Rheumatologic Laboratory Testing and Common Hematological Drugs

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There are multiple tests used to both screen for and make the diagnosis of many rheumatological illnesses such as the following:

- SLE
- Rheumatoid Arthritis
- Sjogren Syndrome
- Vasculitis
- Ankylosing Spondylitis
- Giant Cell Arteritis
- Wegener’s Granulomatosis
- Polyarteritis Nodosa
- Cryoglobulinemia
- Inflammatory Bowel Associated Arthritis
- Etc.............

(I am not going to discuss each of these illnesses in detail, just the labs associated with them so you are more familiar when you see them)
**ESR-Erythrocyte Sedimentation Rate**

- Very nonspecific test of inflammation and noninflammatory conditions (infection, rheumatic, malignancies, and pregnancy, diabetes mellitus, and endstage kidney disease)

- This value increases with age and it is higher in women than men, so the reference ranges on labs need to be interpreted in such a manner.
  - A good rule of thumb is for women over 50 – her upper limit of ESR is:
    \[
    \text{Her age} + \frac{10}{2} = \text{upper limit of normal for ESR}, \quad \text{and for men Age/2}.
    \]
**ESR-Erythrocyte Sedimentation Rate**

- Low ESR is associated with abnormal RBC shape or attraction such as Polycythemia vera, multiple myeloma, sickle cell disease, and spherocytosis.
- Low ESR is also seen in low fibrinogen states such as CHF or liver failure.

- A markedly elevated ESR (>100) in someone with vision changes and proximal muscle weakness and pain is very suggestive of Polymyalgia Rheumatica and Temporal Arteritis.
- Markedly elevated ESR (>100) is also suggestive of metastatic cancer, overwhelming infection or severe autoimmune diseases.
• **CRP-C-reactive protein**
  • An acute phase reactant and it is a direct measure of inflammation and responds more quickly to disease states.
  • It is as nonspecific as ESR in its diagnostic capacity, but it does seem to be normal in diseases such as SLE

• **Complement- C1-C10 and CH-50**
  • A very complex cascade of reactions and events that are present during inflammation, however some disease states such as SLE, Cryoglobulinemia, SBE, Visceral Abscesses, MPGN, Shunt Nephritis “consume” complement so it is low. The tests measured tend to be C3, C4 and a CH-50
• ANA
• Anti ds-DNA
• Anti Smith
• RF
• Anti-CCP Ab
• P-ANCA
• C-ANCA
• Anti-Scl-70
• Anti-Jo-1
• Anti Ro/SSA
• Anti La/SSB

• Anticentromere
• Anti-U1-RNP
• Antihistone

(This is the alphabet soup of Rheumatologic tests and the most important points on each will be given.)
ANA-Antinuclear Ab

- Without symptoms a positive ANA means nothing!!!
- 30% of the normal population has a titer + in 1:40 ratio, 13% have a titer + in 1:80, and 3% have a titer + in 1:320
- The patient/client must have symptoms that fit with a clinical disease state to have diagnostic value.
- 95% sensitive for SLE (so a negative test strongly urges against SLE)

Anti-ds DNA

- Correlates with lupus disease and active kidney involvement (think 2 kidneys or double DNA)

Anti-Smith

- This is the most specific test for lupus 99% - so it rules in the diagnosis of lupus if suspicious and the ANA isn’t diagnostic.
- ANA is good screening test
- Anti-Smith is good confirmatory
RF - Rheumatoid Factor

- Present in 70% of those with RA, but can be positive in other rheumatological illnesses (SLE, Sjogren’s, cryoglobulinemia) and 10% of general population.
- The key factor again, is does the patient/client have symptoms of the disease!
- SO... 30% of RA patients are what we call “seronegative” meaning they are RF (-).

Anti-CCP (cyclic citrullinated peptide)

- More specific for RA than the RF - 95% (rule in the diagnosis) than RF which is 80%.
- Anti-CCP Ab is positive in 1/3 of those seronegative RA patients.
- Correlates with erosions of the joints and predicts disease progression in patients with arthritis.
- RF is decent screening test
- Anti-CCP Ab is better diagnostic
## COMMON RHEUMATOLOGICAL LABORATORY TESTING

### C-ANCA
- Positive in Wegener’s Granulomatosis (granulomas in upper airway, lung and kidneys)
- 90% sensitive when the disease is active and correlates with disease and granuloma formation

### P-ANCA
- Also known as antimyeloperoxidase antibody
- Seen in Polyarteritis nodosum, microscopic polyangiitis, Churg-Strauss Syndrome – (all cause damage to the small vessels of the lungs and kidneys and sometimes the upper airways.)
- They are also seen in disease states such as ulcerative colitis
### Anti-Scl-70
- Not very sensitive for systemic sclerosis (10-30%) but it correlates with pulmonary fibrosis and interstitial lung disease in these patients
- The ANA pattern is SPECKLED
- Skin involvement past distal forearms, and knees, ILD, serositis, sclerodermal renal crisis, they get pulmonary hypertension.

### Anticentromere
- Not very sensitive, for limited systemic sclerosis (10-30%) but it too correlates with pulmonary fibrosis and interstitial lung disease
- The ANA pattern is CENTROMERE
- (CREST – calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyl, telegiectasias)
- Can develop Pulmonary hypertension

**COMMON RHEUMATOLOGICAL LABORATORY TESTING**
**Anti Ro/SSA**

- Sjögren's Syndrome-positive in 60-75%
  - Dry eyes, dry mouth and presents commonly with other rheumatologic diseases such as SLE and RA
  - Higher risk of B-cell lymphoma so particular attention to lymph nodes (44-Fold increase in lymphoma)
  - Standard mortality risk is only slightly higher than general pop.

**Anti La/SSB**

- Sjögren's Syndrome-positive in 40%
  - May need parotid gland or lip biopsy for confirmation.

**COMMON RHEUMATOLOGICAL LABORATORY TESTING**
**Anti U1-RNP**

- 100% sensitive for MCTD (Mixed Connective Tissue Disease)
- Many overlapping qualities of diseases such as systemic sclerosis, SLE, RA, etc.... (really easy to diagnose....)

**Antihistone**

- Seen in 95-100% of patients with drug induced lupus
  - Hydralazine
  - Procainamide
  - Isoniazid
  - Methyldopa are all common meds associated with it.
A stepwise approach to treatment of most rheumatologic diseases takes into account other comorbid illnesses, other medications, risk factors, tolerance and cost.

A “start low and go slow” approach is best used on patients with more severe disease.

The objective of these next few slides is to become familiar with some of the older medications that are still considered very effective and to introduce some of the newer medications that have revolutionized the treatment of some of the most common hematological illnesses.
NSAIDS (No steroidal Anti-inflammatories)

- **Ibuprofen, Naproxen Sodium**
  - Block COX enzymes and thereby block PGE synthesis leading to decrease in inflammation.
  - PGE’s maintain gastric lining and kidney blood flow – so these meds can cause ulcers, kidney injury and hypertension
  - They can decrease PGE’s in the lung causing asthma type symptoms

- COX-2 selective (celecoxib) meds are no safer on the kidneys nor heart, but they confer slightly lower GI side effects
  - Naproxen reduces CV risk
  - Proton pump inhibitors are given with NSAIDS in elderly who are going to be on them long term.
  - Key-use the lowest doses possible and watch for toxicities
Analgesics

- Acetaminophen, Tramadol, Opioids
  - Strictly for pain relief
  - No antiinflammatory effect
  - Acetaminophen, even at moderate doses can cause liver toxicity
  - Tramadol more potent than acetaminophen and has less abuse potential – it engages natural opiate receptors and raises serotonin levels!

Analgesics

- These medications have limited roles in the management of mild arthritis conditions and would be used adjunctly with more disease modifying agents.
- Both NSAIDS and Analgesics are used to treat osteoarthritis, tendon and ligament injuries but not usually diseases such as RA, SLE, etc.
Colchicine

- Commonly used to treat Gout, Pseudo gout and Familial Mediterranean Fever
- Directly impair the myeloid lineage of inflammatory cells - especially NØs and macrophages
- Treat patients with acute gout until they get diarrhea, that’s when you know it is working!
- Can cause bone marrow suppression and kidney damage
DMARDs (Disease Modifying Antirheumatic Drugs)

- These are immunosuppressive agents that can slow or block the autoimmune damage to joints and other organs and are considered the first line agents for inflammatory rheumatologic conditions.
**Methotrexate**

- Gold standard therapy for RA and is also used for psoriatic arthritis, vasculitis, polymyositis
- Folic acid antagonist and so it MUST always be given with Folic acid 1 mg daily
- Given usually as a weekly dose 10-20 mg once a week
- Serial CBC and CMP to watch for liver damage and macrocytic anemia
- Avoid in alcohol abuse patients
- Can cause interstitial pulmonary fibrosis (rare)

- In women wishing to get pregnant MUST stop the medication at LEAST 3 months before attempting to conceive

Key: Very effective at monotherapy for RA of any severity or duration of time.
<table>
<thead>
<tr>
<th>Hydroxychloroquine</th>
<th>Sulfasalazine</th>
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<tbody>
<tr>
<td>• For SLE and RA and has a modest benefit but excellent side effect profile!</td>
<td>• Combo of salicylate and sulfapyridine</td>
</tr>
<tr>
<td>• In SLE it may prevent disease flares and reduce morbidity and mortality</td>
<td>• Has moderate benefit in RA</td>
</tr>
<tr>
<td>• Regular retinal examinations to look for pigment deposition is main risk</td>
<td>• Used mostly for IBD to deliver 5ASA to the colon</td>
</tr>
<tr>
<td>• Given at 200-400 mg daily</td>
<td>• Toxicities include GI symptoms, HA, hepatitis and agranulocytosis</td>
</tr>
<tr>
<td>• Should <strong>not</strong> be discontinued in a pregnant female with SLE</td>
<td>• Considered <strong>safe</strong> in pregnancy</td>
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**DMARDS (Disease Modifying Antirheumatic Drugs)**
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**Azathioprine**
- Used as a “steroid sparing” or maintenance agent in SLE, vasculitis, polymyositis
- TPMT is an enzyme used to metabolize this medication and a deficiency can lead to toxicity
- Do not use in those taking allopurinol for gout
- Some rheumatologist advocate checking the TPMT enzyme prior to starting this medication.

**Leflunomide**
- Is as effective to treat RA as Methotrexate
- Same side effect profile as MTX (hepatic, bone marrow, ILD)
- **MUST never** be used in pregnancy and stopped three months before pregnancy
- It has a long half life so if it needs removed from the body – use cholestyramine TID for a week to absorb and get rid of it in order to conceive.
<table>
<thead>
<tr>
<th>Mycophenolate Mofetil</th>
<th>Cyclophosphamide</th>
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<tbody>
<tr>
<td>Developed to treat transplant rejection in those with organ transplants</td>
<td>Use for life threatening lupus and severe vasculilitis</td>
</tr>
<tr>
<td>Used for SLE, specifically LUPUS NEPHRITIS</td>
<td>SEVERE side effects – anemia, leukopenia, inc. bacterial &amp; fungal infections, <strong>hemorrhagic cystitis and bladder cancer</strong>, lymphoma and other cancers</td>
</tr>
<tr>
<td>Just as effective as cyclophosphamide for nephritis but with fewer and milder SE’s</td>
<td>Never used in pregnancy unless the life of the mother is at stake</td>
</tr>
<tr>
<td>Very teratogenic and should not be used in pregnancy</td>
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</table>

**DMARDS (Disease Modifying Antirheumatic Drugs)**
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Cyclosporine

- Suppresses target T cells and used in many diseases such as RA, SLE, Myositis, Psoriasis, Pyoderma gangrenosum, IBD
- Many toxicities (HTN, kidney disease, tremor, hirsutism)
- Used as a third line agent due to side effect profile

Key Points:

- All of the disease modifying antirheumatic drugs need to be prescribed by qualified personnel
- All need close monitoring for side effects, kidney and liver disease and eye exams
- They are all very effective in some level at decreasing symptoms of and controlling the respective disease states that they treat.
Biologic agents offer greater specificity at treating via targeted immunity with greater efficacy and less side effects.

Care must be taken to watch for opportunistic infections (those that would affect someone with a weakened immune system).

Latent TB screening is used prior to starting all of these agents.

They should be held when there is an intercurrent illness requiring antibiotics.
DO NOT use two or more biologics together at any one time—this is because of the much higher increased risk of infections with not much benefit.

Avoid live vaccines (MMR, Varicella)

Primary immunization to killed vaccines may be limited, so may need to be given prior to starting the biologics, especially rituximab and abatacept.
TNF Alpha Inhibitors (Tumor Necrosis Factor)

- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab

- Decrease disease activity and inhibit progression of structural damage in RA especially when combined with Methotrexate
- Suppress cutaneous and articular disease in psoriasis patients
- Joint symptoms improved in AS
- Also used for Uveitis, Behcet’s Disease, IBD, pyoderma gangrenosum
- Can impair intercurrent infections and delayed use until they resolve is key.
- Reactivation of TB, Histoplasmosis, HBV, coccidiomycosis can be an issue
- Overall cancer incidence is not higher than for patients with RA
TNF Alpha Inhibitors (Tumor Necrosis Factor)

- Etanercept*
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab

- Etanercept is not used for Behcets, uveitis, IBD, pyoderma gangrenosum but rest are
- Can be used in patients with HCV and HIV infections
- Can cause drug induced lupus, psoriaform skin lesions and demyelinating syndromes (GBS)
- Higher rate of nonmelanoma skin cancers associated with their use
- Most see a clinical response in 2-3 months
**Chimeric Monoclonal Antibody**

- Rituximab
- Tocilizumab
- Ustekinumab
- Belimumab

- Very complex Abs that deplete CD20 B-cells, IL-6 receptor,
- IL-12 and IL-23 and B cell activating factors respectively!

**Rituximab**

- Use in combination with MTX and for those who did not respond to a TNF alpha inhibitor
- Used in ANCA positive vasculitis
- Can get a reactivation of JC virus causing PML (Progressive Multifocal Leukoencephalopathy)
**Chimeric Monoclonal Antibody**

- **Rituximab**
- **Toclizumab**
- **Ustekinumab**
- **Belimumab**

**Toclizumab**
- Used in RA patients who have had a poor response to TNF alpha inhibitors
- Caused decreased blood cell counts, platelets, and elevated transaminases (LFTs)
- Increases serum lipids as well.

**Ustekinumab**
- Treats several autoimmune diseases such as Crohn’s, Psoriasis, RA
- Has a higher rate of infections of TB, fungal, and Salmonella infections

**Belimumab (same as above)**

**BIOLOGICS (BDMAD)**
**Abatacept**
- Binds antigen presenting cells and blocks signals to T-lymphocytes
- Given as IV monthly infusion
- Takes 6 months to work
- Used in patients with refractory disease after exposure to multiple DMARDs or in those with inadequate response to TNF alpha drugs
- Increased risk of lymphoma and lung cancer and flares of COPD
- Do not use in combination with other biologics

**IL-1 Receptor Blockers (Anakinra, Rilonacept)**
- Used in Adult Onset Stills Disease and Periodic Fever syndromes
- Not very effective for RA
- Used also for refractory Gout

**BIOLOGICS (BDMAD)**
WHEW... THE END !!!!!