  - At this level 5% of women and up to 20% of males will have increased baseline levels
- Not only gender but race plays a role in baseline levels
- One analysis looking to establish the 97.5\(^{th}\) percentile for serum CK
  - Caucasian Females: 217
  - Caucasian Male: 336
  - African American Male: 414
  - African American Female: 801

Brewster et al 2007
Myopathies - Inflammatory

- There are many antibodies that occur exclusively in patients with myositis
- Occur mainly in two groups:
  - Anti-nuclear Antibodies*****
  - Anti-cytoplasmic antibodies
    - Anti-synthetase antibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ & anti-EJ)
    - Non-synthetase antibodies (anti-SRP)
- Clinical syndromes are important and associated with myositis such as malignancy
  - Dermatomyositis >> Polymyositis
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Myositis Specific</th>
<th>Myositis Associated</th>
<th>PM</th>
<th>DM</th>
<th>Anti-synthetase Syndrome</th>
<th>Overlap Syndrome</th>
<th>Juvenile Myositis</th>
<th>ILD</th>
<th>Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mi-2</td>
<td>4 – 14%</td>
<td>Not Applicable</td>
<td>Rare</td>
<td>Common</td>
<td>Not Applicable</td>
<td>Common</td>
<td>10%</td>
<td>Rare</td>
<td>Occasional</td>
</tr>
<tr>
<td>SRP</td>
<td>4%</td>
<td>Not Applicable</td>
<td>Common</td>
<td>Occasional</td>
<td>Not Applicable</td>
<td>Not Described</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Jo-1</td>
<td>20%</td>
<td>Not Applicable</td>
<td>Common</td>
<td>Occasional</td>
<td>Marker</td>
<td>Common</td>
<td>Reported</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>PL-7</td>
<td>1 – 4%</td>
<td>Not Applicable</td>
<td>Occasional</td>
<td>Common</td>
<td>Marker</td>
<td>Common</td>
<td>Reported</td>
<td>Common</td>
<td>Common</td>
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<tr>
<td>PL-12</td>
<td>1 – 4%</td>
<td>Not Applicable</td>
<td>Occasional</td>
<td>Common</td>
<td>Marker</td>
<td>Common</td>
<td>Reported</td>
<td>Common</td>
<td>Common</td>
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<tr>
<td>OJ</td>
<td>1 – 4%</td>
<td>Not Applicable</td>
<td>Occasional</td>
<td>Common</td>
<td>Marker</td>
<td>Common</td>
<td>Reported</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>EJ</td>
<td>1 – 4%</td>
<td>Not Applicable</td>
<td>Occasional</td>
<td>Common</td>
<td>Marker</td>
<td>Common</td>
<td>Reported</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>PM/Scl</td>
<td>Not Applicable</td>
<td>8%</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Not Applicable</td>
<td>Common (~25%)</td>
<td>Occasional</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Ku</td>
<td>Not Applicable</td>
<td>% Unknown</td>
<td>Not Described</td>
<td>Not Described</td>
<td>Not Applicable</td>
<td>Common</td>
<td>Occasional</td>
<td>Not Described</td>
<td>% Unknown</td>
</tr>
<tr>
<td>U2 snRNP</td>
<td>Not Applicable</td>
<td>% Unknown</td>
<td>Not Described</td>
<td>Not Described</td>
<td>Not Applicable</td>
<td>Common</td>
<td>Not Described</td>
<td>Not Described</td>
<td>% Unknown</td>
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</tbody>
</table>
HMGCR Antibody Associated Myopathies

• In the past decade reports of chronic myopathies after statin use have been noted

• In 2010 antibody discovered that was IgG binding to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in patients with presumed immune myopathies that usually have no lymphocytic cell foci that were termed HMGCR Antibodies

• Distinct clinical entity of necrotizing myopathies that damage perimysial connective tissues and muscle fibers

• Reference ranges were established and test available but not done routinely in practice yet likely coming when clinical algorithm can be established

  • False positive rate with this antibody shocking low for this necrotizing myopathy
  • Antibody does not seem to be present in other forms of immune based myopathies
  • Up to 30% Anti-HMGCR positive patients have not been exposed to statins

Myositis – Take Homes

• Know what you are working up – Myalgia or Myopathy

• Underlying cause can affect labs – toxic vs inflammatory vs other

• Creatine Kinase
  • If not clinically impressive ponder if value could be baseline for patient
  • Eliminate other causes when minimal or no clinical symptoms found
  • Be wary of patients with cardiopulmonary symptoms or dysphagia as these patients require urgent referral***

• As you “build” abnormal labs likelihood of disease increases
  • Elevated CK, abnormal ESR, Elevated LAEs, Abnormal ANA……………..
Scleroderma

- Most common antibody is simply an ANA
  - Typically Nucleolar pattern (scl-70 antibodies are uncommon)
- Other antibodies occur infrequently but when present have clinical importance
  - They can help to guide therapy
  - They are useful in helping direct monitoring of patients
- Higher the titer of specific antibody the greater concern for associated clinical illness
  - Not having the particular antibody does not exclude the illness or complication
- Important to know patterns of disease in relevance to serology to assess risk and follow patients most appropriately
<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Prevalence</th>
<th>Clinical Syndromes</th>
<th>Associated Clinical Features</th>
</tr>
</thead>
</table>
| Anti-Nuclear Antibody                | Extremely High     | *Nucleolar pattern suggests RNA-polymerase III, Anti-PM/Scl, Anti-Th/To & Antifibrillarin (15-40%)* | Increased frequency in pulmonary fibrosis  
Increased mortality rate  
Renal involvement not uncommon |
| Anti-Scl-70 (Anti-Topoisomerase 1)   | 20%                | Highly specific for diffuse cutaneous SSc                                           | Greater overall mortality rate |
| Anti-RNA Polymerase III              | 20%                | Highly specific for diffuse cutaneous SSc                                           |                                      |
| Anti-Centromere                      | 20 – 30%           | Limited SSc/CREST Variant                                                           | Increased risk pulmonary hypertension  
Lower frequency of pulmonary fibrosis  
Raynauds Phenomenon predominant  
Higher risk of calcinosis and ischemic digital loss  
More prevalent in Caucasian ethnicity |
| Anti-Th/To                           | 2 – 5%             | SSc with milder skin and systemic involvement                                     | Severe pulmonary fibrosis (poor prognosis)  
Pulmonary Hypertension |
| Anti-U1 RNP                          | 8%                 | SSc with less cutaneous and renal involvement                                      | Mixed Connective Tissue Disease (strong positive)  
Pulmonary disease and pulmonary hypertension  
Esophageal Disease |
| Anti-Fibrillarin (U3 RNP)            | < 10%              | Diffuse Cutaneous SSc                                                              | Renal Disease  
Associated with myositis  
Pulmonary Hypertension  
More prevalent in African-American ethnicity |
| Anti-PM/Scl                          | 2% 24%             | SSc with limited skin disease  
Polymyositis-SSc overlap syndromes                                                   | Arthritis  
More prevalent in African-American ethnicity |
Human Leukocyte Antigen B27 (HLA-B27)

• Class I surface antigen encoded by the B locus in the Major Histocompatibility Complex (MHC) on chromosome 6 and presents antigenic peptides to T cells

• Seen in 85-95% of Caucasian patients with AS yet their presence in a patient is not diagnostic of spondyloarthritis
  • Sensitivity changes based on race,
  • Marker present in 8% of the general population
    • Estimated that around 10% of individuals with this gene will develop spondyloarthritis
    • Associated with a variety of diseases like ankylosing spondylitis, psoriasis, inflammatory bowel disease, reactive arthritis among other entities

• Positive result does not absolutely confirm or exclude spondyloarthritis
  • About 10-20% of patients with AS will test negative – sensitivity worse for other subtypes
Uric Acid

• This is only a diagnostic test for hyperuricemia **NOT** Gout

• 2007 US Census Statistics
  • 228 Million - US Adult Population\(^4\) – ~43 Million Hyperuricemic\(^5\) – ~6 Million Gout\(^6\)

• Many medications, disease states (e.g. psoriasis) or comorbidities affect level

• Gold standard for diagnosis of gout is still arthrocentesis for MSUM crystals

• Timing of test plays a role in finding hyperuricemia in Gout patients
  • Serum uric acid baseline may decrease by as much as 50% during flare\(^6\)

Uric Acid

- Patients with established Gout not treated to a target sUA <6
  - Are still symptomatic
  - Have ongoing joint damage even during asymptomatic periods
  - Continue to develop tophaceous deposits

- KEYS TO REMEMBER:
  - Likelihood of Gout in hyperuricemic patient ~1/10
  - Likelihood of Gout in hyperuricemic patient with joint pain ~1/2.5
  - sUA can be used as a target for treatment with Gout with a goal of < 6 mg/dL
    - Some evidence women should have a lower target
    - Patients with tophaceous deposits or severe disease should be targeted < 5mg/dL

7: Rheumatology, Volume 57, Issue suppl_1, 1 January 2018, Pages i20–i26
Vasculitis Workup

Workup and differential has always been driven by size of affected blood vessel involved

- Large
  - Takayasu’s arteritis
  - Giant Cell Arteritis
- Medium
  - Polyarteritis Nodosa
  - Kawasaki’s Disease
  - Central Angiitis / Isolated CNS Vasculitis
- Small
  - Immune Complex Associated
    - Hypersensitivity vasculitis
    - Cryoglobulinemic vasculitis
    - Henoch-Schönlein purpura
  - Pauci Immune Associated
    - Granulomatosis with Polyangiitis
    - Microscopic Polyangiitis
    - Churg-Strauss vasculitis
  - Malignancy Associated
  - CTD related
  - Mimics
What Lab Tests are Useful in Evaluation?

• **Tests for Systemic Inflammation**
  - CBC – anemia, thrombocytosis, eosinophilia
  - ESR – usually >100 mmHg in absence of infection
  - CRP - usually >10mg/dL in absence of infection
  - Low Albumin – “negative acute phase reactant”

• **Tests for Organ Involvement**
  - Creatinine and Urinalysis
  - LAEs
  - Creatine Kinase
  - Stool for occult blood
  - Chest radiographs
  - Abdominal CTA or conventional angiogram
  - Brain MRI / MRA
What Should Be Done for Initial Lab Workup?

- CBC, CMP, CK and Urinalysis with microscopic analysis to screen for extent
- RF – Endocarditis first then Rheumatoid Vasculitis in long standing RA but most commonly this is a marker cryoglobulins will be positive
- ANA – think SLE but could be Sjögrens among many others
- Cryoglobulins
- HBV and HCV
- CH50 C3 C4
- C-ANCA and P-ANCA
- Blood Cultures
- SPEP
What Lab Tests are Useful in Evaluation?

- Tests suggesting ANCA associated vasculitis
  - C-ANCA (PR3) – most likely GPA less likely MPA
  - P-ANCA (MPO) – consider MPA and CSS (and possibly anything else – IBD, infections)

- Tests suggesting etiology
  - Blood Cultures – helps to rule out SBE
  - Infectious Serologies – helps to suggest: HBsAg (PAN-25%), HCV (Cryoglobulinemia, PAN-rare), parvovirus IgM (GPA, PAN), Herpes CMV and HIV (any vasculitis)
  - SPEP – helps to rule out multiple myeloma
  - CSF Studies – helps to rule out herpes and varicella-zoster
Clinical Utility of ANCA

• What are they?
  • Antibodies directed against components of granules in the cytoplasm of neutrophils
    • Patterns noted in:
      • cytoplasm (C-ANCA) → commonly associated with proteinase 3 antibodies
      • peri-nuclear (P-ANCA) → commonly associated with myeloperoxidase antibodies
      • Atypical peri-nuclear → seen in Ulcerative Colitis patients frequently

• Doesn’t every ANCA Associated Vasculitis patient have a (+) ANCA?
Clinical Utility of ANCA

- **C-ANCA / PR3 Ab**
  - Present in ~90% in GPA
  - Sensitivity decreases to 60% in limited disease
  - Titers rarely useful in monitoring activity of disease

- **P-ANCA / MPO Ab**
  - ~90% ANCA associated GN, ~75% of MPA, 75% EGPA
  - False positives very common in SLE, UC, PBC, PSC, AIH, Goodpastures, RA, Myositis, Sjögrens

- Drug induced ANCAs common
  - PTU, minocycline, hydralazine are testworthy but list is **LONG**

- Infections also associated
  - SBE, Cystic Fibrosis, HIV, HCV, HBV, Acute Malaria
<table>
<thead>
<tr>
<th>Disease Category</th>
<th>C-ANCA</th>
<th>P-ANCA</th>
<th>ANTI-MPO</th>
<th>ANTI-PR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with Polyangiitis (GPA)</td>
<td></td>
<td>1+</td>
<td>1+</td>
<td>3-4+</td>
</tr>
<tr>
<td>Active – generalized</td>
<td>3-4+</td>
<td>1+</td>
<td>1+</td>
<td>3-4+</td>
</tr>
<tr>
<td>Active – limited</td>
<td>2-3+</td>
<td></td>
<td>&lt;1+</td>
<td>2-3+</td>
</tr>
<tr>
<td>Idiopathic Necrotizing and Crescentic Glomerulonephritis without Immune Deposits (Pauci-Immune)</td>
<td>Rare</td>
<td>4+</td>
<td>3-4+</td>
<td>Rare</td>
</tr>
<tr>
<td>Microscopic Polyangiitis (MPA)</td>
<td>1+</td>
<td>2-3+</td>
<td>2-3+</td>
<td>1+</td>
</tr>
<tr>
<td>Eosinophilic Granulomatosis with Polyangiitis (EGPA)</td>
<td>1+</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>Classic Polyarteritis Nodosa Polyangiitis Overlap Syndrome</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td>Inflammatory Bowel Disease</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>Absent</td>
<td>2-4+</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>Absent</td>
<td>1+</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Grading System: 1+ (15-25%); 2+ (26-50%); 3+ (51-75%); 4+ (76-100%)
Summary

• Rheumatology Labs are more often less diagnostic than they are confirmatory

• Frequently our “base workup” is more reliable in suggesting severity of disease
  • Titers are less frequently as significant as organ involvement

• Trust your clinical impressions independent of labs
  • The hypertensive young woman with skin thickening and raynaud’s that can’t complete a sentence talking to you is an emergency even if the ANA is negative and ESR in normal

• Know when that labs do matter
  • Elevated ESR with temporal headaches and jaw claudication in GCA
  • Petechial rashes with organ dysfunction
  • dsDNA with chronic hematuria and a mild increase in renal function
1) **What constitutes a significant ANA?**
   - Symptoms of connective tissue disease not attributable to other causes in association with the ANA. (significant titer 1:160)

2) **How predictive is a positive rheumatoid factor in diagnosing Rheumatoid Arthritis?**
   - Sensitivity is about 2/3 of cases. As titer increases it becomes more likely associated with disease. Likelihood of disease additionally increases if associated with other autoantibodies.

3) **What positive results could indicate a need for more urgent referral?**
   - Elevated ESR/CRP with GCA features, elevated ESR/CRP with signs of vasculitis and any organ dysfunction, elevated CKs with cardiopulmonary or gastrointestinal involvement, Abnormal dsDNA and hematuria, patients with (+) ANA and low C’ or any organ dysfunction, RF/CCP with severe debility or any systemic features.