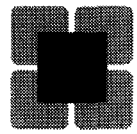

PATHOLOGY FEATURE
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C-reactive protein: the best laboratory indicator available for monitoring disease activity

■ Recent technical advances in measurement of serum C-reactive protein (CRP) have made this laboratory test highly specific, sensitive, reproducible, quantitative, and easy and rapid to perform. Several studies have shown that serial and quantitative measurement of serum CRP can be very helpful in monitoring disease activity in a wide variety of clinical situations, and that CRP testing offers distinct advantages over testing for any of the other acute-phase reactants. CRP testing is superior to erythrocyte sedimentation rate (ESR) measurements on clinical, scientific, and practical grounds, and it is strongly recommended that serious consideration be given to replacing ESR with CRP testing for monitoring disease activity.

□ INDEX TERM: C-REACTIVE PROTEIN □ CLEVE CLIN J MED 1989; 56:126–130

C-REACTIVE PROTEIN (CRP) was first described in 1930 by Tillet and Francis[1] as a protein present in the sera of patients with pneumococcal pneumonia, that could form a complex with the C-polysaccharide isolated from pneumococci in a flocculation reaction. Shortly after the initial discovery of CRP, serum elevations of this protein were demonstrated during acute stages of a wide variety of diseases, including acute bacterial, viral, and other infections and noninfectious illnesses such as rheumatic diseases, myocardial infarction, and various malignant diseases. Thus, any pathological condition associated with inflammation and tissue destruction appeared to be accompanied by elevation of CRP in the patient's serum.

In the 1940s and 1950s CRP was one of the most frequently requested clinical laboratory tests for initial evaluation of patients with acute inflammation of any origin. With the laboratory methods available then, CRP was not detectable in the sera of normal healthy individuals. However, nonspecificity of the test was a major problem in clinical interpretation, and also the qualitative nature of the old procedure for CRP determination made correlations between severity of the clinical disease and positivity of the test impossible. As a result, the CRP test gradually lost its popularity and by the 1970s very few laboratories were performing this test in any significant numbers. Another reason for its loss of popularity was the development of other tests for monitoring acute-phase reactions. The test most commonly used for this purpose now is the erythrocyte sedimentation rate (ESR).

However, during the past decade significant developments have occurred with respect to isolation of pure CRP, its chemical and physical characterization, production of highly specific antibodies to CRP, and introduction of highly sensitive, specific, and rapid procedures for quantitative measurements of CRP. Also, recent clinical studies have demonstrated the value of CRP measurements in monitoring disease activity in a wide variety of clinical situations. Concurrent with these clinical developments, reports have appeared demonstrating an important biologic role for this molecule as an immunomodulator with respect to activation of the complement system,[2] activation of neutrophils,[3] and more recently, activation of the monocyte-macrophage

system[4,5] to generate tumoricidal activity.

These recent developments call for a serious reappraisal of CRP testing and its potential role in the clinical laboratory. This review of relevant clinical and laboratory information emphasizes methodology and clinical disease correlations to support the idea that CRP testing has distinct advantages over testing for any of the other known acute-phase reactants.

METHODS FOR CRP DETERMINATION

In the past 50 years a wide variety of immunological techniques has been used for measuring CRP in serum or plasma. In the 1940s and 1950s these procedures were essentially qualitative and involved precipitation or agglutination techniques in which the degree of reactivity of a given sample was recorded as 1+ to 4+. The most popular of these methods, developed by Singer et al,[6] used a latex agglutination procedure similar to that developed for detection of rheumatoid factor. The major disadvantage or limitation of these procedures was their relatively low sensitivity; the lower limit of detection was in the range of micrograms per milliliter. The qualitative nature of the test result also made demonstration of any significant correlation with clinical disease activity difficult.

With the purification and physical and chemical characterization of CRP in 1978,[7] highly specific and quantitative methods for measurements of CRP could be developed. Coupled with advances in technology, including laser nephelometry, enzyme immunoassays, and radioimmunoassays, CRP could then be measured in the picogram (10^{-12} g) range. Of these more recently developed techniques, the laser nephelometric assay is probably the most popular among clinical laboratories because of its ease, rapidity, and reproducibility. According to proficiency testing surveys performed by the Diagnostic Immunology Resources Committee of the College of American Pathologists, approximately 70% of the clinical laboratories in the United States use laser nephelometry for CRP determinations.

CRP can now be detected in various serous fluids, including cerebrospinal, synovial, amniotic, pleural, ascitic, and even blister fluids. The normal CRP values for these other body fluids have not been determined as yet, although it is well known that increased levels of CRP are present in disease states. The development of these specific, sensitive, and quantitative tests for CRP has caused renewed interest in CRP measurement for monitoring disease activity, and several recent studies support use of CRP testing in this area.

CRP V OTHER ACUTE-PHASE REACTANTS AS INDICATORS OF DISEASE ACTIVITY

Initially CRP was thought to be an abnormal protein, not normally found in healthy individuals, but as mentioned earlier, recent studies with highly sensitive techniques have demonstrated that CRP is present in various body fluids of normal individuals. Any clinical disease characterized by tissue injury and/or inflammation is accompanied by significant elevation of serum CRP, and at present, many studies focus on the quantitative degree of elevation of CRP level and its correlation with disease activity. Other well-known acute-phase proteins of interest are alpha-1 antitrypsin, haptoglobin, ceruloplasmin, alpha-1 acid glycoprotein, transferrin, and fibrinogen. The serum levels of all of these proteins increase during acute inflammation and/or tissue injury. However, there is a clear difference in the kinetics or the temporal sequence and magnitude of their elevations compared with that for CRP.[8] The rise in serum CRP occurs much earlier (within 4 to 6 hours) after tissue injury (such as that resulting from a surgical procedure) than that in all the other acute-phase proteins, which increase over a much longer period (24 hours or more).

The magnitude of the increase is also significantly greater for CRP, which can rise 100-fold to 1,000-fold. The other acute phase reactants tend to increase less than 10-fold. In general, most recent studies indicate that CRP is an earlier and more reliable indicator of clinical disease and its severity than the other serum acute-phase reactants.

CRP AND POSTOPERATIVE RECOVERY

Elective surgery represents one example of tissue injury in a controlled setting. Studies by Fisher et al[9] in patients undergoing various elective surgical procedures showed that following surgery, serum levels of CRP begin to increase within 4 to 6 hours and reach a peak value, usually 25 to 35 mg/dL, in 48 to 72 hours. In uncomplicated surgical cases, the CRP level begins to decrease after the third postoperative day and reaches normal values of 3 mg/dL or less between the fifth and seventh postoperative day. When the postoperative clinical course is complicated by infection or some other process involving tissue damage or necrosis, the serum CRP values show a distinctly different pattern; the high serum levels persist for a much longer time, depending on the duration of complication. Thus serial, quantitative determinations of CRP can be helpful in monitoring postoperative recovery.

CRP measurements appear to be more reliable than the traditional parameters used for this purpose, such as body temperature, white blood cell count, or ESR.[10] Similar observations have been made in studies in our own laboratories.[11] It is important for postoperative monitoring that the preoperative CRP level be determined as a baseline, and that CRP testing be done serially rather than at single isolated point. Also, the CRP levels must be quantitative to be clinically meaningful and useful.

CRP LEVELS IN VARIOUS CLINICAL DISEASE ENTITIES

Numerous studies have been carried out correlating CRP levels with various clinical disease entities. The results of these studies have been summarized in recent review articles.[12–14] Only the highlights of these studies will be discussed here.

Infectious diseases

The CRP level is significantly elevated in various infectious diseases including bacterial, fungal, parasitic, and viral diseases; however, in viral infections the elevations of CRP appeared to be somewhat lower.[12] In acute bacterial infections the CRP elevations tend to be in the range of 30 to 35 mg/dL whereas for most acute viral infections, the levels tend to be less than 20 mg/dL. This distinction is not an absolute one and therefore the CRP level in a given situation cannot be used to differentiate between bacterial and viral infection. However, serial measurements of CRP can be used in patients with infections to monitor either spontaneous recovery or recovery following therapy.

Measurements of CRP are particularly useful in monitoring infections in patients with various malignancies, including leukemias and lymphomas, and in patients receiving chemotherapy in whom other parameters such as ESR may not be reliable. In a recent study by Rose et al,[15] 25 patients with leukemia who had 34 episodes of infection were evaluated serially for CRP levels to monitor response to antibiotic therapy. CRP levels rose above 10 to 15 mg/dL in all of these patients, although the elevation of CRP did not always parallel a rise in temperature during episodes of infection. A significant number of these patients had bone marrow depression and pancytopenia, and therefore ESR measurements were not helpful for monitoring. On the other hand, CRP levels did reflect recovery from infections following antibiotic therapy. CRP measurements have also been reported to be helpful in monitoring acute infectious episodes complicating chronic pulmonary and renal diseases.[13]

Inflammatory bowel diseases

The value of CRP measurements in Crohn's disease and ulcerative colitis has been studied by several investigators.[16–19] Serum levels of CRP were significantly greater in patients with these diseases than in normal controls; moreover, most patients with Crohn's disease had CRP levels significantly higher than similar patients with ulcerative colitis.[16,19] CRP levels were higher in Crohn's disease than in ulcerative colitis for all categories of disease severity. ESR measurements were also carried out in these studies; although these were also higher in Crohn's disease, they did not closely reflect disease activity in individual patients. CRP levels, on the other hand, corresponded closely with clinical and pathological indices of relapse, remission, and response to therapy. Buckell et al[17] made similar observations in patients with ulcerative colitis.

Rheumatic diseases

Pepys et al[20] studied CRP elevation in patients with rheumatoid arthritis and systemic lupus erythematosus and reported that serum CRP concentrations correlated with activity of the disease in rheumatoid arthritis, and therefore CRP determinations were helpful in monitoring either spontaneous or therapy-induced remissions and exacerbations. On the other hand, the correlation with CRP levels was not as good in active, mild, or inactive systemic lupus erythematosus, and in some patients with severe active disease little or no elevation of CRP was observed. However, microbial infections in SLE were associated with significantly high serum CRP levels. In SLE, therefore, CRP measurements were helpful primarily for diagnosing infection and monitoring response to antibiotic therapy. In other related studies, CRP was found to be localized in the synovium of patients with rheumatoid arthritis and also in arterial lesions of patients with vasculitis, as demonstrated by radioisotopic and immunofluorescence techniques.[21,22] The significance of these findings is not entirely clear at present. In patients with polymyalgia rheumatica, giant-cell arteritis, and polyarteritis nodosa, CRP levels have been reported to be significantly elevated.[23] Again, a good correlation was observed between CRP levels and disease activity.

Myocardial infarction

Pepys et al[20] studied patients with definite myocardial infarction, patients with noncardiac chest pain, and some undergoing exercise testing. All patients with definite myocardial infarction had elevated CRP levels and the peak CRP level correlated significantly with the

peak level of CK-MB, the specific myocardial isoenzyme of creatine kinase. In patients in whom continuing heart tissue damage was thought to take place, the CRP level remained elevated in the days after infarction. In persons with spontaneous or exercise-induced angina or with noncardiac chest pain, no CRP elevation was seen.

Transplantation

Van Lente et al[24] studied CRP levels in patients with kidney or heart transplants and observed CRP to be a sensitive indicator of renal, but not cardiac, allograft rejection. Similar observations have been made by Valenzuela (personal communication) in our Department of Immunopathology. CRP elevation in this instance, however, is nonspecific and does not, in itself, indicate graft rejection.

In studies on patients with bone marrow transplantation for leukemia,[25] CRP elevations occurred either as a result of graft *v* host disease or infectious episodes; therefore, the CRP levels in themselves were not helpful in differentiating infection from graft *v* host disease. However, CRP measurement was still thought to be helpful in monitoring response to treatment.

CRP V ESR FOR MONITORING DISEASE ACTIVITY

The question whether CRP or ESR is preferable for monitoring disease activity has been receiving increasing attention in recent years.

Sliwinski et al[26] compared CRP and ESR measurements as a monitor for infectious episodes in patients undergoing peritoneal dialysis. In all of these patients, CRP levels were elevated and decreased with improvement. On the other hand, ESR did not correlate as well and was not as helpful.

In a study of 33 patients with rheumatoid arthritis in various stages of activity, Clough (Departments of Rheumatology and Clinical Immunology and Immunopathology; personal communication) compared CRP and ESR values on the same specimens and observed, by regression analysis, a correlation coefficient of 0.742, indicating good correlation between the two parameters.

Various other studies, as discussed earlier, have compared CRP and ESR values in specific disease states; for the most part, CRP has been observed to be a more reliable indicator of disease activity. In no instance has the reverse situation been reported.

As mentioned previously, most clinical laboratories still continue to rely on ESR as an indicator of disease activity. Our institution is no exception and over the past five years we have been requested to perform approximately 16,000 ESR determinations per year, in contrast to 3,000 to 4,000 CRP determinations per year during the same period. However, in light of all the information available at present, there appear to be no rational, clinical, technical, or practical reasons for choosing ESR over CRP. Instead, all the laboratory evidence available at present is overwhelmingly in favor of choosing CRP over ESR. First of all, ESR deals with a physical phenomenon, the rate at which red cells sediment, in contrast to measuring a specific quantitative molecular entity as for CRP. The ESR is affected by various factors such as size and shape of red cells and plasma composition, whereas CRP measurement is not affected by any of these factors.

Other reasons for favoring CRP include: the ease, rapidity, and reproducibility of the test procedure; the earlier occurrence of changes in CRP; the quantitative nature of CRP determinations, whereas ESR is essentially a qualitative test; the sensitivity of the CRP determination, which is far greater than that for the ESR test; and the feasibility of storing specimens for CRP for extended periods of time, which cannot be done for ESR. Finally, in this era of cost-containment, one must also look at the cost factors involved; in most institutions, the charges for CRP and ESR testing are comparable.

There appears to be no justification for continuing to use ESR determinations at the high level that we are experiencing. In the light of all the present evidence, it is strongly recommended that our clinical colleagues consider CRP for monitoring their patients.

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