

Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine

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ABSTRACT

Introduction: Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are widely used laboratory markers of systemic inflammation.

Objective: A thorough understanding of the similarities and differences between these two serological markers, including factors that affect measurements, is necessary for the proper utilization and interpretation of ESR and CRP.

Methods: This review summarizes the current published literature (searched on MEDLINE through February 2016) surrounding the history and utilization of ESR and CRP, and examines factors that affect ESR and CRP measurements and discordance amongst these two inflammatory markers.

Results: As ESR and CRP lack sensitivity or specificity, these tests should be used only in combination with clinical history and physical exam for diagnosis and monitoring of pathological conditions. The clinical application of these tests in diagnosis is best applied to conditions in which there is high or low clinical probability of disease. Importantly, discrepancies between ESR and CRP measurements commonly have been reported in both inpatient and outpatient settings and this problem may be particularly prevalent in chronic inflammatory diseases. Numerous physiological factors, including noninfectious conditions and resolution of inflammation can contribute to abnormally high ESR/low CRP readings or vice versa.

Conclusions: Although discordance may be encountered in certain settings, proper utilization of ESR and CRP measurements continues to play an important role in clinical management of many inflammatory and other conditions.

BACKGROUND

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly ordered laboratory tests that may

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aid clinicians in accurately diagnosing and following many complex disease states. Although these tests have a low index of specificity and are influenced by numerous disease factors, they may provide the clinician with valuable information and additional focus when used in conjunction with other clinical and diagnostic data. ESR and CRP may be particularly important as a component of the rapid yet complex decision making that is required in individuals with multiple comorbidities and in the intensive care unit.

DISCUSSION

Erythrocyte Sedimentation Rate

The ESR measures the rate at which erythrocytes fall or settle in the plasma of a randomly drawn anticoagulated blood specimen over a specified period of time (usually 60 minutes) in millimeters (mm)/hour; however, newer methods involving centrifugation can generate results in approximately 5 minutes.^{1,2} This phenomenon was first observed in 1897 by Dr

Edmund Faustyn Biernacki, who found that the rate at which blood settled varied among individuals and that red blood cells (RBCs) settled more quickly in the presence of increased levels of fibrinogen.³ In 1918, Dr Robert Fahraeus noted that ESR differed in pregnant versus nonpregnant women and saw the test as a possible indicator of pregnancy.³ In 1921, Dr Alf Vilhelm Albertsson Westergren used ESR as a laboratory indicator of the prognosis of patients with pulmonary tuberculosis.⁴ Dr Westergren defined the measurement standards for the ESR test that still are used widely today, including utilization of sodium citrate as an anticoagulant.

The ESR can be confounded by many factors, leaving this widely used test vulnerable to misinterpretation in clinical practice.^{5,6} Aggregation of erythrocytes promotes falling and increases the ESR; however, RBCs are negatively charged and tend to repel

Table 1. Conditions Associated With a Change in CRP and ESR

Conditions Associated With a Mild Rise in CRP	Conditions Associated With a Major Rise in CRP	Conditions Associated With a Mild Rise in ESR	Conditions Associated With a Major Rise in ESR
<ul style="list-style-type: none"> • Viral infections • Late pregnancy <p>Mucosal Infections</p> <ul style="list-style-type: none"> • Periodontitis • Stomatitis • Sinusitis • Baginitis • Intestinal hyperpermeability • Bacterial translocation <p>Noninfectious Causes of Mild Inflammation</p> <ul style="list-style-type: none"> • Obesity • Insulin resistance • Pancreatitis • Smoking • Uremia • Cardiac ischemia • Oral hormone replacement therapy • Sleep disturbance • Chronic fatigue • Mild alcohol consumption • Depression • Increasing age 	<ul style="list-style-type: none"> • Active inflammation • Severe bacterial infection • Burns 	<ul style="list-style-type: none"> • Increasing age • Female gender • Pregnancy • Anemia • Red blood cell abnormalities (including macrocytosis) <p>Technical factors:</p> <ul style="list-style-type: none"> • Dilutional problem • Increased temperature of specimen • Tilted ESR tube <p>Elevated fibrinogen level:</p> <ul style="list-style-type: none"> • Inflammation • Infection • Malignancy • Diabetes • Renal disease • Heart disease • Collagen vascular diseases 	<ul style="list-style-type: none"> • Malignancy • Temporal arteritis • Renal disease • Collagen vascular diseases

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

one another. Thus, the presence of positively charged, large, asymmetric acute phase proteins such as fibrinogen and immunoglobulins increases the ESR. The rate of erythrocyte settlement can be influenced by a wide variety of immune and nonimmune factors, including alterations of the quality and quantity of the RBCs, as well as changes in the normal patterns and amounts of various plasma proteins. Anemia and polycythemia (primary and secondary) represent quantitative changes in erythrocytes in various clinical conditions and will increase and decrease the ESR, respectively. Similarly, hemoglobinopathies and conditions associated with altered erythrocytes such as sickle cell disease have a low sedimentation rate during sickle crises that increases in the presence of moderate to severe infections.^{7,8} Significant alterations in the array of plasma proteins and their ratio to one another also can have a major effect on the ESR, such as with cytokine-induced elevations in acute-phase proteins in response to infection, inflammation, or trauma. As a result of various factors—both cellular and noncellular—that affect the sedimentation rate, it is difficult to determine a “normal” or reference range. However, normal ESR commonly is defined in men as age in years divided by 2 and for women, age in years plus 10.⁹ The ESR is thus higher in women, particularly during menses and pregnancy.

Alterations in circulating levels of plasma proteins such as fibrinogen and immunoglobulins that are typically associated with systemic illnesses are known to influence ESR. These individual proteins may provide useful information with respect to the specific disease process causing an elevated ESR.¹⁰ Due to the long half-life of some plasma proteins and perhaps a longer amplified response time, the ESR does not change rapidly at the beginning of the inflammatory process and normalizes more slowly than that of other acute phase reactants, an important point to consider when applying the results to clinical practice. As discussed later in this paper, the characteristics of these temporal changes may account for discrepancies identified between ESR and other acute phase reactants.

C-reactive Protein

CRP was discovered by Tillet and Francis in 1930 in patients with pneumococcal pneumonia, where it was found to interact with the C-polysaccharide of streptococcus pneumoniae cell wall, hence the term C-reactive protein.¹¹ Originally CRP was measured qualitatively using the Quelling reaction, which involved precipitation of C-polysaccharide in serum and gave a simple “positive” or “negative” response.¹² However, more precise methods of measurement (often expressed in mg/dl) that give results in approximately 15

to 30 minutes have been developed using light scattering from CRP-specific antibody aggregates. High-sensitivity assays also are commonly used to quantitate low levels of CRP.

CRP is a nonspecific acute phase reactant that is a member of the pentraxin proteins, which are pattern recognition proteins that are an integral part of the innate immune system. CRP is produced and synthesized in the liver in response to inflammatory cytokines and assists in complement binding and phagocytosis by macrophages. Thus, one of the major roles of CRP is the recognition and elimination of certain foreign pathogens, including endotoxemia.¹³ CRP also may help with clearance of necrotic or apoptotic cells.¹⁴ More generally, CRP is one of the many acute phase reactants that is elaborated in response to inflammation and/or tissue injury, and its rise is commensurate with inflammatory mediators (cytokines) produced by cells actively participating in the milieu of tissue injury such as IL-6, IL-1, TGF- β , and TNF- α .^{15,16} The level of CRP tends to be proportional to the intensity of the inflammatory process, and levels of this marker are therefore sensitive to subtle changes in the acute-phase response.^{15,17,18} Accordingly, levels of CRP fall quickly because of its short half-life (4 to 7 hours) once inflammation subsides.

When Is It Appropriate to Use ESR and CRP in Clinical Practice?

Clinical application of ESR and CRP—The acute phase reactants ESR and CRP are used clinically for diagnosis and monitoring of inflammatory conditions such as infections, trauma, infarction, neoplasm, inflammatory arthritis, and systemic autoimmune disease (Table 1). However, because ESR and CRP lack sensitivity or specificity, they should not be used exclusively for diagnosis. Furthermore, a normal result should not necessarily dissuade one from a clinical diagnosis. For example, elevations in ESR may be diagnostic of temporal arteritis or polymyalgia rheumatica, although patients diagnosed with these conditions sometimes exhibit low or normal ESR.^{19,20}

ESR and CRP levels also may provide insight into the underlying disease process. Elevations in ESR reflect disease states that involve increased plasma protein/fibrinogen levels such as autoimmune conditions or cardiovascular disease. Increased levels of CRP generally are reflective of underlying inflammation, such as that resulting from trauma or infection. In contrast, deceptively low CRP levels may be found in patients with infections caused by low virulence organisms or in those treated with antibiotics. In the case of functional disorders such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and somatic symptom disorders, a normal ESR and CRP may help to distinguish these conditions from organic pathology.²¹

Although ESR and CRP have been utilized in combination to diagnose and monitor various conditions for many years, CRP is somewhat preferred as a serological marker for acute dis-

ease.²² In acute inflammatory conditions, CRP can rise as much as 50 to 100 mg/L within 4 to 6 hours of a mild to moderately noxious stimulus, such as an uncomplicated skin infection, cystitis, or bronchitis. CRP levels double every 8 hours and peak 36 to 50 hours after the onset of inflammation or injury.¹² Mild increases in CRP between 2 mg/L and 10 mg/L are considered to be metabolic inflammation. Conversely, markedly elevated levels of CRP (>100-500 mg/L) are strongly associated with bacterial infections.¹⁵ The ESR, in contrast, begins to rise within 24 to 48 hours of the onset of inflammation, decreases slowly as inflammation resolves, and can take weeks to completely normalize.^{12,23} Importantly, investigation of underlying etiology should be carried out in patients with ESR values greater than 100 mm/hour as the positive predictive value for an identifiable cause of marked ESR elevation is 90%.²⁴ As CRP values tend to drop quickly with treatment, ESR has been proposed to be a better marker for clinical monitoring, following the course of disease over time, and predicting treatment response/duration for temporal arteritis, polymyalgia rheumatica, rheumatoid arthritis, and Hodgkin's disease.²⁵ CRP may be used to follow the course of disease and to monitor treatment effectiveness for bacterial infections, rheumatoid arthritis, malignancies, and acute pancreatitis. Similarly, serial measurement of CRP may be beneficial for predicting the occurrence of postoperative and neonatal sepsis.^{26,27} ESR and CRP levels at admission also can be useful in predicting severity of soft-tissue infections and thus prolonged hospitalization or a poor response to treatment.

Utilization of ESR and CRP for Medical Decision Making

in Clinical Practice—As ESR and CRP lack sensitivity or specificity, for a patient with indeterminate clinical suspicion of disease, an ESR and/or CRP measurement does not alter disease probability sufficiently to change medical decision making and course of treatment. However, for a patient with low clinical suspicion of disease, a low ESR and/or CRP measurement may decrease the posttest probability to an even greater extent, giving the physician additional confidence in ruling out disease. A high ESR and/or CRP measurement in patients with low clinical suspicion of disease may prompt the physician to examine test conditions for errors and/or monitor ESR/CRP values over time. On the other hand, for a patient with high clinical suspicion of disease, a high ESR and/or CRP measurement may increase posttest probability to aid with identification of a definitive diagnosis, whereas a low ESR and/or CRP measurement does not change the clinician's disease suspicion enough to alter the course of treatment. A highly generalized bedside clinical approach for use of ESR and/or CRP tests based on these principles is summarized in the Figure.

Based on Bayes' rule and the generalized bedside clinical approach described above and in the Figure, an ESR/CRP test result can be used to aid medical decision making based on pre-

Figure. Utilization of ESR and/or CPR Tests to Aid in Clinical Decision Making

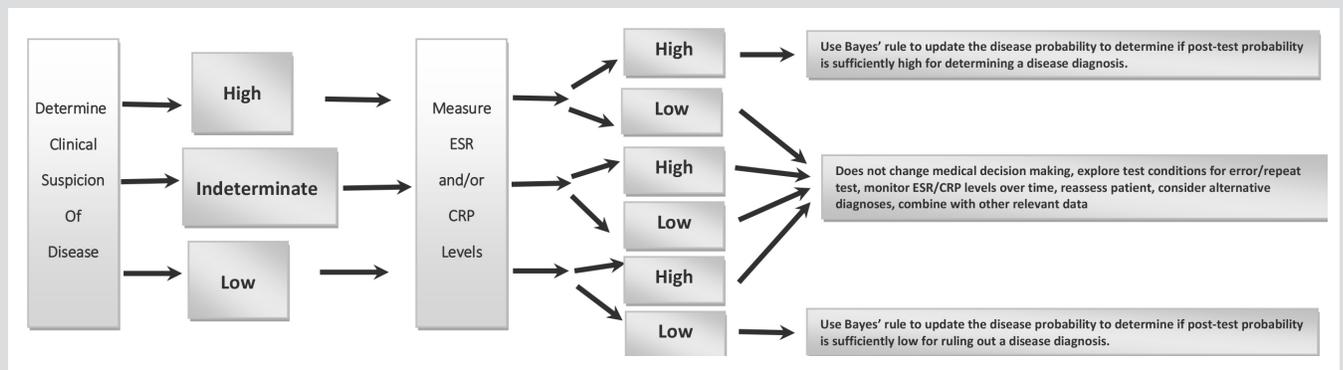


Table 2. Discordant Values in Hospitalized Patients

High ESR/Low CRP	High CRP/Low ESR
<ul style="list-style-type: none"> • Infections (Bone and joint) • Connective tissue disease (SLE) • Ischemic stroke • Malignancy • Renal insufficiency • Low serum albumin 	<ul style="list-style-type: none"> • Infections (urinary tract, gastrointestinal tract, lung and bloodstream) • Myocardial infarction • Venothromboembolic disease • Rheumatoid arthritis • Low serum albumin

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SLE, systemic lupus erythematosus.

test versus posttest disease probability. For example, in a study by Hopstaken et al, the pretest probability (prevalence) of pneumonia among patients with lower respiratory tract infections was 13%. At an ESR cut-point of ≥ 10 mm/hour, the sensitivity was 97% and specificity 28% for diagnosing pneumonia.²⁸ Applying Bayes' rule, the posttest probability of pneumonia in a patient with an ESR measurement < 10 mm/hour dropped to 1.6% while the posttest probability of pneumonia in a patient with an ESR measurement ≥ 10 mm/hour increased to 16.8%.

In another example based on a study by Falk et al, the pretest probability (prevalence) of community-acquired pneumonia (CAP) was 14.6%. At a CRP cut-point of ≤ 20 mg/L, the positive likelihood ratio was 2.1 and negative likelihood ratio 0.33, with a pretest probability of a patient having CAP of 14.6%.²⁹ Applying Bayes' rule in a patient with a CRP measurement ≤ 20 mg/L, the posttest probability of CAP dropped to 5.3%, while the posttest probability of having CAP with a CRP measurement > 20 mg/L increased to 26.5%.

How Should Discordant ESR and CRP Measurements Be Managed?

ESR, CRP, and other positive acute phase reactants generally rise in tandem with inflammation. However, this is not seen uniformly among all patients. In chronic inflammatory conditions, the accuracy and sensitivity of ESR and CRP has been a topic of debate. For example, in infections or malignant neoplasms, ESR has been

found to have low sensitivity but high specificity. Similarly, CRP is synthesized in the liver, and hepatic failure has been reported to markedly impair CRP production in the setting of overwhelming sepsis.³⁰

Previous studies have reported up to a 12% discordance rate (approximately 1 in 8 patients) between ESR and CRP values in hospitalized patients.^{16,31} Examples of conditions in which a high ESR/low CRP or high CRP/low ESR may be observed are summarized in Table 2. This frequent discordance between ESR and CRP may be attributable to various factors, including differences in cytokine stimulation, inherent differences in normalization, or false positive/false negative characteristics of individual acute phase reactants. In addition, it is important to consider age, gender, and adiposity, as ESR increases with age in healthy subjects, high ESR/low CRP discordance tends to be observed in women (likely due to their propensity to develop connective tissue disorders), and CRP levels generally increase in overweight and obese individuals.^{5,32}

Although correlation coefficients between ESR and CRP measurements may be statistically significant across cohorts,^{22,31} many patients exhibit conflicting results. Discordant values seen in various disease states may be caused by (1) resolution of recent inflammation, (2) presence of increased globulins such as in IgG4-related disease, Waldenstrom's macroglobulinemia and multiple myeloma (normal-mild-moderate CRP/elevated ESR), (3) medical conditions interfering with CRP such as connective tissue disease and stroke (low-normal CRP/elevated ESR), or (4) lack of sensitivity of ESR in the setting of known inflammation as in mucosal infections, myocardial infarction, venothromboembolism, renal disease, and disturbances in serum albumin (elevated CRP/low-normal ESR). For example, in systemic lupus erythematosus (SLE), ESR is often elevated—sometimes markedly—while the CRP response shows a less robust elevation, possibly related to interferon suppression of CRP production. In patients with giant cell arteritis, taking statin and nonsteroidal antiinflammatory medications was associated with a lower ESR.³³ Discordance of ESR and CRP in patients with rheumatoid arthritis has been

attributed to differences in inflammatory response timing, with a rapid rise in CRP coupled to a slower increase in ESR.³⁴

CONCLUSION

ESR and CRP can aid the physician in the diagnostic algorithm and clinical monitoring of various infectious or inflammatory conditions. Because of the limitations of ESR and CRP described above, these tests are more useful in confirming a provider's clinical suspicion for an inflammatory or infectious process rather than generating a specific diagnosis or initiating a protocol-driven treatment plan. Clinicians should be aware of the limitations of these tests and the conditions that may account for discordant results and utilize them within the clinical context in which they are obtained.

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