Use and Interpretation of Common Rheumatologic Tests: Do's and Don't's

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Disclosures:
Advisory boards, speaker, clinical trials.....

- Amgen
- Pfizer
- Novartis
- BMS
- Novartis
- Janssen
- UCB
- Roche
- Takeda
- Astra Zeneca
- Abbott
- P & G

Objectives

- To better understand the interpretation and significance of common Rheumatological lab tests
- To improve skills in appropriate ordering of rheumatolgic lab investigations depending on the clinical context
- To use this knowledge to enhance quality of patient referrals
- To apply these skills in daily practice in order to improve patient diagnosis and care

Laboratory Investigations: General Principles

- Guided by patient history and physical exam
- If no clue to diagnosis after history and exam, odds of making diagnosis with lab is poor
- Order tests that address most likely diagnosis
- “Arthritis panel” ie: shotgun approach - should not be used
- Choose subsequent tests to refine diagnosis, monitor disease progress, ensure safety of Rx

Commonly used Rheumatologic and Immunologic tests

- Rheumatoid factor
- ANA
- ENA
- ANCA
- Antiphospholipid antibody
- Complement levels
- Anti-CCP

- ESR
- CRP
- Uric Acid
- Synovial Fluid Analysis
- HLA B27

Case

- **You see a 24 year old woman with a few months of polyarthralgia and fatigue, which started post partum**
  - Among other things, your differential diagnosis includes rheumatoid arthritis and systemic lupus erythematosus

How do you screen for RA and SLE?

- **Primarily by history and physical examination**
  - Increase your “pretest probability” by asking questions that support the diagnosis of inflammatory arthropathy or systemic rheumatic disease
  - Look for clues on physical examination

- Example: morning stiffness, swollen joints, rash, fatigue, other systemic symptoms……

What blood tests do you order?

- Routine blood tests may reveal helpful information
  - Anemia, other cytopenias
  - Urinary abnormalities
  - Elevated creatinine
  - Thyroid
  - Abnormal chest Xray

Should you order ESR or CRP?

- **Nonspecific tests**
- **Assess acute phase response in the blood**

ESR

- Increased by
  - Acute phase reactants
  - Paraproteins
  - Anemia (fewer cells, less repellent forces)
- ALSO
  - Age, gender, pregnancy, diabetes, renal failure, malignancy, infection

    tissue damage (MI, CV)

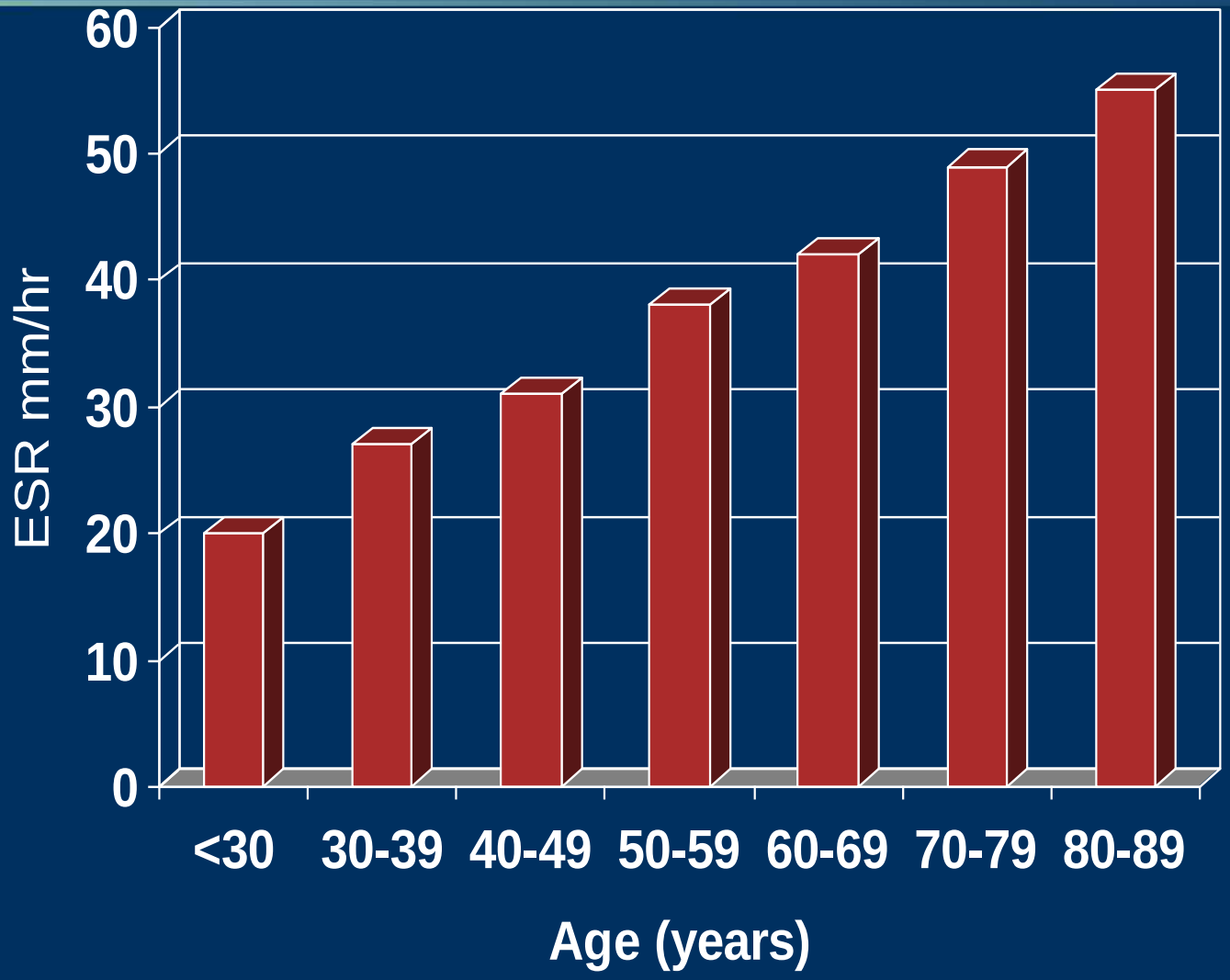
A good rule of thumb,…

- **For Men**
  - **Upper limit of normal of ESR = $\frac{\text{Age}}{2}$**
- **For Women**
  - **Upper limit of normal of ESR = $\frac{\text{Age} + 10}{2}$**

Thus, test is of limited value in the elderly population!

ESR & Age

M=Age/2
F=Age+10/2



CRP

- **Direct measure of acute phase reactants**
  - **Less sensitive to irrelevant factors**
  - Shorter onset to rise, and resolves more quickly
  - **More expensive**
  - **May be more sensitive to disease activity in PMR/GCA**

Key Concepts

- **ESR, CRP**
  - **Nonspecific indicators of inflammation**
  - **Not useful as screening tests for rheumatic diseases**
  - **Cannot differentiate one disease from another**
  - **Useful in PMR/GCA, and to monitor RA disease activity**

Should you order a Rheumatoid Factor?

Rheumatoid factor

- The higher the level of RF the higher the likelihood of disease
- RF levels are not useful in monitoring RA
- RF should be ordered in patients with a high pretest probability of RA
- RF is associated with nodules and vasculitis in RA patients
- Once test is positive, no value in re-testing as does not change with disease activity

- RF is cheap

Rheumatoid Factor

- **Sensitivity 80% *in patients with RA***
- **Specificity ranges from 80-90%**

- **Prevalence of RA is 1%**

So, lots of positive RF are false positive!

Other conditions causing positive Rheumatoid Factor

- Other systemic rheumatic diseases
- Cryoglobulinemia
- Infections- bacterial endocarditis
  - Hepatitis, TB, Syphilis, parasitic disease, viral
- Pulmonary diseases
- Malignancy

- **Thus, RF is not diagnostic for RA on its own**
- **Testing is most useful when there is a moderate level of suspicion for RA**

Pretest probability	Post-test Probability **RF +**
1%	**16%**
25%	**84%**
90%	**99%**

What About anti-CCP ?

- Anti-cyclic citrullinated peptide antibody
- As sensitive & more specific than RF
- Appears earlier in disease
- A marker for poor prognosis, so can help guide treatment choices
- May be detected in healthy people years before onset of RA

Key Concepts

- **Rheumatoid Factor**
  - **Rheumatoid factor is not diagnostic for rheumatoid arthritis**
  - **The test's utility is greatest when there is a moderate pre-test probability of disease**
- **Anti CCP now commercially available, more specific, and may help guide treatment**

Should you order an ANA?

ANA

- **Sensitivity 95% in patients with SLE**
  - **Almost all patients with SLE have positive ANA**
- **The ANA test is not specific for SLE**
- **ANA not synonymous with a diagnosis of Lupus**

ACR Criteria For Lupus

A. **MUCOCUTANEOUS**
   1. Malar Rash
   2. Discoid Rash
   3. Photosensitivity
   4. Oral ulcers

B. **SYSTEMIC INFLAMMATORY**
   5. Arthritis
   6. Serositis – pleuritis or pericarditis
   7. Cerebritis – seizures or psychosis
   8. Nephritis – >0.5g proteinuria

C. **LABORATORY**
   9. Hematologic – Leucopenia, lymphopenia, thrombocytopenia or hemolytic anemia
   10. Immunologic – dsDNA, Sm, or Antiphospholipid antibodies
   11. ANA

4 out of 11 for diagnosis

ANA

- **ANA 1:40** **Seen in almost 32%** of normals
- **ANA 1:80** **Seen in almost 13%**
- **ANA 1:160** **Seen in almost 5%**
- **ANA 1:320** **Seen in almost 3%**

- ***There is no set titer that can distinguish between those with and without SLE***
- ***Most people with positive ANA don't have disease***

Non-rheumatic conditions causing positive ANA

- **Normal individuals:** females > males, increasing age, relatives of patients with rheumatic disease, pregnancy
- **Hepatic diseases:** eg. **chronic active hepatitis**
- **Pulmonary diseases:** **eg. idiopathic pulmonary fibrosis**
- **Chronic infections**
- **Malignancies:** **lymphoma, leukemia, melanoma, solid tumors (ovary, breast, lung, kidney)**
- **Hematologic disorders:** **idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia**
- **Drug- induced** (procainamide, hydralazine, quinidine, TCN, TNF inhibitors)
- **Miscellaneous:** **autoimmune thyroiditis, type 1 diabetes mellitus**

ANA Patterns

PATTERN	NUCLEAR ANTIGEN	DISEASE
Homogeneous	Histone/DNA	SLE, Drug induced SLE
Speckled	Saline-ENA's	MCTD, SLE, Sjogrens syndrome, poly/dermatomyositis, infection and neoplasia
Nucleolar	RNA associated antigens	Scleroderma
Peripheral	DNA	SLE
Centromere	Centromere	Limited Scleroderma

Once ANA screen is positive…consider more specific autoantibody tests

- Specific autoantibody tests possess diagnostic significance in the right clinical setting ex: anti-dsDNA, ENA, anti-Histones(drug induced LE)

- ENA (extractable nuclear antigen) panel includes
  - Anti Sm(Smith)
  - Anti RNP(Ribonucleoprotein)
  - Anti SS-A,SS-B
  - Anti Scl-70
  - Anti Jo-1

- **Anti-dsDNA**
  - **Specific for SLE (60-70%)**
  - ***May fluctuate with disease activity***
- **Anti-Sm (Smith)**

  - Highly specific for SLE
- **Anti-RNP**
  - **Part of criteria for mixed connective tissue disease (MCTD)**

- Anti-centromere antibody (ACA)
  - Associated with scleroderma (CREST)
- Anti-topoisomerase I (Scl-70)
  - Associated with diffuse scleroderma
- Anti-Ro (SS-A) and La (SS-B)
  - Associated with Sjogren's
  - Can be seen in SLE
  - May be associated with neonatal heart block in babies of mothers with this antibody
- Anti-Jo-1 (anti-histidyl-tRNA synthestase)
  - Specific for myositis associated with interstitial lung disease, Raynaud's

Malar Rash

- Fixed
- May be flat or raised
- Erythematous
- Over the malar eminences
- Sparing the nasolabial folds

Photosensitivity

- Erythematous rash in sun exposed areas
- May look like sunburn or prickly heat
- Sun exposure may cause new DLE or other rashes.
- May flare internal disease with arthralgias and fatigue.

Gottron's Papules: Dermatomyositis

Drug induced lupus

- Seen with
  - Procainamide
  - Sulfasalazine
  - Hydralazine
  - Minocycline
  - Isoniazid
  - Anti-TNF agents
- Rare in African Americans
- ANA and Anti Histone positive.
- Usually resolves on stopping the drug

Key Concepts

- **ANA**
  - **Not recommended as a screening test**
  - **Greatest utility for diagnosis of lupus with moderate pre-test probability**
  - **Virtually rules out SLE when negative**
  - **If ANA strongly positive, use more specific Ab testing (in the correct clinical context) to help you refine the diagnosis**

What other tests might be helpful?

ANTIPHOSPHOLIPID SYNDROME
Revised Sapporo Criteria

Diagnosis requires 1 clinical and 1 laboratory criteria

- CLINICAL:
  - One or more arterial, venous or small vessel thrombosis
  - Complications of pregnancy
    - One or more unexplained deaths of normal fetus >10 weeks
    - One or more premature births of nomal neonate <34 weeks.
    - Three or more consecutive unexplained miscarriages before 10 weeks
- LABORATORY (on 2 occasions at least 12 weeks apart):
  - Anticardiolipin Ab
    - IgG or IgM (>40 units GPL).
  - Anti β_2 Glycoprotein I antibodies
    - IgG or IgM (>99th centile)
  - Lupus Anticoagulant

Wilson WA. et al., Arthritis and Rheumatism, 42;7:1309-131

Miyakis S. et al, J Thomb Haemost 2006; 4:295

Serum complements

- Not an antibody test, but useful for monitoring disease activity in SLE

- Low C3, C4
  - Reflect consumption of complement
  - Usually caused by presence of immune complexes in SLE, particularly nephritis

  -Seen in some forms of vasculitis

  - Complement deficiency states may predispose to SLE

- **ANCA most strongly associated with necrotizing vasculitis**
  - **C-ANCA (PR3)→ GPA (Wegener's granulomatosis)**
  - **P-ANCA (MPO)→ EGPA/ MPA (Microscopic polyangiitis Churg-Strauss vasculitis)**
    - May also be positive in Crohns, UC, Hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis

HLA-B27

- May be of help in patient with inflammatory sounding back pain but no sacroiliitis visible on plain Xray
- HLA B27 of limited value in diagnosing usual patient with back pain
- HLA B27+ in 8% of normal population
- Not required to confirm a clinical and radiologic diagnosis of ankylosing spondylitis

HLA B-27

- ASSOCIATION WITH SPONDYLOARTHROPATHIES:
  - A.S. : 95% SENS
  - REACTIVE: 80-85% SENS
  - PSORIATIC: 70% SENS
  - IBD: 50% SENS
  - Normal population: 8%

Uric Acid

- An isolated gout attack may have normal uric acid
- Best time to measure uric acid is about 2 weeks after an attack
- Treat to target of <360

Summary: Key Concepts

- Use clinical picture to guide ordering
  - Tests don't usually make the diagnosis!
- Watch out for false positives
- Pretest probability matters
- "Routine" tests may have more important information than serology
- Avoid using "rheumatology panel" to screen for rheumatic disease