

# Erythrocyte Sedimentation Rate and C-Reactive Protein: How Best to Use Them in Clinical Practice

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## Abstract

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are markers of inflammatory conditions and have been used extensively by clinicians both in outpatient and inpatient settings. It is important to understand the physiologic principles behind these two tests so clinicians may use them appropriately. For example, fibrinogen (for which ESR is an indirect measure) has a much longer half-life than CRP, making ESR helpful in monitoring chronic inflammatory conditions, whereas CRP is more useful in diagnosis as well as in monitoring responses to therapy in acute inflammatory conditions, such as acute infections. Many factors can result in falsely high or low ESR and CRP levels, and it is important to take note of these. Therefore, if used wisely, ESR and CRP can be complementary to good history taking and physical examination in the diagnosis and monitoring of inflammatory conditions. [*Pediatr Ann.* 2014;43(10):417-420.]

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Inflammatory processes are associated with changes in the production of a class of proteins known as acute phase reactants. Serum levels of these proteins may either increase (positive acute phase reactants) or decrease (negative acute phase reactants) in response to inflammation. In the clinical setting, these proteins function as biomarkers of inflammation; examples include fibrinogen, which contributes to the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). ESR and CRP are two of the most commonly used laboratory tests in both the outpatient and inpatient settings, by general practitioners and specialists alike. It is important to understand the physiologic principles behind these two tests so that clinicians may use them appropriately.

## ERYTHROCYTE SEDIMENTATION RATE

ESR measures the distance through which erythrocytes fall within 1 hour in a vertical tube of anticoagulated blood.<sup>1</sup> ESR and its significance was first reported by Dr. Edmund Faustyn Biernacki in 1897.<sup>2</sup> He observed that the rate at which blood settled varied among different individuals, that blood with smaller amounts of erythrocytes settled more quickly, and that the rate of settling depended on plasma fibrinogen levels. He also noted that ESR was high in patients with febrile diseases associated with high fibrinogen levels (eg, rheumatic fever),

whereas it was low in defibrinated blood. In 1918, Swedish hematologist Robert Sanno Fåhræus presented the results of his analyses of the differences in erythrocyte sedimentation rates in pregnant and non-pregnant women, seeing the test as a possible indicator of pregnancy.<sup>2</sup> In 1921, Dr. Alf Vilhelm Albertsson Westergren, a Swedish internist, published his observations of erythrocyte sedimentation in patients with pulmonary tuberculosis.<sup>2</sup> Westergren defined standards for the performance of the ESR test, and the Westergren method of measuring ESR is still widely used today. In modern medicine, the ESR test is sometimes referred to as the Fåhræus-Westergren test.<sup>3</sup>

## Methods of Measuring ESR

In the Westergren method, a fixed amount of blood is drawn into a vertical tube anticoagulated with sodium citrate. The blood is left to settle for 1 hour, after which the distance between the top of the blood column and the top layer of the red blood cells (RBCs) below is measured. The ESR is thus reported in millimeters/hour. Newer methods employ a special centrifuge and automated machines and can yield results in as quickly as 5 minutes.<sup>3,4</sup>

## Physiology of ESR

Erythrocyte aggregation is influenced by the surface charge of red cells and the dielectric constant of the surrounding plasma, with the latter de-

pending on the concentration and symmetry of plasma proteins. The negatively charged erythrocytes tend to repel one another, but in the presence of positively charged large asymmetric proteins, erythrocyte aggregation and rouleaux formation are promoted.<sup>5,6</sup> Erythrocyte aggregates fall faster, thereby increasing the ESR.<sup>5</sup> Fibrinogen, one of the major acute phase reactants and a highly asymmetric protein, has the greatest effect on ESR.

Immunoglobulins in high concentrations also increase erythrocyte aggregation.<sup>6</sup> Immunoglobulin G (IgG) is the most abundant of the immunoglobulins with the highest rate of synthesis, and it has a half-life ranging from 7 to 21 days depending on the subclass.<sup>7</sup> Fibrinogen has a half-life of approximately 100 hours.<sup>8</sup> Because fibrinogen and immunoglobulins are two of the major proteins affecting ESR, and because both have relatively long half-lives, ESR remains elevated for days to weeks after resolution of inflammation.<sup>4</sup>

#### False Results

Non-inflammatory factors can also affect ESR. Erythrocyte shape and size as well as blood viscosity affect erythrocyte aggregation. With a reduced hematocrit (ie, anemia), the upward flow of plasma increases and erythrocyte aggregates fall faster, increasing ESR. With polycythemia, crowding of erythrocytes decreases the compactness of the rouleaux, slowing ESR.<sup>1</sup> Sickled and anisocytotic RBCs have a decreased tendency to form rouleaux, so ESR decreases in these states as well.<sup>1,4</sup> Because erythrocyte aggregation is facilitated by the presence of high molecular weight proteins, patients with hypo- or afibrinogenemia as well as those with hypo- or agammaglobulinemia can have a falsely low ESR in the face of active inflammation. Similarly, IVIg therapy, despite its anti-inflam-

matory effects, typically increases the ESR due to the increase in serum IgG, as happens in Kawasaki disease patients after treatment with IVIg.<sup>9-11</sup>

#### C-REACTIVE PROTEIN

CRP was first discovered in 1930 by Tillet and Francis during their serologic studies of patients with pneumococcal pneumonia.<sup>12</sup> They observed precipitation in the serum of sick patients, noting that precipitation decreased as patients recovered. They determined that precipitation occurred due to a protein in the serum that reacted with the C-polysaccharide of pneumococcal cell walls, hence the name "C-reactive protein."<sup>12</sup>

#### Methods of Measuring CRP

CRP was originally measured via the Quellung reaction, wherein precipitation of the C-polysaccharide in the serum was determined.<sup>13</sup> Before quantitative methods were developed, CRP was reported merely as being either "present" or "absent."<sup>6</sup>

Eventually, more precise quantitative methods were developed, of which the most commonly used today is nephelometry. With this technique, light scattering from CRP-specific antibody aggregates is measured, yielding results in as little as 15 to 30 minutes.<sup>14</sup> Today, high-sensitivity assays are being utilized to detect even low levels of CRP, which helps to determine cardiovascular risk, particularly in the adult population.<sup>15</sup>

#### Physiology of CRP

Synthesis of CRP occurs in the liver and is stimulated by the presence of cytokines, particularly interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF). It increases within 4 to 6 hours after the onset of inflammation or injury, doubling every 8 hours and peaking at 36 to 50 hours. Because of the short half-life (4-7 hours), plasma concentra-

tion depends only on the rate of synthesis; CRP levels thus drop quickly after inflammation resolves.<sup>14</sup>

#### False Results

CRP is synthesized by the liver; therefore, hepatic failure may impair CRP production. In a small study by Silvestre et al.,<sup>16</sup> CRP levels were found to be markedly low despite overwhelming sepsis in patients with fulminant hepatic failure. The authors proposed that in patients with fulminant hepatic failure, CRP should be used more as a marker of liver dysfunction rather than of infection.<sup>16</sup>

#### DIFFERENCES BETWEEN ESR AND CRP

CRP levels fall more quickly than the ESR, normalizing 3 to 7 days after resolution of tissue injury, whereas ESR can take up to weeks to normalize. Therefore, it is appropriate to use CRP for monitoring "acute" disease activity such as acute infection (eg, pneumonia, orbital cellulitis). In contrast, measurement of ESR is beneficial in the monitoring of chronic inflammatory conditions such as systemic lupus erythematosus or inflammatory bowel diseases. As discussed above, many factors can falsely increase or decrease ESR, whereas CRP is less likely to be affected (except in cases of liver failure<sup>16</sup>). ESR requires a fresh specimen of whole blood, whereas CRP can be measured from stored specimens of serum or plasma. CRP changes minimally with age, whereas ESR rises with age and is generally higher in females.<sup>14</sup>

#### CLINICAL APPLICATION OF ESR AND CRP

Both ESR and CRP are known to lack specificity and sensitivity, and neither should be used by itself for diagnosing any infectious or inflammatory disorder. However, if used correctly

and as an adjunct to a good clinical history and physical exam, they play an important role in clinical practice. One has to be careful in interpreting CRP results because CRP is reported either as mg/L or mg/dL, and it is important to be aware of the units used by a specific laboratory.

### Infection

Neonates may not present with the typical clinical and laboratory manifestations of sepsis (eg, fever and leukocytosis). CRP can be used to help determine the need for starting antibiotics.<sup>14</sup> It has been a common practice in many centers to use a high CRP level as an aid in clinical diagnosis of neonatal sepsis, thereby allowing the clinician to start empiric antibiotic therapy while waiting for culture results. Monitoring the trend in CRP levels can also be used to ascertain response to therapy, particularly when it is difficult to assess response clinically. A neonatal study by Benitz et al.<sup>17</sup> proposed that if two CRP levels measured 24 hours apart and 8 to 48 hours after clinical presentation are less than 10 mg/L, then bacterial infection should be considered unlikely. The authors noted that the sensitivity of a normal initial CRP was not so high as to justify withholding antibiotics, hence they recommended checking at least two levels 24 hours apart. Although a high CRP was found to be of low positive-predictive value, in the setting of neonatal sepsis, a test with high negative-predictive value (ie, one that effectively rules out sepsis when negative), is of greater importance than one that has high positive-predictive value. Starting empiric antibiotic therapy in a neonate with a falsely elevated CRP is more clinically acceptable than failing to do so in a septic baby.<sup>14,17</sup>

Generally, acute bacterial infections tend to elevate CRP to levels of 150 to 350 mg/L, whereas acute viral infections are usually associated with lower

levels. Of note, uncomplicated infections caused by adenovirus, influenza, and cytomegalovirus can also be associated with CRP levels of up to 100 mg/L.<sup>14</sup> A systematic review by Sanders et al.<sup>18</sup> in 2008 studied the accuracy of CRP for the diagnosis of serious bacterial infections in infants and children. Using six studies, they calculated a sensitivity of 0.77 and specificity of 0.79 when CRP was used to differentiate between serious bacterial infections and benign or non-bacterial infections. The study concluded that CRP was a moderate and independent predictor of the presence (or absence) of serious bacterial infections in children presenting with fever.<sup>18</sup>

ESR, along with leukocyte count, has traditionally been used as an adjunct for diagnosis and monitoring of pediatric osteomyelitis and septic arthritis.<sup>19</sup> Many clinicians use both ESR and CRP together at diagnosis and throughout antibiotic treatment. Both markers tend to be significantly elevated at the time of diagnosis,<sup>20</sup> but CRP has been found to decrease faster than ESR during the course of therapy, making it a more favorable tool to use in monitoring response to treatment in these infectious conditions.<sup>19-21</sup>

### Inflammatory Disorders

ESR and CRP are also widely used to evaluate and monitor inflammatory and autoimmune disease states. Both markers are almost always elevated in Kawasaki disease, with some variability in the degree of elevation between each marker. It is, therefore, recommended to measure both at initial presentation. The CRP level usually returns to normal within a few days after treatment of Kawasaki disease. Persistently elevated CRP levels strongly suggest continuing inflammation and may suggest a need for additional therapy. As discussed, IVIg therapy will cause ESR to rise; therefore, CRP is definitely a better

marker to monitor inflammatory activity in patients treated with IVIg.<sup>9,11</sup>

CRP is considered to be the most sensitive marker for diagnosis and monitoring of disease activity in Crohn's disease, but has been found to be less sensitive in ulcerative colitis. A persistently elevated CRP of greater than 45 mg/L in patients with inflammatory bowel disease indicates uncontrolled inflammation and may indicate a need for colectomy given the risk for developing colorectal cancer.<sup>12,22</sup> Some clinicians have proposed that in children with ulcerative colitis, once ESR and CRP correlation with disease activity has been established, there is little need for obtaining both for monitoring, as one should do well enough on its own.<sup>23</sup>

ESR can be used to determine inflammatory activity in rheumatoid arthritis, polymyalgia rheumatica, and temporal arteritis. However, CRP has been shown to correlate better with disease activity in rheumatoid arthritis both clinically and radiographically. Polymyalgia rheumatica and temporal arteritis are almost always associated with an ESR greater than 50 mm/hr.<sup>6,24</sup>

ESR has been shown to correlate better with flares in patients with systemic lupus erythematosus (SLE). Patients with active SLE often show only mild to moderate elevations of CRP unless they have a concurrent infection. Some clinicians propose that ESR and CRP taken together may help distinguish if a patient with known SLE is experiencing an exacerbation (which would present with a high ESR but only mildly elevated CRP) versus an infection (which would present with a markedly high CRP). It must be noted, however, that CRP may be elevated in those with SLE if they have serositis or erosive arthritis even without a concurrent infectious process.<sup>25-27</sup>

### CONCLUSION

ESR and CRP both play an important role in clinical practice. In certain

disease states, one may be a more favorable tool to use over the other. It is important to take note of the situations during which it is advised to obtain both, and those during which it would be redundant to do so. Most importantly, one must never forget that these markers are useful only if they are used as adjuncts to clinical history and physical exam.

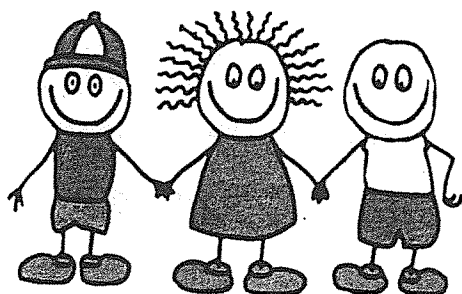
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