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Laboratory Tests in Rheumatology

A comprehensive history and thorough physical examination is the best screening test in diagnosis of autoimmune diseases. Blood tests are useful adjuncts in confirming suspected diagnosis. In certain cases they may be useful to monitor disease activity, estimate disease severity, determine response to treatment, and assess prognosis. The pretest probability of a test is an important determinant in the value of a test to diagnose a certain condition. A positive result for a test with high pretest probability helps to confirm diagnosis, whereas a negative test with low pretest probability will help to rule out diagnosis.

The improper use of tests is fraught with pitfalls. A positive test result in an inappropriate clinical setting can cause unnecessary patient anxiety. It can lead to further advanced testing and potentially dangerous treatments. Serial testing, such as ANA in lupus, does not add any new clinical information and increases the overall cost of health care. Another issue is the lack of standardized methods in interpreting results. The reporting range often can be confusing for primary care physicians when laboratories have a low threshold for a positive result. This can lead to a higher number of false positives.

The objective of the article is to discuss laboratory tests commonly used in evaluating rheumatologic diseases and help primary care physicians to evaluate and interpret common positive and negative test results, and therefore lead to more judicious use of available resources. The common laboratory tests discussed in the article are shown in Table 1.

Acute Phase Reactants

Acute phase reactants are plasma proteins whose concentration increases or decreases during inflammatory conditions. The change in concentration should be at least 25% for the test to be of value.[1] Positive reactants increase and negative reactants decrease during inflammatory states. (*See Table 2.*)

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) is the most widely used marker for inflammation. ESR is an indirect measure of serum acute phase plasma protein concentrations, especially fibrinogen. The ESR is the measure of the quantity of red blood cells (RBC) that precipitate in a tube in a defined time. This is based on serum protein concentrations and RBC interactions with these proteins. RBC shape and number also have an influence on the rate of the fall. The sample needs to be processed within a few hours to ensure test accuracy.

The ESR rises in inflammatory states. However, high ESR result can be falsely seen in the presence of anemia,[2] renal disease, and hypergammaglobulinemia. It is also influenced by patient's age and gender.[3] (*See Table 3*). The ESR can be spuriously low in hemoglobinopathies, polycythemia, and cryoglobulinemia.

The changes in ESR correlate with rheumatoid arthritis (RA) activity, polymyalgia rheumatica (PMR), and giant cell arteritis.[4] The ESR at the time of PMR diagnosis may have prognostic value. The ESR also may rise with trauma, infection, ischemia, and malignancy. The rate of change in ESR is slow and usually lags behind the decrease in inflammation.

Executive Summary

Rheumatologic and autoimmune disease patients often present with very complex manifestations that can be confusing and challenging to accurately diagnose. Clinicians increasingly depend on both common and arcane laboratory testing to facilitate arriving at a confident final diagnosis, even though most diagnoses are made through thorough history taking and careful physical examination.

- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) need to be corrected for gender and age and for low hematocrit for ESR. The ESR can be spuriously low with hemoglobinopathies, polycythemia, and cryoglobulinemia.
- Non-inflammatory causes of mild CRP elevations need to be considered.
- Antinuclear antibodies (ANA) is a highly sensitive test but poorly specific for systemic lupus erythematosus and scleroderma. A quarter of healthy controls can have positive ANA at low titers.
- The types of ANA can be helpful in increasing the specificity of disease diagnosis.
- The specificity of rheumatoid factor (RF) in rheumatoid arthritis (RA) is 50-80% and sensitivity is 80-85% with one-fifth of RA patients never developing RF positivity and up to 10% of healthy patients having positive RF.
- Antineutrophilic cytoplasmic antibodies testing plays a critical role in diagnosis and classification of various vasculitides.

C-Reactive Protein

C-reactive protein (CRP) is an innate immune protein. The role of the protein is to help opsonize pathogens for phagocytosis. It also activates the complement system. The production is under the control of IL-1, IL-6, and TNF-alpha. CRP rises rapidly after inflammation and tissue injury. CRP levels are not subjected to fluctuations secondary to anemia etc., unlike ESR. CRP levels do change with age, gender, and race of the patient. (*See Table 3.*) CRP levels of < 0.2 mg/dL are considered normal. Levels > 1 mg/dL are indicative of ongoing inflammation.

CRP may be reported as mg/dL or mg/L. Usually, high sensitivity CRP (hsCRP), which detects very low grade inflammation, is reported in mg/L.[5] hsCRP is a more sensitive CRP test and elevations indicate very low grade inflammation. CRP values between 0.2-1 mg/dL may be present in certain non-inflammatory states (*See Table 4*). Values > 1 mg/dL are indicative of significant inflammation.

Patients with systemic lupus erythematosus (SLE) tend to have normal or mildly high CRP levels. Elevation of CRP levels in lupus patients may signify infection, vasculitis, serositis, or synovitis. Elevation of CRP in RA has prognostic value. The combination of using both ESR and CRP improves sensitivity of either test alone.

Ferritin

Serum ferritin concentration is influenced by intracellular iron, TNF-alpha, IL-1, IL-6, oxidative stress, and growth factors. This may be elevated in various rheumatologic diseases. Marked elevations in serum ferritin may be seen in Still's disease and hemophagocytic syndromes. Serum ferritin may be as high 10,000 ng/mL (normal 40-200 ng/mL) in patients with Still's disease. The levels correlate with disease activity.

Antinuclear Antibodies

Autoantibodies to nuclear antigens are a diverse group of antibodies that react against nuclear, nucleolar, or perinuclear antigens. Antinuclear antibodies (ANA) is commonly associated with autoimmune diseases; however, it is also one of the most inappropriately ordered tests.

ANA is detected using immunoflourescence testing of patient's serum using cell substrate obtained from human epithelial tumor cell line (Hep 2 cells). Another method is through ELISA. Using Hep 2 cells allows detection of fluorescent pattern (homogenous, diffuse, speckled, peripheral, and rim). (*See Table 5.*) These patterns may help association with certain autoimmune diseases. However, ELISA is cheaper and more widely available. There is higher incidence of false positives

Table 1: Common Laboratory Tests in Rheumatology

- Acute phase reactants
- Anti-nuclear antibodies
- Rheumatoid factor
- Anti-cyclic citrullinated peptide antibodies (CCP)
- Anti-neutrophil cytoplasmic antibodies (ANCA)
- Antiphospholipid antibodies
- Complement
- Cryoglobulins

Table 2: Acute Phase Reactants

Positive Reactants	Negative Reactants
C-reactive protein	Albumin
Ceruloplasmin	Transferrin
Alpha-1 antitrypsin	Transthyretin
Complement components	
Ferritin	
Fibrinogen	
Haptoglobin	
Serum amyloid A	

Table 3: ESR and CRP Correction for Age, Gender, and Hematocrit

Gender and age correction for upper limit of reference range for ESR
Men: Age in years/2
Women: Age in years +10/2

ESR correction for low hematocrit
Corrected (Westergren) ESR = ESR – [(Std. Ht - Actual Ht) x 1.75], where Std. Ht (standard hematocrit) is 45 for males and 42 for females

CRP correction for age and gender
The upper limit of the reference range (mg/dL) =
Men: Age in years/50
Women: (Age in years/50) + 0.6 for women

Table 4: Non-inflammatory Causes of Mild CRP Elevation

- Periodontitis
- Smoking
- Uremia
- Aging
- Oral hormone replacement therapy
- Alcohol consumption
- Obesity
- Diabetes mellitus
- Hypertension
- Sedentary lifestyle
- Chronic fatigue
- Depression

with the ELISA method.

ANA is a highly sensitive test (negative test helps to exclude the diagnosis) and a poorly specific test (positive test does not help in establishing a diagnosis) for SLE and scleroderma (*See Table 6*). Patients with Raynaud's phenomenon should have ANA testing done only if signs of connective tissue disease are present. A positive ANA in a patient with Raynaud's phenomenon increases the risk of developing systemic rheumatic disease from 19%-30%, whereas a negative test reduced this risk to 7%.[6] Presence of ANA in juvenile idiopathic arthritis patients helps stratify risk for developing uveitis.

Various other diseases (autoimmune, chronic infectious, and malignancy) may be associated with positive ANA (*See Table 7*).

Studies have shown that 25-30% of healthy controls have positive ANA at lower titers (1:40), 10-15% at 1:80, and < 5% at 1:160. The frequency increases with age, especially in women. In healthy subjects, ANA titer of 1:40 can be seen in 25-30% of relatives of patients with rheumatologic condition.[7] Therefore, ANA testing should be limited to cases where there is strong clinical suspicion of systemic autoimmune disease. There is also no utility of serial ANA testing in diseases such as SLE and scleroderma.

Table 5: Patterns of ANA Staining

Pattern of ANA Staining	Stained Material	Disease Associations
Homogenous	Nucleus (DNA-histone complex)	SLE, RA, drug-induced lupus
Peripheral (rim)	dsDNA Nuclear envelope proteins	SLE
Speckled	Extractable nuclear antigens (e.g., Scl70, Smith)	SLE, Sjogren's, scleroderma, normal subjects
Nucleolar	Nucleoli	Scleroderma, polymyositis

Types of Antinuclear Antibodies

Anti-dsDNA. The antibodies directed against double-stranded DNA are highly useful in diagnosing SLE. There are four methods to detect dsDNA: Farr assay, Crithidia luciliae assay, ELISA, and flourescent beads. Crithidia assay and ELISA are more commonly used. Crithidia assay uses principle of indirect immunoflourescence by using dsDNA from the hemoflagellate organism. It has a sensitivity of 50-80%. ELISA test is positive in 70-80% patients with SLE. Overall, dsDNA antibody has a sensitivity of 57.3% and specificity of 97.4% in diagnosing SLE.[8] Less than 1% of patients may have positive dsDNA antibodies in the absence of positive ANA.

Anti-dsDNA antibody titers may correlate with disease activity. In lupus nephritis, anti-dsDNA antibodies tend to increase when disease is active. However, in some patients this may not occur. In such patients, serial testing may not be of much value. Anti-dsDNA antibodies may be found in other conditions (*See Table 8*).

Anti-Smith and anti-U1RNP antibodies. The Smith and U1 RNP autoantigens localize in small nuclear ribonucleoprotein particles (snRNPs). They are frequently found in patients with SLE. The anti-Smith (anti-Sm) is highly specific for SLE but has poor sensitivity (sensitivity 24-30%, specificity 96-98%).[9] The anti-Sm antibody remains positive in patients regardless of disease activity. Therefore, it is useful in diagnosing patients who may be in remission.

Anti-U1RNP is part of the essential diagnostic criteria for mixed connective tissue (MCTD). Hence, it is found in 100% of patients with MCTD. Between 3-69% of SLE patients may have anti-U1RNP.

The anti-Sm and anti-U1 RNP antibodies are detected using ELISA- and flow cytometery-based assays. The antigen preparation in these solid phase assays may be contaminated with other antigens and can cause false positive results.

Anti-SSA/anti-SSB antibodies. Traditionally associated with Sjogren's syndrome and SLE, anti-SSA may also be found in other autoimmune conditions (RA, primary biliary cirrhosis, polymyositis, etc.).

Table 6: Sensitivity and Specificity of ANA

Autoimmune Disease	Sensitivity (%)	Specificity (%)
SLE[7]	93-95	57
Scleroderma[7]	85	54
Sjogren's syndrome	48	52
Raynaud's phenomenon	64	41
Polymyositis, dermatomyositis	61	63
Rheumatoid arthritis	41	56
Juvenile idiopathic arthritis	57	39

Anti-SSA is directed against two antigens: Ro 52 and Ro 60. Anti-SSB is directed against La antigen. These antibodies are detected using counter immunoelectrophoresis, ELISA, and Western blot.

Anti-SSA antibodies (Anti-Ro antibodies) are present in 50-60% of patients with primary Sjogren's syndrome, 10-15% of patients with secondary Sjogren's syndrome, and 35-40% of SLE patients.[4] Their presence in pregnant women is associated with neonatal lupus and congenital heart block. Anti-SSA antibodies are also found in patients with "ANA negative lupus" and should be checked in patients with high clinical suspicion of SLE who have negative ANA. Anti-SSA antibodies may precede development of SLE. Anti-SSA antibodies are also associated with subacute cutaneous lupus erythematosus (SCLE). Anti-SSB antibodies are present in 40-50% of patients with Sjogren's syndrome and 15% of patients with SLE. Patients with primary Sjogren's syndrome in the presence of anti-Ro and anti-La are at greater risk of developing extra glandular manifestations.[4]

Anti-histone antibodies. More popularly associated with drug-induced lupus, the anti-histone antibodies are in fact found in 80% of patients with idiopathic lupus. They are present in more than 95% patients with drug-induced lupus.

Antiribosomal P protein antibodies. The antiribosomal P protein antibodies are specific for neuropsychiatric lupus. These are found in only 10-20% of lupus patients.

Anti-Scl 70, anti-centromere, and anti-U3RNP antibodies. Anti-Scl 70 is found in some patients with systemic sclerosis. It is highly specific (100%) for diffuse systemic sclerosis.[10] The presence of antibody is associated with greater progression to pulmonary disease and widespread skin involvement. Anti-centromere is associated with limited systemic sclerosis. Anti-Scl 70 and anticentromere are mutually exclusive and do not coexist.

Anti-U3RNP is a predictor of pulmonary hypertension and skeletal muscle involvement in scleroderma patients. Anti-PM/Scl autoantibody is associated with overlap syndrome (myositis with scleroderma). Anti-RNA polymerase lll is associated with development of scleroderma renal crisis.

Antibodies in inflammatory myopathies. Myositis-specific antibodies occur in about 30% of patients with dermatomyositis and polymyositis. Three major categories of myositis-specific antibodies are listed in Table 9.

Rheumatoid Factor (RF). RF are autoantibodies that are directed against the Fc portion of IgG molecule. The most common RF used in clinical practice is IgM RF. RF is most commonly used to diagnose RA. A positive RF can be found in rheumatic and non-rheumatic conditions and in healthy subjects (*See Table 10*).

The specificity of RF in RA is 50-80% and sensitivity is 85-90%. One fifth of RA patients may never develop RF positivity and up to 10% of healthy individuals may have positive RF. Hence, the test is not very useful in confirming or excluding diagnosis of RA. RF factor positivity in a patient with RA is a prognostic marker for more severe,[12] erosive disease and extra articular involvement. RF titer does not correlate with disease activity and serial RF titers are of no value in clinical practice. However, high RF titer (> 1:160) has a higher predictive value for RA.

Anti-cyclic citrullinated petptide antibodies (anti-CCP). Anti-CCP antibodies are directed against the citrulline residues present on proteins after post-translational modification of arginine. They are highly specific for RA (95-98%); however, their sensitivity is only 30-60%. The presence of anti-CCP antibodies helps to confirm diagnosis of RA. They may

Table 7: Positive ANA in Diseases Other than Systemic Autoimmune Disease

- Hepatitis C
- HIV infection
- Tuberculosis
- Graves disease
- Hashimotos' thyroiditis
- Primary biliary cirrhosis
- Primary autoimmune cholangitis
- Crohn's disease
- Lymphoproliferative disorders
- Infectious mononucleosis
- Subacute bacterial endocarditis
- Idiopathic pulmonary hypertension

Table 8: Diseases with Positive dsDNA Antibody

- SLE
- Rheumatoid arthritis
- Sjogren's syndrome
- Scleroderma
- Drug-induced lupus
- Raynaud's phenomenon
- Mixed connective tissue disease
- Discoid lupus
- Myositis
- Chronic active hepatitis
- Uveitis
- Graves disease
- Women with silicone breast implants

Table 9: Myositis Specific Antibodies[11] SRP Signal Recognition Peptide

Anti-Jo1	Directed against the anti–histidyl–tRNA synthetase Anti-synthetase antibodies Associated with interstitial lung disease, Raynaud's, mechanic's hands, and arthritis
Anti-SRP	SRP involved in translocation of proteins into endoplasmic reticulum Occur in polymyositis alone Associated with severe disease Poor response to treatment
Anti-Mi2	Antibody against helicase involved in transcription of protein Found in classic dermatomyositis with "shawl sign"

Table 10: Conditions with Positive Rheumatoid Factor

Rheumatic Condition	Non-rheumatic Condition
Rheumatoid arthritis	Bacterial endocarditis
Cryoglobulinemia	Infections: hepatitis, tuberculosis
Polymyositis, dermatomyositis	Malignancy
Sjogren's syndrome	Pulmonary disease: pulmonary
SLE	fibrosis, sarcoidosis, silicosis
Systemic sclerosis	Primary biliary cirrhosis
	Healthy subjects

also be present several years before the development of clinical manifestations of RA. Hepatitis C patients with arthritis may have RF. In such patients, presence of anti-CCP antibodies helps to confirm diagnosis of concomitant RA.

Early, effective treatment of RA may lead to decrease in anti-CCP titers. Anti-CCP positivity is associated with aggressive, erosive disease.[13] Anti-CCP antibodies may be positive in other diseases including tuberculosis and alpha-1 antitrypsin deficiency. Cigarette smokers with shared epitope have higher incidence of anti-CCP positive RA.

Antineutrophilic cytoplasmic antibodies (ANCA). ANCA testing plays a critical role in diagnosis and classification of various vasculitides. These antibodies stain the cytoplasmic granules in neutrophils. ANCA testing is done using immunoflourescence and ELISA. Immunoflourescence is a screening method that indicates either cytoplasmic or perinuclear staining, causing c-ANCA and p-ANCA pattern, respectively. c-ANCA is classically associated with granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) and p-ANCA with microscopic polyangiitis and Churg Strauss syndrome.

ANCA staining is operator dependent[14] and false positives may occur, especially in the presence of positive ANA. A positive test is further confirmed using ELISA, which detects antibodies against specific antigens, namely PR3 and MPO. PR3 is usually associated with c-ANCA and MPO with p-ANCA. The overall ANCA positivity and pattern prevalence in ANCA associated vasculitides is shown in Table 11.

ANCA positivity with the presence of either PR3 or MPO improved positive predictive value for the diagnosis of vasculitis. Biopsy is the gold standard for diagnosis of vasculitis. ANCA and specific antigen positivity should be used only as an adjunct to diagnosis.

Certain drugs (minocycline, hydralazine, propylthiouracil) may be associated with development of ANCA vasculitis. ANCA positivity is seen in various other conditions besides vasculitis (*See Table 12*). The pattern is usually pANCA or atypical patterns in such cases.

ANCA titers do not correlate with disease activity consistently. Hence, rising ANCA titers alone cannot be used to diagnose relapse.[15] However, ANCA negativity in a vasculitis patient with prior history of positive ANCA may be consistent with remission in some cases.

Antiphospholipid antibodies. Antiphospholipid antibodies are tested when there is suspicion for antiphospholpid syndrome and in patients with SLE. Patients may have history of recurrent arterial or venous thrombi, pregnancy morbidity, and recurrent fetal loss. The presence of biologic false positive serologic test for syphilis may be the first clue to presence of anticardiolpin (aCL), antiß2 glycoprotein1 (antiß2GP1), or lupus anticoagulant.

LAs are antibodies directed against plasma proteins, which also bind phosholipid surfaces. In half of the cases, they may cause prolonged activated partial thromboplastin time (aPTT). When patient's plasma is mixed with normal plasma, there is no correction of aPTT. This suggests presence of inhibitor since normal plasma would correct any factor deficiency. Thereafter, confirmatory test is performed, usually dilute Russell viper venom time or the hexagonal lipid neutralization test. In the confirmatory tests, the addition of phospholipid corrects the clotting time. LA should not be checked if the patient is on an anticoagulant.[16] In such cases, aCL or antiß2GP1 should be checked.

aCL and antiß2GP1 antibodies are measured by ELISA. The titers may be reported as low, medium, or high. These antibodies should be present in medium-to-high concentration on at least two occasions at least 12 weeks apart to qualify for diagnostic criteria for APS.

Complement

Complement system is part of the innate immune system. Complement deficiency may be inherited (uncommon) or acquired (common). Acquired complement deficiency may occur due to reduced hepatic synthesis

Table 11: Vasculitides and ANCA Prevalence

Disease	ANCA Positive (%)	Pattern (%)
Granulomatosis with polyangiitis	90	PR3-cANCA (80-90)
MPO-pANCA(10-20)		
Microscopic polyangiitis	70	MPO-pANCA (> 90)
Churg Strauss	50	MPO-ANCA (> 70)
Renal limited pauci-immune vasculitis	> 90	MPO-ANCA (75-80)
Anti-GBM disease	10-40	MPO-ANCA (60-90)

(e.g., liver failure) or accelerated consumption by immune complexes (e.g., SLE, cryoglobulinemia, rheumatoid vasculitis, autoimmune hemolytic anemia, autoimmune pancreatitis, membranoprolifertaive glomerulonephritis, and parvovirus infection).

CH50 (total hemolytic complement) assesses classic complement pathway components (C1 to C9). CH50 is low when there is deficiency of any single component. Low C3 and low C4 are present in up to 50% of SLE patients at some point in their course. Low complement levels correlate with lupus nephropathy.[17] However, their use as predictors for lupus flare is controversial.

Inherited deficiency of C1, C2, and C4 may predispose to SLE. Complete C3 deficiency can cause severe recurrent pyogenic infections. Partial C4 deficiency may predispose to SLE. Deficiency of C1 esterase inhibitor leads to low C4 levels and may predispose to SLE.

Cryoglobulins

Cryoglobulins consist of immunoglobulins and complement components that precipitate upon refrigeration of serum. The collection of blood in prewarmed syringe (at 37° C) is imperative to avoid false negative. A cryocrit is determined at 4° C by measuring the packed volume of the precipitate in the wintrobe tube as percentage of total serum collected.

Three types of cryoglobulins are associated with hematologic malignancies, viral infections, and connective tissue disorders (*See Table 13*). The presence of cryoglobulin does not confer increased morbidity or mortality risk. The prognosis depends on underlying condition. However, severe complications, such as cryoglobulinemic vasculitis or renal failure, may predict poorer outcomes.

Clinical Case Example

An example of how to approach a patient who is believed to have an autoimmune disease might play out like this: A 35-year-old female patient with chest pain on deep breathing and finger joint swelling and pain presents to her primary care physician. After a thorough history and a good physical examination (which revealed a few basilar rales and a 1 cm cervical lymph node), laboratory and x-ray findings may help identify the patient's problem. Differential diagnoses may include SLE, RA, endocarditis, sarcoidosis, pulmonary embolus (PE) with osteoarthritis, hepatitis C, etc. However, she seems to fit SLE the best. So an ANA is ordered and turns up negative. ANA is a sensitive test but is not very specific, so it is a good test to rule out a diagnosis of SLE if it is negative, since 98% of patients with SLE have a positive ANA. Now there is no need to do a whole battery of tests for SLE, which will save the patient hundreds of dollars. Meanwhile, RF and CCP both were negative, which gave about 80-85% assurance that the patient doesn't have RA. The hepatitis C screen was negative, as was a VQ scan for PE. A chest x-ray showed some enlarged hilar lymph nodes and early pulmonary fibrosis changes. The lymph node was biopsied and a diagnosis of sarcoidosis was made. The lesson to be learned is to use screening tests first before

Table 12: ANCA Positivity in Non-vasculitic Conditions

- Systemic autoimmune diseases (SLE, RA, etc.)
- Ulcerative colitis
- Primary sclerosing cholangitis
- Crohn's disease
- Autoimmune hepatitis
- Leprosy
- Buerger's disease
- Malaria
- Preeclampsia and eclampsia
- Subacute bacterial endocarditis
- Diffuse alveolar hemorrhage
- Chronic graft-versus-host disease
- Acute parvovirus B19 infection
- Acute infectious mononucleosis
- Cocaine-induced osteochondral destruction (cocaine-induced midline destructive lesions)

Table 13: Types and Disease Association with Cryoglobulins

Type 1	Type 2		Type 3
% in total CG patients	5-25%	40-60%	40-50%
RF binding activity	Monoclonal IgG or IgM	Monoclonal IgM/IgA +Polyclonal Ig	Polyclonal Ig
Associated diseases	Waldenstrom's macroglobulinemia, Multiple myeloma	Hepatitis C, HIV, Viral infections	Connective tissue disease (SLE, SS, SSc, RA, PM, sarcoidosis)

Routine Laboratory Tests in Rheumatology

Patients being treated for rheumatologic and autoimmune diseases should have the following tests every 2-3 months to monitor drug toxicity and disease activity.

CBC: The Complete Blood Count (CBC) provides several clues as to disease activity in the rheumatologic diseases. The most common is a normocytic anemia, which is present with systemic inflammation. This is especially seen in SLE, RA, vasculitis, and serious autoimmune diseases. A low white blood count also can be seen in SLE. High platelets frequently are found as an acute phase reactant in patients with active RA and to a lesser extent in other autoimmune diseases. The mean corpuscular volume is often elevated in methotrexate toxicity.

Routine Complete Chemistry: The most common tests followed in rheumatic diseases include the creatinine monitoring drug toxicity and active disease, especially in SLE and vasculitis. The liver function tests are important to follow for medication toxicities, especially for methotrexate and other hepatotoxic drugs. An elevated alkaline phosphotase sometimes indicates active autoimmune hepatitis or lupus hepatitis. Serum protein levels are often high in active autoimmune diseases and return to normal when the disease is in remission.

Urinalysis: This is one of the least expensive and most important tests in rheumatology. It is essential that patients with SLE, systemic vasculitis, and all autoimmune diseases that affect kidneys have a urinalysis done at each clinic visit.

Uric Acid: The uric acid test is not a good indicator of whether a patient is going to have a gout attack, since frequently patients have attacks with normal serum uric acid levels. However, it is important to follow the serum uric acid in patients who are being treated for gout with drugs such as allopurinol, since the goal of therapy is to get the uric acid level below 6 mg/dL (in most textbooks). At our clinic, we aim to get the level below 4 mg/dL.

delving into numerous more specific tests that may not be needed.

Summary

When ordering laboratory tests, a physician needs to have a good reason for doing the test. (*See Box above for a description of routine laboratory tests in rheumatology.*)The patient's history should suggest a reason to order a specific test in order to properly interpret the result obtained. In rheumatology, a diagnosis is dependent on the history for about 85% of the information to make that diagnosis. About 10% is dependent on the physical examination. Laboratory and imaging tests make up about 5% of the information for diagnosis. Therefore, it is important to do tests in context with the suspected diagnosis and not go on a "fishing expedition" for lab tests that have little relevance to the patient's problem. It is very important to know the sensitivity and specificity of a laboratory test in relation to the disease that one is suspecting and the reason for the test one is ordering.

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CME questions

1. ESR is elevated in which of the following noninflammatory conditions?
   a. Fatigue
   b. Renal failure
   c. Polycythemia
   d. Alcohol consumption
2. What is the prevalence of positive ANA in a healthy population?
   a. 5-10%
   b. 25-30%
   c. 45-50%
   d. 80-85%
3. Which of the antibodies is associated with subacute cutaneous lupus?
   a. Anti-Ribosomal P
   b. Anti-SRP
   c. Anti-Ro
   d. None of the above
4. Which of the following drugs is most commonly associated with ANCA positivity?
   a. Levofloxacin
   b. Warfarin
   c. Diclofenac
   d. Propylthiouracil
5. The blood sample for testing cryoglobulins should be collected at what temperature?
   a. 4 degrees C
   b. 0 degrees C
   c. 42 degrees C
   d. 37 degrees C

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Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■