

## Markers of Inflammation and Rheumatology Tests—An Update for Internists

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### Abstract

**Importance:** The rapid proliferation of laboratory tests related to rheumatology, the recent interest in C-reactive protein as a possible marker for cardiovascular disease risk, and the need to contain the costs of medical care by avoiding unnecessary testing have indicated the need for a review of these tests aimed at general internists.

**Objective:** To provide internists with guidance for when to use specific rheumatology related laboratory tests.

**Evidence Review:** Literature reviews as well as important rheumatology references were appraised in order to give an updated review of the rheumatology laboratory tests included in this review.

**Findings:** Certain rheumatology tests should be employed when an internist suspects a particular autoimmune or connective tissue disease.

**Conclusions and Relevance:** A detailed review of symptoms and examination is of primary importance, while laboratory tests usually serve to support or argue against possible diagnoses.

**Keywords:** Rheumatology tests; Rheumatoid factor; C-reactive protein; Erythrocyte sedimentation rate

### Introduction

The rapid proliferation of laboratory tests related to rheumatology, the recent interest in C-reactive protein stemming from its use as a possible marker for cardiovascular disease risk, and the need to contain the costs of medical care by avoiding unnecessary testing have indicated the need for a review of these tests aimed at general internists. The organizers of the 2013 meeting of the American College of Physicians (ACP) recognized this need by designating a Meet the Professor on this topic. The section headings below are derived from the questions that the organizers of that meeting suggested be addressed.

#### What do an elevated sedimentation rate and/or C-reactive protein mean?

There is considerable uncertainty about what to regard as “elevated” sedimentation rate (ESR) and C-reactive protein (CRP). Neither of these measures yields a Gaussian distribution in presumably healthy populations. Although we commonly refer to the ranges our laboratories provide us as “normal values,” they are, in fact, “reference ranges”. It seems that reference ranges have been arbitrarily defined for both measures. These ranges are clearly influenced by normal physiologic variables such as age, gender, pregnancy, and body mass. The ESR is determined by how far red blood cells in anticoagulated blood fall through plasma in an hour. It generally reflects the concentrations of a number of plasma proteins, especially fibrinogen, an acute phase protein, but is also influenced by the size, shape and number of red blood cells, by immunoglobulin concentrations,

medications, and by unknown factors [1]. There is not universal agreement as to what should be regarded as an elevated ESR value. Various sources cite values in the general range of 15-20 mm/hr or somewhat higher. However, a widely used formula [2] that adjusts for age and for gender generally yields higher cutoff points: for men:  $\text{age} \div 2$ , and for women:  $(\text{age}+10) \div 2$ . Because the number of red cells affects the ESR, the ESR value could be corrected by the haemoglobin level; this is no longer commonly used as false “normal” values can occur in commonly inflamed states (eg sepsis) [3].

There is even less agreement as to what should be regarded as an elevated CRP level. We have observed that the upper limits of the reference range cited by different laboratories range from 2.0 to 10.0 mg/L, and everything in between. Additional confusion results from the fact that standard CRP results, usually reported as mg/dL, are sometimes reported as mg/L, while determination of the concentration of this protein employing a highly sensitive assay (hs-CRP) is routinely reported as mg/L. It should be emphasized that “high sensitivity CRP” does not detect any special kind of CRP; “high sensitivity” merely indicates that a highly sensitive assay was used to determine the concentration of plain old CRP below the range detected by older standard CRP assays. (In fact, the confusing term “hs-CRP” should be discarded. It makes no more sense than using “high-sensitivity creatinine” for current measures of serum creatinine, now often reported to 2 decimal places, rather than 1 decimal place as previously reported using older assays.) As with ESR, a formula has been proposed that attempts to adjust for age and gender [4]: for men:  $\text{age} \div 5$ ; for women:  $(\text{age}+30) \div 5$  (mg/L). Further complicating the situation are the relatively high intra-individual and inter-individual coefficients of variation of CRP compared to other plasma proteins [5].

Nonetheless, a number of studies have indicated that CRP concentrations over 10 mg/L reflect clinically significant inflammation [6-8] and may result from a wide variety of conditions, including infections, tissue injury or infarction, malignancy, and a large number of non-infectious inflammatory processes. Finding CRP levels in this range should initiate a search for such conditions.

Reports that the CRP (or ESR, for that matter) is “elevated” actually convey little information. Different degrees of CRP elevation have vastly different clinical implications. Modest CRP elevation may result from relatively minor inflammatory processes such as periodontitis, while bacterial infection is suggested by values >50 mg/L, and very strongly suggested (80-85%) by values >100 mg/L [6,9-11].

CRP concentrations between 3 and 10 mg/L are frequently seen, occurring in about 30% of the American population [12]. Such minor CRP elevation is associated with a wide variety of relatively common, generally benign medical conditions, lifestyles and dietary patterns, in the absence of classic signs of inflammation [13], and appears to reflect some degree of metabolic stress rather than inflammation as we have traditionally thought of it [14]. Obesity is often the cause. We do not feel that finding CRP values in this range should be an indication for initiation of cholesterol-lowering therapy, as has been suggested [15], for several reasons. The very high prevalence of such CRP levels in the population generates just too much background noise; we don't know how many false positives there are. Since CRP levels reflect all the risk factors for atherosclerosis [16], a thorough risk factor history would provide comparable information, and save money as well [17]. Indeed, recent studies support the view that quantitation of CRP levels adds little to determination of cardiac risk [18].

ESR and CRP values within the reference range do not rule out pathologic conditions. This is well illustrated by polymyalgia rheumatica (PMR) and giant-cell arteritis (GCA). Two studies found what the investigators regarded as low ESR values in 22% and 7.3% of patients with PMR [19,20]. While one might object that the diagnosis of PMR was arrived at solely on the basis of a clinical picture, it is telling that 4% of patients with biopsy-proven GCA were found to have both “normal” ESR and CRP values [21].

Dissociation between ESR and CRP is not uncommon. This is often due to the timing of the test, since ESR rises and falls relatively slowly following the onset of an inflammatory stimulus while the concentration of CRP increases and declines very quickly. An example: ESR and CRP are often used to monitor treatment of osteomyelitis; ESR was found to remain elevated for 3 months following treatment, while CRP fell to near-normal levels within 7 days [22]. An elevated ESR without elevated CRP might suggest a monoclonal gammopathy. Intriguingly, active systemic lupus erythematosus is often accompanied by significantly elevated ESR, but relatively modest CRP levels [23]. Often, however, dissociation between ESR and CRP is unexplained.

### **When to test for anti-nuclear antibodies and what to do when it comes back positive?**

The anti-nuclear antibody test (ANA) can be useful when a systemic autoimmune disease, especially systemic lupus erythematosus (SLE), is suspected. The ANA is a screening test for the presence of antibodies directed against any of a variety of antigens within the nucleus. Currently two methods are commonly employed to test for ANA: 1) Immunofluorescence and 2) Solid phase assays such as enzyme-linked-immunoassays (ELISA). The American College of

Rheumatology has issued a position statement stating that testing for ANA by immunofluorescence should be the gold standard. While solid phase assays have the advantage of being faster and less expensive, they are less sensitive and probably less specific [24].

There are over 100 known antigens in the nucleus. They are often concentrated in different areas within the nucleus, resulting in different patterns of staining when screened by immunofluorescence. These patterns may give some indication of the nature of the antigen against which the ANA is directed and, at times, of the underlying disease. For example, a pattern of staining around the periphery of the nucleus suggests antibodies to double-stranded DNA (dsDNA), strongly indicative of SLE, while a centromeric pattern is typically associated with limited scleroderma.

The major use of the ANA is to determine whether SLE is a feasible diagnosis. However, a positive ANA is not a “positive lupus test.” ANAs are very prevalent, estimated as present in more than 32 million persons in the USA, and are thus not very specific: the positive predictive value of ANA for SLE is only 11% [25]. The titer of ANA matters. An ANA titer of 1:40 has been reported in approximately 25-30% of the population; a titer of 1:80 in 10-15% of the population, and a titer of 1:160 or higher in under 5% of the population [26]. A positive ANA test is found in patients with a variety of connective tissue diseases, but is extremely sensitive for SLE, being present in 95%-97% of patients with SLE. Consequently, a patient with a negative test has a very small chance of having SLE, although the diagnosis can still be made if a strong clinical picture is present. Only very rarely do negative ANA tests turn positive with time in patients with SLE.

While the ANA detects antibodies to any antigen in the nucleus, it is often helpful to test for the presence of antibodies to specific antigens in patients whose ANA is positive. The two most specific antibodies for SLE are anti-dsDNA (or anti-DNA) and anti-Sm (or anti-Smith). Anti-dsDNA are antibodies against double-stranded DNA; these antibodies, 95% specific for SLE, are found in about 70% of SLE patients during active disease. If anti-DNA is detected by solid phase testing, this should be confirmed by the highly specific Crithidia assay [27]. Anti-dsDNA antibodies are found in a high proportion of SLE patients with nephropathy. They are also useful in monitoring disease, since their titer tends to rise and fall with changes in lupus activity. Anti-Sm are antibodies to RNP-binding proteins; these antibodies are essentially pathognomonic for SLE, but are found in only about 25-30% of cases and are not useful for monitoring disease activity.

Many laboratories carry out testing for multiple specific antigens employing an extractable nuclear antigen (ENA) panel. Because of great variation between laboratories, there is no standardized panel of nuclear antigens which are included in an ENA panel. Anti-Sm antibodies are usually included in such panels, while anti-dsDNA antibodies are not. As a rule, there is little value in ENA testing if the ANA screening test is negative. If SLE is suspected and the ANA is positive, further testing should include an ENA panel, anti-dsDNA, urinalysis (checking for proteinuria, casts and hematuria), and complement levels - often low in active SLE.

Some other specific nuclear antibodies associated with autoimmune diseases are listed in Table 1. Anti-SSA (also called anti-Ro) and Anti-SSB (also called anti-La) antibodies are directed against small RNAs that can be present in either the nucleus or cytoplasm of cells, and thus may be detected in patients with a “negative” ANA. They can be found in patients with any of the connective tissue diseases, but are most

closely associated with Sjogren's syndrome (present in >50% of patients), and their presence may suggest this disorder. However, the diagnosis is most appropriately confirmed with a positive salivary gland biopsy or an adequate ocular staining score. Of note, Anti-SSA/Ro antibodies in mother's serum, even in the absence of connective tissue disease, are associated with neonatal lupus and carry a 2% risk of fetal congenital heartblock in a first-time pregnancy [27].

Auto Antibody	Autoimmune disorder associated with auto antibody
Anti-RNP	Mixed connective tissue disease (MCTD)
Anti-SS-A/Anti-Ro	Sjogren's syndrome
Anti-SS-B/Anti-La	Sjogren's syndrome
Anti-Scl-70	Diffuse Scleroderma
Anti-centromere	Limited Scleroderma (formerly CREST syndrome)
Anti-Jo-1	Polymyositis, Anti-synthetase Syndrome

**Table 1:** Antibodies to extracted nuclear antigens and associated autoimmune diseases

### What is the role of antibody testing for rheumatoid arthritis and when is specific testing of clinical value?

Two laboratory tests are helpful in diagnosing rheumatoid arthritis (RA), but differ in their value because of differences in their specificity. Rheumatoid factor (RF) is an IgM antibody to the Fc portion of IgG, while anti-cyclic-citrullinated peptide antibodies (CCP) are antibodies against proteins in which the amino acid arginine has been modified to the non-native peptide, citrulline. (More recently, the latter test is referred to as anti-citrullinated protein antibody [ACPA]). The suspicion of RA should be pursued by ordering both CCP and RF. These autoantibodies are both found in about two thirds of patients with clinical rheumatoid arthritis, but the specificity of CCP (96-99%) is significantly higher than that of the RF (75%) [28,29]. Importantly, the CCP is also a better predictor of erosive disease than is RF [30]. It is important to emphasize that rheumatoid arthritis remains a clinical diagnosis that is merely supported by serologic testing. Because of its relatively high specificity, the finding of a positive CCP strongly supports the likelihood that a given patient has RA.

RF is also found in a number of other autoimmune diseases. It is highly prevalent in Sjogren's syndrome, mixed connective tissue disease, mixed cryoglobulemia, and to a lesser extent in SLE. RF is also present in some chronic infections; most importantly Hepatitis C infection, which can cause both arthritis and high titers of RF. (In such cases a positive CCP indicates that the arthritis is due to RA rather than Hepatitis C) RF can also be elevated in inflammatory disorders (sarcoidosis, primary biliary cirrhosis) and some malignancies (lymphomas). False positive CCP tests are relatively rare but have been reported in a variety of autoimmune (lupus, Sjogren's syndrome, Psoriatic Arthritis) and infectious diseases. Some authors have suggested that its presence in those autoimmune diseases may be associated with a more severe form of arthritis.

### When is it useful to order ANCA testing and how does one interpret positive and negative results?

ANCA antibodies are antibodies against neutrophilic cytoplasmic antigens present in some vasculitides, notably Granulomatosis with Polyangiitis (GPA; formerly referred to as Wegener syndrome), microscopic polyangiitis (MP), Eosinophilic Granulomatosis with Polyangiitis (EGPA; formerly Churg-Strauss syndrome), and idiopathic rapidly progressive glomerulonephritis. In addition, ANCA antibodies have been associated with kidney-limited and drug induced vasculitis [31,32]. These diseases have overlapping features and are often lumped together as ANCA-associated vasculitides.

There are 2 methods to test for ANCA. The immunofluorescence assay is considered a screening test and may show either a cytoplasmic pattern (c-ANCA) or a perinuclear (p-ANCA) pattern of staining. A positive immunofluorescence assay should be pursued by ELISA, which is antigen-specific. Most, but not all, antibodies that give a cytoplasmic pattern are directed against Proteinase 3 (P3), while the target antigen responsible for most perinuclear patterns is myeloperoxidase (MPO). ANCA (most often PR3 antibodies) are found in 80-90% of patients with GPA, whereas MPO antibodies may be present in about 70% of patients with microscopic polyangiitis and 50% of patient with EGPA. There is some overlap in antibody specificities, and all of these diseases may occur in the absence of a positive ANCA. ANCA titers do not correlate well with disease activity and are thus of little use in monitoring disease activity [33]. Our understanding of the neutrophil antigen specificities that produce a positive ANCA test and their relevance in various clinical disorders continues to evolve.

In considering the diagnosis of GPA, positive ANCA results should be confirmed by tissue biopsy in most cases. However, when the clinical history is strongly suggestive of GPA (sinus involvement, pulmonary and renal disease) the positive predictive value of ANCA testing alone is very high and may preclude the need of tissue biopsy [32].

It is worthy of note that p-ANCA is found in the majority of patients with vasculitis caused by levamisole-contaminated heroin or cocaine [34,35]. In contrast to the classic ANCA-associated vasculitides, both PR3 and MPO antibodies can be present simultaneously and titers are much higher [36].

### What is the role of hepatitis serology and abnormal liver function tests in rheumatology?

Since both hepatitis C (HCV) and B (HBV) infections can have rheumatologic manifestations, testing for viral hepatitis should be considered in patients with rheumatic symptoms. Hepatitis C can cause non-specific myalgia, arthralgia, and less frequently, frank arthritis [37]. Type II (mixed) cryoglobulinemia occurs in almost half of HCV patients, but clinically manifests as systemic vasculitis in only about 10% of them [38], usually accompanied by positive rheumatoid factor and hypocomplementemia.

Polyarteritis Nodosa (PAN), a systemic necrotizing vasculitis often involving medium sized arteries, occurs in one third of Hepatitis B patients. In fact, the presence of hepatitis B surface antigen or antibody in serum is recognized as one of the criteria for PAN diagnosis [39]. Recently PAN has been described in patients with HCV as well [38].

Elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually thought of as reflecting hepatocyte

necrosis, and these tests are often included in panels of so-called liver function tests (LFTs). However, it is important to remember that these enzymes are found in high concentration in muscle cells as well. Elevated levels of these enzymes may reflect myositis or rhabdomyolysis.

### How to interpret serum uric acid levels

An elevated serum uric acid level is not synonymous with the diagnosis of gout. Gout is an inflammatory arthritis, monoarticular 85% of the time, resulting from the intra-articular release of monosodium urate (MSU) crystals that have been deposited in peri-articular tissues as a result of hyperuricemia, usually of some duration.

Hyperuricemia is highly prevalent in the population (21.4%). Only 4% have had gout, but there is evidence that the incidence is increasing [40]. The risk of gout is related to both the duration and magnitude of hyperuricemia: the higher the serum uric acid level, the higher the likelihood that a gout attack will occur in the next year [41].

During an acute attack of gout, serum uric acid levels are not elevated in about 30% of cases [42] and may therefore be misleading. In such cases, a patient's serum uric acid level should be checked during asymptomatic periods. At present, the American College of Rheumatology makes no recommendation on the treatment of asymptomatic hyperuricemia [43].

### How helpful is analysis of synovial fluid, particularly in acute monoarthritis?

Synovial fluid white blood cell count (WBC), differential, microscopic examination for crystals, Gram stain, bacteriologic culture and lactic acid determination may all be of use in diagnosis (Table 2). The WBC and differential are helpful in placing the arthritis in the general categories of non-inflammatory, inflammatory or septic, although these boundaries are ill-defined. A WBC count less than 2,000 is generally found in non-inflammatory or minimally inflammatory conditions such as osteoarthritis. WBCs between 2,000 and 50,000 are seen in inflammatory conditions such as gout, rheumatoid arthritis and early septic arthritis. WBC's of 40,000 or greater suggest septic arthritis, generally with >90% polymorphonuclear cells. Synovial fluid glucose concentrations <50% of the serum glucose level are often found in septic arthritis, and synovial fluid lactate levels may also be helpful in suggesting intra-articular infection [44].

	WBC	% PMN	Glucose (% of serum glucose)	Crystals (Birefringent light)	Culture & Gram-stain
<b>Normal</b>	<200	<25	95-100	0	0
<b>Non-inflammatory</b>	<2,000	<25	95-100	0	0
<b>Inflammatory</b>	2,000-50,000	50-75	70-90	0	0
<b>Crystal-induced</b>	2,000-50,000	>75	80-100	+	0
<b>Septic</b>	>40,000	>90	<50	0	+

**Table 2:** Characteristics of Synovial fluid

Microscopic examination of synovial fluid may be diagnostic in crystal-induced arthritis, in which the birefringent characteristics of crystals distinguish between gout (sodium urate) and pseudogout (calcium pyrophosphate), and in septic arthritis, in which Gram stain often permits identification of infecting organisms before results of bacterial culture are available.

### Closing Admonition

In most rheumatologic illnesses, a detailed review of symptoms and examination is of primary importance, while laboratory tests usually serve to support or reduce the likelihood of possible diagnoses. Laboratory tests bear economic and emotional burdens and should be employed with discretion, when the clinician believes they can be helpful in diagnosis and management. As patients are now often able to access their own laboratory test results electronically, it is increasingly more important that physicians educate patient regarding the diagnostic and prognostic value of test results as part of their overall patient management.

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