

Rheumatic Disease: How to Use the Lab in the Workup

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ABSTRACT: The basic screening studies for rheumatic diseases are a complete blood cell count, a determination of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, a rheumatoid factor assay, an antinuclear antibody (ANA) test, a measurement of serum uric acid level, and a urinalysis. Test results must be interpreted within a clinical context; for example, a positive ANA assay suggests the possibility of a rheumatic disorder, but it is not specific for any diagnosis. Tests that reveal the nature and extent of target-organ involvement, such as renal function studies in patients with systemic lupus erythematosus, can help guide the selection of therapy. Laboratory results also reflect disease activity; the ESR and CRP level are useful gauges of the activity of most inflammatory rheumatic disorders. Finally, laboratory monitoring can help you minimize the significant toxicity associated with many of the drugs used to manage rheumatic diseases.

Thomas Carlyle once said: "Man is a tool-using animal. . . . Without tools he is nothing, with tools he is all." Carlyle's observation applies no less to medicine than to other human endeavors. The practice of contemporary medicine depends on the use of modern tools. The laboratory is among the most valuable of these, but, like all tools, it can be misused.

Just as the ultimate value of any tool depends on the skill of the user, the value of any given laboratory test depends on the clinician's familiarity with it and the setting in which the

test is applied. This is particularly true in the care of patients with rheumatic disease, who are generally afflicted with a chronic, painful, debilitating disorder that may be difficult to diagnose and will require ongoing treatment with any number of potentially toxic medications.

While you might not use many of the arcane laboratory studies frequently ordered by rheumatologists, understanding when to order the most common tests and what to do with their results will undoubtedly be helpful in your initial evaluation of the patient with rheumatic disease. The focus here is on what you can—and cannot—learn from several key studies, including measurement of the erythrocyte sedimentation rate (ESR) and assays for C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) antibody, antinuclear antibodies (ANA), complement levels, *HLA-B27* gene, antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, and anti-Lyme antibodies.

WHEN—AND WHY—TO ORDER LABORATORY TESTS

Too often clinicians order a "shopping list" of laboratory studies, without a clear understanding of what the studies mean. Before ordering such tests, ask yourself what you will learn from the results and how therapy will be affected. There are basically 5 reasons for ordering any laboratory test.

Screening. A number of laboratory studies help you "screen" a patient for the likelihood of a rheumatic prob-

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lem. Screening studies vary from region to region, even within the United States. For example, in New England, where rheumatic fever and Lyme disease are significant problems, screening for antistreptolysin-O and Lyme antibodies may be reasonable. However, in Southern California, where those diseases are unusual, these same studies would be of little value.

In most areas of the country, the basic screening studies for rheumatic diseases are a complete blood cell (CBC) count, a determination of the ESR or C-reactive protein level, a rheumatoid factor assay, an ANA test, a measurement of serum uric acid level, and a urinalysis. If the results of these studies are normal and if no rheumatic problems are apparent from the history and physical examination, ordering any more exotic and expensive rheumatologic laboratory tests would be unreasonable. Diagnostic efforts would best be directed elsewhere.

Making a diagnosis. When applied in the proper clinical setting, some tests allow you to make a specific diagnosis. For example, a positive result from an ANA assay suggests the possibility of a rheumatic disorder, but it is not specific for any diagnosis. On the other hand, the presence of high titers of anti-double-strand DNA or anti-Sm antibodies is virtually diagnostic of systemic lupus erythematosus (SLE). Similarly, laboratory determinations of cryoglobulins, Lyme antibodies, rheumatoid factors, and anti-Scl 70 and anti-PM 1 antibodies can help confirm diagnoses but only in a reasonable clinical context.

Defining target-organ involvement. Once a rheumatic disorder has been diagnosed, the nature and extent of target-organ involvement need to be determined before a reasonable therapeutic regimen can be formulated. In a patient with scleroderma, the serum creatine phosphokinase level must be measured to ascertain whether inflammatory muscle disease is present. If a

Table - Using laboratory tests to best advantage in rheumatic diseases

Study	Assay
Erythrocyte sedimentation rate	Westergren method (preferred)
Rheumatoid factor	Nephelometry replacing latex fixation as the most common and reliable assay; common assays detect IgM rheumatoid factors only
Anti-cyclic citrullinated peptide antibodies	ELISA
Antinuclear antibodies	Indirect immunofluorescence
Complement levels	Total hemolytic complement (CH50) assay; C3 and C4 assays most commonly used
HLA-B27 antigen	Lymphocyte microcytotoxicity
ANCA	Indirect immunofluorescence, ELISA
Antiphospholipid antibodies	Russell viper venom assay detects lupus anticoagulant; ELISA detects anticardiolipin and anti- β_2 -glycoprotein 1 antibodies
Lyme antibodies	Indirect immunofluorescence assay and ELISA sensitive but nonspecific; Western blot specific but not sensitive

RA, rheumatoid arthritis; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus; ANCA, antineutrophil cytoplasmic antibody.

Results	Clinical significance
Elevated rate	Signals the presence of inflammation; dramatically high levels suggest polymyalgia rheumatica/giant cell arteritis
Low rate	Suggests congestive heart failure or cryoglobulinemia
Positive	Present in 75% of patients with RA; also seen in other autoimmune disorders, infectious diseases, malignancies, and liver diseases
Positive	More specific but less sensitive than rheumatoid factor in the diagnosis of RA; predictive of severe, erosive disease
Positive	Positive in more than 95% of patients with SLE and in 30% to 80% of those with other autoimmune disorders; anti-double-strand DNA and anti-Sm antibodies virtually diagnostic of SLE
Depressed	May reflect presence of circulating immune complexes or hereditary complement deficiency; reflects activity of immune complex-mediated disease in SLE
Positive	Increases the likelihood of spondylopathy; present in 95% of patients with ankylosing spondylitis, 80% of those with reactive arthritis, 50% of those with psoriatic arthritis, and 25% to 75% of those with chronic inflammatory bowel disease
c-ANCA	Found in over 90% of patients with systemic Wegener granulomatosis, 75% of those with limited Wegener granulomatosis, and 40% of patients with microscopic polyarteritis
p-ANCA	Common in Churg-Strauss syndrome, microscopic polyarteritis, and idiopathic crescentic glomerulonephritis and occasionally seen in polyarteritis nodosa, Crohn disease, ulcerative colitis, sclerosing cholangitis, chronic active hepatitis, RA, and primary biliary cirrhosis
Positive	Increased risk of arterial and venous thrombosis and of fetal wastage
Positive	Diagnostic of Lyme disease in proper clinical setting

patient has SLE, the decision to initiate cytotoxic therapy depends on the presence of renal disease detected by the laboratory evaluation. In a patient with rheumatoid disease who complains of anterior neck pain, antithyroid antibody titers should be obtained to detect autoimmune thyroiditis. Anti-SSA and anti-SS-B determinations are necessary to rule out Sjögren syndrome in patients with sicca complaints. If a patient has polyarteritis nodosa, everything from renal function to liver involvement needs to be evaluated.

Assessing disease activity. Because most rheumatic diseases are chronic, frequent laboratory testing to assess disease activity is necessary. For example, in addition to being useful screening tools, the ESR and C-reactive protein level are indexes of the activity of most inflammatory rheumatic disorders, including rheumatoid arthritis (RA), ankylosing spondylitis, Wegener granulomatosis, and septic arthritis. The complement level is a helpful gauge of the activity of SLE: the lower the complement level, the more active the disease. In patients who have dermatomyositis, the higher the serum creatine phosphokinase level, the greater the degree of muscle inflammation.

To the extent that laboratory studies can help you evaluate disease activity, they help you determine ongoing therapy. For instance, signs of increasing activity may warrant the institution of different or more aggressive treatment. In contrast, laboratory evidence of decreasing disease activity may suggest that therapy can be tapered.

Monitoring for drug toxicity. The pharmacologic agents that are used to manage rheumatic disorders, including the fast-acting NSAIDs, are associated with significant toxicity. Laboratory tests are invaluable in helping you monitor, and thereby minimize, their toxic side effects.

If long-term NSAID therapy is being considered, first order a CBC

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count, renal function tests, and liver function studies. If it is safe to initiate therapy, repeat these studies in 1 to 3 months. If the results have remained stable, the tests need to be repeated only every 6 to 12 months thereafter.

In patients with RA who are receiving methotrexate or leflunomide, a CBC count, platelet count, and liver function tests need to be done every 2 to 4 weeks initially and every 2 to 3 months after a stable regimen has been established. Even more careful monitoring is required for patients taking such cytotoxic drugs as mycophenolate mofetil, azathioprine, cyclosporine, and cyclophosphamide. No specific laboratory tests are required for many of the new biologic agents, such as etanercept, infliximab, and adalimumab, but careful monitoring is still necessary because these drugs are almost always used in combination with other antirheumatic agents.

KEY TESTS—AND WHAT THEY CAN TELL YOU

There are a host of laboratory studies that might be helpful in diagnosing and managing any given rheumatic disease. Here I can discuss only a few of the most common tests that are particularly valuable (Table).

The ESR measurement may be the most valuable single test in the diagnosis and management of rheumatic diseases.¹ An elevated ESR indicates the presence of increased amounts of acute-phase reactants—such as α_1 -proteins, haptoglobin, or fibrinogen—or of polyclonal or monoclonal hypergammaglobulinemia. These protein anomalies reflect inflammation of any kind, including that associated with infection, autoimmune disease, vasculitis, or malignancy. The diseases perhaps most closely linked to a dramatically elevated ESR are polymyalgia rheumatica and giant cell arteritis. These diseases cannot be diagnosed or managed without assessing the ESR. A low

ESR is seen in congestive heart failure and in cryoglobulinemia.

The Westergren method is the recommended technique for measuring the ESR. This simple, inexpensive study allows you to distinguish inflammatory from noninflammatory diseases, to monitor inflammatory disease activity, and to make appropriate changes in therapy based on an objective measure of that activity.

Although there is a tendency to try to use the ESR to rule out disease, remember that some rheumatic disorders are noninflammatory. In fact, the most common form of arthritis—osteoarthritis—is a noninflammatory disorder characterized by a normal ESR.

The rheumatoid factor assay detects the presence of antibodies directed against the Fc portion of IgG.² A positive test for rheumatoid factor is one of the most important diagnostic criteria for RA.³

Commonly available assays detect only IgM rheumatoid factors. IgG and IgA rheumatoid factors can be found using research techniques, but such methods are not widely available. Nephelometry—a technique that uses the diffraction of a beam of light to measure the concentration of immune complexes that form when a test serum is added to a known antigen—is replacing latex fixation as the most common and reliable assay of rheumatoid factors.

Although rheumatoid factors are detectable in 75% of patients with RA, they are also seen in a number of other disorders. Ninety percent of patients with Sjögren syndrome and 100% of those with types II and III cryoglobulinemia have rheumatoid factors.⁴ The cryoprecipitate in type II cryoglobulinemia is an immune complex composed of monoclonal rheumatoid factor—usually but not always IgM—and its target, polyclonal IgG. The cryoglobulin in type III cryoglobulinemia is a complex of polyclonal rheumatoid factors and their target IgG.

High titers of rheumatoid factors can be present in a variety of autoimmune disorders, such as SLE, progressive systemic sclerosis, and mixed connective tissue disease. They are also sometimes seen in infectious diseases, such as bacterial endocarditis; in malignancies, particularly lung cancer; and in acute and chronic liver disease.

As with any laboratory study, the rheumatoid factor assay has diagnostic value only within a specific clinical setting. For example, a positive assay is helpful in diagnosing RA in a patient with morning stiffness and a polyarticular, symmetric inflammatory arthritis affecting small proximal joints. On the other hand, a positive assay in a patient with weight loss, hemoptysis, and a history of smoking is more consistent with lung cancer than RA.

The anti-cyclic citrullinated peptide (anti-CCP) antibody assay—a new test now becoming available—appears to be more specific than the rheumatoid factor assay for the diagnosis of RA. The presence of anti-CCP antibodies in asymptomatic patients has been shown to predict the eventual development of RA.⁵ In patients with early-stage RA, anti-CCP antibodies are associated with an increased likelihood of erosive, severe, deforming disease.⁶

The test is often positive in juvenile idiopathic arthritis but not as frequently as it is in adult rheumatoid disease. Anti-CCP antibodies are not seen in seronegative arthritic conditions or in nonrheumatic diseases. The test is not as sensitive as a routine IgM rheumatoid factor assay, but when used in combination with this assay, it adds significant specificity and predictive value. Therefore, it is valuable in planning an appropriate therapeutic regimen.

The antinuclear antibody (ANA) assay should be considered a screening test for autoimmune disorders.⁷ A positive test reflects the presence of antibodies against any of a variety of

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specific nuclear antigens, including double-strand DNA, histone, and the acid-extractable nuclear antigens, such as SS-A, SS-B, ribonucleoprotein, Sm, topoisomerase-1, Jo-1, and PM-1. The screening test is positive in more than 95% of patients with SLE; however, it is also positive in 30% to 80% of those with other autoimmune diseases, such as progressive systemic sclerosis, CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome, Sjögren syndrome, mixed connective tissue disease, dermatomyositis, Raynaud disease, autoimmune thyroiditis, and RA. If the screening ANA assay is positive, other specific assays can be used to identify antibodies that allow a more definitive diagnosis of certain diseases.⁸ For instance, anti-double-strand DNA and anti-Sm antibodies are virtually diagnostic of SLE, and anti-topoisomerase-1 is seen only in scleroderma.

The ANA test may become positive in patients taking certain medications, such as hydralazine, procainamide, or infliximab.⁹ In these patients, the specific antibodies tend to be anti-histone or anti-single-strand DNA antibodies. On occasion, patients with diseases as diverse as subacute bacterial endocarditis or acute and chronic liver disease may have a positive ANA assay. Antinuclear antibodies can also be found, although in low titers, in up to 3% of healthy persons (generally older women).

Complement level assays are used in patients with SLE to help gauge disease activity and guide treatment decisions. The term "complement" refers to a family of proteins that act sequentially to mediate the diverse processes associated with inflammation, including increased vascular permeability, diapedesis of leukocytes, enhanced phagocytosis, and lysis of cell membranes.¹⁰

The "classic" pathway of complement activation requires the presence

of immune complexes, while the "alternative" pathway can be activated by certain IgA or IgG immunoglobulins or by lectins that recognize microbial polysaccharides. A single terminal effector pathway is stimulated by either activation pathway.

A number of complement level assays are currently available. The total hemolytic complement (CH50) assay measures the integrity of the entire complement cascade. In some patients, this is the most sensitive assay; however, it is also the most expensive. The C3 and C4 assays, which measure the concentration of the third and fourth components of the complement cascade, are easier to perform and are less expensive.

A depressed serum complement level may reflect either the presence of circulating immune complexes that have activated the complement cascade or a hereditary complement deficiency. In many patients with SLE, the degree of complement depression correlates with disease activity and can be a guide to therapy: the lower the complement level, the higher the concentration of circulating immune complexes, the more active the disease, and the more aggressive the treatment required.¹¹ Unfortunately, this correlation is not as straightforward as we would like it to be. In patients with SLE, complement levels are depressed both by activation of the complement cascade and by a decrease in the production of complement components. In any event, the decrease in complement levels is frequently a valid measure of disease activity. If a hereditary complement deficiency is suspected, assays for most of the complement components are available.

The *HLA-B27* gene assay is often helpful in making the diagnosis of a spondylopathy.¹²

Although the importance of genetic susceptibilities in the pathogenesis of rheumatic disorders is well rec-

ognized, determining the genotype of a given patient is generally of no clinical benefit. One of the major exceptions is the *HLA-B27* gene.

The *HLA-B27* gene codes for a class I major histocompatibility antigen found on the surface of most nucleated cells.¹³ The *HLA-B27* antigen is found in more than 95% of patients with ankylosing spondylitis, in 80% of those with reactive arthritis, in 50% of those with psoriatic spondylitis, and in 25% to 75% of those with the arthritis of chronic inflammatory bowel disease (the percentage is higher in patients in whom the axial skeleton is involved). The antigen is also present in about 7% of healthy white persons in North America.

The role of the *HLA-B27* assay in diagnosing the spondylopathies is controversial. A positive result is not absolute proof of the presence of an inflammatory spondylopathy, just as a negative result does not absolutely rule out this type of disorder. However, if you are confronted with a young patient with a cryptic painful back syndrome and the pretest probability of reactive arthritis is 50%, a positive *HLA-B27* assay would significantly increase the likelihood of this diagnosis.

The **antineutrophil cytoplasmic antibody (ANCA) assay** is one of the newer tests used to diagnose vasculitis. Two distinct immunofluorescent patterns can be seen based on the type of antibodies present.¹⁴ Antibodies directed against the serine protease, proteinase 3, produce a characteristic cytoplasmic pattern, designated the "c-ANCA." These antibodies are found in more than 90% of patients with typical Wegener granulomatosis, in 75% of patients with limited Wegener granulomatosis, and in 40% of patients with microscopic polyarteritis.¹⁵

In addition, a number of antibodies directed against a variety of cytoplasmic constituents produce a perinuclear pattern, called the "p-ANCA."¹⁶ Ninety-five percent of the positive

CLINICAL HIGHLIGHTS

- The erythrocyte sedimentation rate (ESR) may be the most valuable test in the diagnosis and management of rheumatic diseases. An elevated ESR reflects the presence of increased amounts of acute-phase reactants—such as α_1 -proteins, haptoglobin, or fibrinogen—or of polyclonal or monoclonal hypergammaglobulinemia. The Westergren method is recommended for measuring the ESR.
- The anti-cyclic citrullinated peptide (anti-CCP) antibody assay is a new test that appears to be more specific than the rheumatoid factor assay for the diagnosis of rheumatoid arthritis (RA). In asymptomatic patients, the presence of anti-CCP antibodies predicts the development of RA. In patients with early-stage RA, anti-CCP antibodies are associated with an increased likelihood of erosive, severe, deforming disease.
- If the screening antinuclear antibody (ANA) assay is positive, more specific tests can be used to identify antibodies characteristic of certain diseases. For instance, anti-double-strand DNA and anti-Sm antibodies are virtually diagnostic of systemic lupus erythematosus (SLE), and anti-topoisomerase-1 is seen only in scleroderma.
- The ANA test may become positive in patients taking certain medications, such as hydralazine, procainamide, or infliximab. In these patients, the specific antibodies tend to be anti-histone or anti-single-strand DNA. Antinuclear antibodies can also be found, although in low titers, in up to 3% of healthy persons (generally older women) and occasionally in patients with subacute bacterial endocarditis or liver disease.
- In many patients with SLE, the degree of complement depression correlates with disease activity and can be a guide to therapy: the lower the complement level, the higher the concentration of circulating immune complexes, the more active the disease, and the more aggressive the treatment required.

p-ANCA assays seen in patients with Churg-Strauss syndrome, systemic necrotizing vasculitis (including polyarteritis nodosa), or idiopathic crescentic glomerulonephritis are caused by the presence of antimyeloperoxidase antibodies. Antilactoferrin antibodies cause the p-ANCA pattern in patients with primary sclerosing cholangitis, ulcerative colitis, or RA.

A p-ANCA pattern is also caused by undefined antibodies in a number of disorders presumed to be autoimmune in nature, including chronic inflammatory bowel disease,¹⁷ chronic active hepatitis, and primary biliary cirrhosis. Furthermore, 5% of healthy persons exhibit a p-ANCA pattern.

Antiphospholipid antibodies are associated with an increased risk of arterial and venous thrombosis and an increased incidence of spontaneous abortion.¹⁸ Some of these antibodies—termed lupus anticoagulants—can be detected by their ability to prolong the activated partial thromboplastin time or the Russell viper venom time,¹⁹ while leaving the prothrombin time unaffected. Anticardiolipin antibodies are antiphospholipid antibodies that are detected by enzyme-linked immunosorbent assays. They are not identical to lupus anticoagulants, but they are also associated with an increased risk of thrombosis or repeated miscarriages.²⁰ In fact, experimental data sug-

gest that it is not anticardiolipin antibodies per se but a complex of anticardiolipin, target phospholipid, and a cofactor termed β_2 -glycoprotein 1 that is responsible for the clinical disease seen in patients with antiphospholipid antibodies.

Antibodies against several other negatively charged phospholipids, including phosphatidylserine, phosphatidylinositol, and phosphatidic acid, also carry an increased risk of thrombosis and spontaneous abortions. These antibodies are seen in patients who have SLE, polyarteritis, or giant cell arteritis. They may also be present in patients who have the antiphospholipid antibody syndrome; this unique disorder is defined by increased arterial or venous thrombosis, recurrent spontaneous abortions, and thrombocytopenia.

Long-term anticoagulation is indicated for patients who have the lupus anticoagulant, anticardiolipin antibodies, or elevated β_2 -glycoprotein 1 levels and clinical disease. Many clinicians believe that even asymptomatic patients with these antibodies should receive low-dose aspirin.

Detection of Lyme antibodies in the appropriate clinical setting is helpful in the diagnosis of Lyme disease.²¹ Lyme antibodies are directed against numerous antigens of the spirochete *Borrelia burgdorferi* and can be detected in several ways.

The indirect immunofluorescence and enzyme-linked immunosorbent assays are sensitive but relatively nonspecific. False-positive tests can occur in patients with other *Borrelia* infections, syphilis, or SLE, particularly if anticardiolipin antibodies are present. If you strongly suspect the diagnosis on clinical grounds and merely want to confirm the presence of Lyme antibodies, these assays are the best choices.

The Western blot is less sensitive but more specific than the other available assays. If you are faced with a di-

agnostic dilemma or suspect that a previous test might be falsely positive, the Western blot would be the superior study.²²

Although *B burgdorferi* can be cultured from some body fluids and assays for antigens in the urine are available, the serum antibody assays are still the most reliable and easily obtainable laboratory tests to confirm the diagnosis of Lyme disease.

WHEN TO SEEK A RHEUMATOLOGY CONSULTATION

The interpretation of the most common tests for rheumatic disease and subsequent diagnosis and therapy are usually straightforward, and a rheumatology consultation may not be needed. If, however, you encounter difficulties in interpreting the laboratory data or if the diagnosis and therapy are uncertain despite clinical and laboratory data, a rheumatology consultation may be helpful. Rheumatologists are not privy to any unique surgical skills, and they have no endoscopic experience. They do, however, use the laboratory very well. ■

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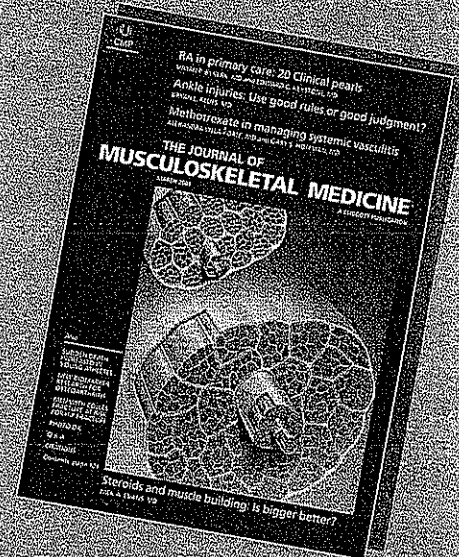
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