

**Focus on Diagnosis: The Erythrocyte Sedimentation Rate and the C-reactive Protein Test**

Sarosh P. Batlivala

*Pediatr. Rev.* 2009;30;72-74

DOI: 10.1542/pir.30-2-72

The online version of this article, along with updated information and services, is located on the World Wide Web at:

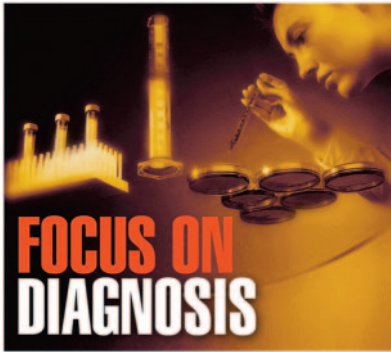
<http://pedsinreview.aappublications.org/cgi/content/full/30/2/72>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2009 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601. Online ISSN: 1526-3347.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™





# The Erythrocyte Sedimentation Rate and the C-reactive Protein Test

Sarosh P. Batlivala, MD\*

## Author Disclosure

Dr Batlivala has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## Introduction

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly used and widely available diagnostic tools employed by physicians to aid in diagnosing and managing various pathologic states. They both are nonspecific measurements of inflammatory processes.

## The ESR

As the name suggests, the ESR measures the distance that red blood cells (RBCs) settle over time. Through various methods, mixed and anticoagulated whole blood is placed in a vertical sedimentation tube for 1 hour, and the ESR is measured (mm/hr) as the distance from the top of the blood column to the top of the RBC layer below.

Numerous factors affect the ESR. In the blood of healthy patients, gravity causes RBCs to settle. However, as they fall, the upward displacement of plasma balances the downward force, resulting in little settling. When RBCs aggregate, forming rouleaux, the downward forces exceed upward forces, and the ESR increases. Plasma proteins have the greatest effect on RBC aggregation, which is directly proportional to the protein's molecular weight and degree of asymmetry.

Needle-shaped fibrinogen, a large and asymmetric molecule, has the greatest effect of all plasma proteins on ESR. When fibrinogen increases,

as in various inflammatory states, the ESR increases concomitantly. For this reason, many clinicians view the ESR as an indirect measure of fibrinogen. Because it is affected by plasma proteins, the ESR tends to rise slowly after the onset of inflammation and can stay elevated for days to weeks after resolution of the inflammation.

Importantly, noninflammatory conditions also affect the ESR. RBCs that have abnormal morphology, as in sickle cell disease, have less of a tendency to form rouleaux, thereby producing lower ESRs. Anemia tends to increase rouleaux formation, and polycythemia decreases it. Understandably, hyperviscosity states slow the ESR, and hypoviscosity states speed the ESR.

## The CRP

CRP is an acute-phase reactant synthesized in the liver primarily in response to cytokines interleukin (IL)-1-beta, IL-6, and tumor necrosis factor-alpha. The name derives from the observation that it reacts with C-polysaccharides of pneumococcal cell walls. CRP functions by binding directly to microorganisms as an opsonin for complement, activating neutrophils, inhibiting platelet aggregation, clearing necrotic host tissue, and possibly activating natural killer cells. The concentration of CRP may increase several hundred-fold in extreme inflammatory states. Its synthesis begins within 4 to 6 hours of the onset of inflammation and peaks between 36 and 50 hours; concentrations decline rapidly because of its short 4- to 7-hour half-life. In general, therefore, the CRP

## Abbreviations

- CRP:** C-reactive protein
- ESR:** erythrocyte sedimentation rate
- IL:** interleukin
- RBC:** red blood cell

\*Chief Resident in Pediatrics, University of Florida, Gainesville, Fla.

both rises and normalizes faster than does the ESR.

Because CRP is a directly measured plasma protein, it is unaffected by the external conditions that alter ESR values. CRP values do increase slightly with age and pregnancy, however. Of note, new technology allows for a relatively rapid and sensitive quantitative measurement.

### Clinical Use

The nonspecificity of both tests limits their use in diagnosing clinical states or as a sole guide to direct therapy. They are better suited as adjuncts to clinical suspicion and best interpreted with serial measurements. Although they can be monitored in adults to determine risk for cardiovascular events, in pediatrics they frequently are used to help in the management of infectious, rheumatologic, and oncologic disorders.

### Infections

ESR and CRP most commonly are measured in infectious states. Recent evidence suggests that CRP is an excellent screen for serious bacterial infections in neonates. Because CRP does not cross the placenta, its presence in a neonate indicates *de novo* production. Thus, some groups advocate measurement of CRP in infants at risk for sepsis. These protocols recommend measuring CRP at the initiation of the “septic evaluation” and subsequently at 24 to 48 hours to determine the trend. Use of the CRP in this situation is limited by the observation that concentrations of this protein also are elevated in noninfectious conditions such as meconium aspiration, respiratory distress, and intraventricular hemorrhage, among others. However, CRP has a high negative predictive value for serious bacterial infections; that is, such infections are ruled out with a

high degree of certainty when consecutive normal values are obtained.

Attempts have been made to use ESR and CRP to differentiate viral from bacterial causes in children who have fevers. Although both the ESR and CRP tend to be higher in patients who have more invasive infections, this relationship is not always observed. Most viral infections tend to cause modest elevations, but higher values of both ESR and CRP have been measured during uncomplicated infections with common viruses, including adenovirus, influenza, and cytomegalovirus. Thus, ESR and CRP have variable responses that prohibit their use in differentiating benign from serious disease in a specific patient.

Recently, the concentration of CRP in cerebrospinal fluid was evaluated for its utility in distinguishing bacterial from viral meningitis. Although one study recommended measuring the concentration of cerebrospinal fluid CRP once to help differentiate the cause, follow-up studies showed significant overlap among diverse microbial infections. Therefore, this measurement is not recommended for this purpose.

Both tests also have been used to screen for bacteremia. Numerous studies have failed to show a correlation between either test and the presence of culture-proven bacteremia. Again, serial measurements of CRP may help determine if a child is responding to therapy and, therefore, may allay concerns that a serious bacterial infection may develop. However, these tests do not provide a reliable screen for bacteremia.

ESR and CRP are used together by some clinicians to direct treatment of osteomyelitis and septic arthritis. After diagnosis, patients are treated with appropriate intravenous antibiotics, and baseline measurements are obtained. On day 10 to 14 of treat-

ment, ESR and CRP values are measured again and subsequently at set intervals, usually every few days. Once the CRP has normalized and the ESR value is significantly lower, many clinicians convert therapy to oral antibiotics to complete the 6-week course. After conversion to oral treatment, just one of the tests may be sufficient for follow-up.

An alternative philosophy recommends measuring only the CRP early in the clinical course because it responds more quickly than the ESR, both in rising and falling, making the test useful in judging the initial degree of inflammation and the early response to therapy. When the CRP returns to normal values, switching to the ESR and following that measurement until normal would assure that all inflammatory markers have returned to baseline.

Both markers have been used to evaluate acute rheumatic fever, as well. Neither has been shown to help in the diagnosis of acute rheumatic fever, but CRP values have been shown to decrease in response to corticosteroid treatment and to remain low after discontinuation of corticosteroids if the disease is suppressed adequately. Again, the markers have been shown to be useful adjuncts to determine the response to treatment.

### Inflammatory Disorders

In addition to infectious diseases, these markers have been used in the management of other inflammatory disorders. In Kawasaki disease, they are used as secondary diagnostic criteria to identify incomplete cases. Numerous studies have attempted to determine a “cut-off” CRP value to predict response to therapy and future development of coronary artery disease. Unfortunately, no definitive CRP values have been found to correlate consistently, although two studies did show that measurements

greater than 150 mg/L were associated with greater treatment failure and development of coronary lesions. Numerous other studies have shown that CRP normalizes rapidly once the child has received adequate treatment with intravenous immune globulin or aspirin.

As with infectious processes, these tests appear to help identify disease flares and complications in certain autoimmune disorders. For example, no reproducible values have been identified to aid in the initial diagnosis in systemic lupus erythematosus and inflammatory bowel disease. However, the inflammatory markers are useful in monitoring for flares and their response to treatment.

Studies also have been undertaken to determine if the markers can help diagnose graft versus host disease in transplant patients. The findings vary by organ, but no cut-off values have been found to correlate consistently.

Importantly, the inflammatory markers have a strong negative predictive value, aiding diagnosis by ruling out diseases. In patients afflicted with periodic fever syndromes, such as familial Mediterranean fever, the inflammatory markers are elevated during acute febrile flares but are normal when the patient is afebrile. Such normalization is not seen with

subacute infections from cytomegalovirus or Epstein-Barr viruses that mimic some periodic fever syndromes. Similarly, normal concentrations of inflammatory markers strongly rule out acute rheumatic fever and serious bacterial infections.

### Normal Values

Normal values for ESR and CRP vary among clinical laboratories primarily because of different assay methods, and clinicians should learn the values for the laboratories they employ. Commonly accepted values for the ESR are 0 to 15 mm/hr for males and 0 to 20 mm/hr for females, using the traditional Westergren and similar methods. A newer rapid test has different normal values. CRP in healthy people generally is below 1.0 mg/L (0.1 mg/dL). As with the ESR, a newer procedure, called the high-sensitivity CRP, may be used in some laboratories and has different normal values from the traditional method.

### Conclusion

The ESR and CRP are excellent tests that aid practitioners greatly but are limited by nonspecificity. Evidence shows that CRP tends to be more accurate and precise when compared with ESR. Such findings are related

to the CRP concentration being less affected by other factors and responding more rapidly than the ESR. Routinely obtaining or following both values serially is unnecessary and unhelpful because they are non-specific reflections of inflammation. It is crucial to remember that these tests never can serve as a substitute for a careful history and physical examination. Their greatest assets are helping to rule out specific disorders and monitoring response to treatment. In general, the most effective use of these tests is to follow only one serially to monitor the trends in a patient's clinical course.

### Suggested Reading

- Brigden ML. Clinical utility of the erythrocyte sedimentation rate. *Am Fam Physician*. 1999;60:1443-1454
- Ehrett SW, Nelson JD. The ESR: methods and uses. *The Report on Pediatric Infectious Diseases*. 1994;4:7-8
- Hilliard NJ, Waites KB. C-reactive protein and ESR: what can one test tell you that the other test can't? *Contemp Pediatr*. 2002;19:64-74
- Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J*. 1997;16:735-747
- Weiner SR. The meaning of the erythrocyte sedimentation rate. *Emerg Med*. 1982;14:252-254

**Focus on Diagnosis: The Erythrocyte Sedimentation Rate and the C-reactive Protein Test**

Sarosh P. Batlivala

*Pediatr. Rev.* 2009;30;72-74

DOI: 10.1542/pir.30-2-72

**Updated Information  
& Services**

including high-resolution figures, can be found at:  
<http://pedsinreview.aappublications.org/cgi/content/full/30/2/72>

**Subspecialty Collections**

This article, along with others on similar topics, appears in the following collection(s):  
**Collagen Vascular and Other Multisystem Disorders**  
[http://pedsinreview.aappublications.org/cgi/collection/collagen\\_vascular\\_other\\_multisystem\\_disorders](http://pedsinreview.aappublications.org/cgi/collection/collagen_vascular_other_multisystem_disorders) **Infectious Diseases**  
[http://pedsinreview.aappublications.org/cgi/collection/infectious\\_diseases](http://pedsinreview.aappublications.org/cgi/collection/infectious_diseases)

**Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://pedsinreview.aappublications.org/misc/Permissions.shtml>

**Reprints**

Information about ordering reprints can be found online:  
<http://pedsinreview.aappublications.org/misc/reprints.shtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

