COLLEGE of AMERICAN PATHOLOGISTS

C-Reactive Protein and Erythrocyte Sedimentation Rate Test Use

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Authors
Sehyo Yune, MD, MPH, MBA, Fellow, Beth Israel Deaconess Medical Center, Boston, MA
Justin T. Kelley, MD, MPH, FCAP, Assistant Professor, Vanderbilt University Medical Center, Nashville, TN

Editors
*Megan O. Nakashima, MD, FCAP, Associate Professor, Cleveland Clinic Lerner College of Medicine, Cleveland, OH, *Aaron Han, MD, PhD, FCAP, Professor, Loyola University Stritch School of Medicine, Maywood, IL, Barbara J. Blond, MBA, MLS, Thomas Long, MPH
*Senior editors

TOPIC FOCUS

This module addresses the optimal utilization of erythrocyte sedimentation rate and C-reactive protein and in the clinical setting to maximize the value of these two tests. Note that the content of this module is applicable to Westergren and automated erythrocyte sedimentation rate methodologies.

SYNOPSIS AND RELEVANCE

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most widely used markers in the clinical evaluation of acute and chronic inflammatory conditions. This module addresses the clinical scenarios in which ESR and CRP are most appropriately used to assess acute and chronic inflammatory conditions to reduce routine ordering of both tests simultaneously.

- CRP is a more sensitive and specific reflection of the acute phase response than ESR.
- ESR is not recommended as a screening test for acute inflammation in patients with undiagnosed conditions.
- Routine ordering of both ESR and CRP is unnecessary and risks clinical misinterpretation if the tests give discrepant results.

OBJECTIVES

1. Describe the pathophysiology and test methodology of ESR and CRP in the acute inflammatory response.
2. State the recommended indications for ESR and CRP ordering in the evaluation of acute inflammation.
3. Discern the unique clinical situations in which concurrent ESR and CRP ordering is useful and how to interpret discrepant results.

BACKGROUND

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) is the rate at which erythrocytes suspended in anticoagulated blood fall when placed in a 2.5 mm-diameter vertical tube, measured as millimeter per hour.[1] Elevations in the ESR are due to rouleaux formation of erythrocytes, which is influenced by the amount of protein in the plasma.[2] The level of acute phase proteins, therefore, influences the ESR, and has historically been used as a marker of acute inflammation. However, the ESR is a physicochemical phenomenon, rather than a specific analyte, and is an indirect and nonspecific measure of inflammation that depends on the balance between factors promoting and hindering sedimentation. Fibrinogen, an acute phase reactant, is the main protein influencing the ESR, but increases in a slow process over 24-48 hours and remains elevated for an extended time, up to weeks, after the inciting event. In chronic inflammation, in contrast, increased immunoglobulins (hypergammaglobulinemia) often play the dominant role in raising the ESR. The ESR can also be affected by multiple factors other than inflammation, such as age and sex, number and size/shape of erythrocytes, amount of albumin and immunoglobulins, renal function, pregnancy and medications.[2-3] While once the gold standard in the assessment of inflammation, the emergence of more sensitive and specific inflammatory markers are replacing the ESR for detecting acute inflammation, but remains valuable in monitoring chronic inflammation due to its persistent and stable elevation.

C-Reactive Protein

C-reactive protein (CRP) is an acute phase reactant that was first discovered in the early twentieth century among patients critically ill with *Steptococcus pneumoniae*, from where the “C” in CRP usually refers to the C polysaccharide of bacteria cell walls. Elevations in CRP are highly sensitive for an acute inflammatory process, whether

asymptomatic or clinical.[4] CRP contributes to the innate immune process by activating complement, binding to Fc receptors and acting as an opsonin for pathogens, nuclear antigens and damaged tissues; damage can include malignancy, burns, surgery, trauma, childbirth, obesity and smoking.[5] Unlike ESR, CRP is a specific protein produced by the liver in the acute phase response, primarily driven by interleukin 6 (IL-6). CRP also has well-defined kinetics, rising 12-24 hours and peaking 2-3 days after an inflammatory stimulus, with a half-life of 19 hours.[1] Therefore, CRP has become the preferred serologic biomarker of acute inflammation, and is useful in both the diagnostic evaluation and therapeutic response. Furthermore, high sensitivity CRP (hs-CRP) testing has emerged as a clinically significant assay for cardiovascular disease by using latex-enhanced immunoturbidimetry to detect very low levels of CRP in the prediction of primary and stratification of secondary cardiovascular events.[6]

ESR and CRP Testing Recommendations

ESR and CRP are the most common laboratory tests used in the screening of inflammatory conditions. Both tests are widely available, and easy to perform.[3] However, CRP is far more sensitive and specific than ESR in the evaluation of acute inflammation. Therefore, routine ordering of both ESR and CRP is unnecessary, and increases the risk of discrepant results between the two tests, which occurs in approximately one-fourth of cases.[7]

For the initial evaluation of idiopathic acute inflammation, CRP testing alone is recommended.[8] ESR, in contrast, remains useful in certain clinical conditions, such as monitoring chronic rheumatologic diseases (eg, rheumatoid arthritis, polymyalgia rheumatica and giant cell arteritis).[3] There are some notable situations in which simultaneous ESR and CRP testing can be useful, including rheumatoid arthritis (RA), systemic lupus erythematous (SLE), giant cell arteritis (GCA), Kawasaki disease, and orthopedic infection.[9] In RA, ESR and CRP are used in the classification system to classify a patient with definite RA.[10] In SLE patients presenting with a fever, each unit increase in the ratio of ESR:CRP is associated with a 17% increase in the odds of the fever being attributable to SLE flare compared to infection.[11] In giant cell arteritis, most patients have both an elevated ESR and CRP, but there can be discordance of the two tests (usually elevated CRP and normal ESR), so the use of both tests provides a greater sensitivity for the diagnosis of GCA than either test alone.[12] In Kawasaki disease, ESR and CRP levels are usually elevated at presentation and return to normal in 6-10 weeks, where the diagnosis is unlikely if ESR and CRP return to normal without treatment after one week.[13] In orthopedic infection, simultaneous ESR and CRP testing can improve diagnostic accuracy, particularly at reducing false positive rates in clinical scenarios with a low-pretest probability for infection.[14]

Careful interpretation of individual and combined tests is key in proper assessment of results, including unique confounding factors and discrepant findings between the two tests. For confounding variables, CRP is notably influenced by obesity and related metabolic abnormalities, while ESR is well-known to be influenced by age and gender (higher in ages >50 years and women).[15] Discrepant results between the two tests may be due to timing of inflammation, where CRP quickly rises and falls in contrast to ESR which slowly rises and falls following an inciting inflammatory event. Furthermore, ESR would remain elevated in settings of Intravenous immunoglobulin (IVIG) therapy, given increased immunoglobulins. CRP is also much more sensitive than ESR in detecting low-level inflammation, in which ESR may not increase much if at all. In summary, concurrent ordering of both ESR and CRP should be avoided except in certain clinical scenarios, and ordering physicians should understand how to interpret possible discrepant results.

INSIGHTS

1. CRP has superior sensitivity, specificity and kinetics than ESR and is the preferred screening test for acute inflammation.
2. ESR remains useful in the diagnosis and monitoring of chronic rheumatologic diseases (eg, rheumatoid arthritis, polymyalgia rheumatica and giant cell arteritis).
3. Simultaneous ESR and CRP testing has unique utility in SLE, GCA and orthopedic infection, and requires judicious planning of combined result interpretation.

INTERVENTIONS

1. Provide education on appropriate ordering of ESR and CRP, including targeted interventions and feedback for clinical providers and/or units with high inappropriate test ordering.
2. Create a nonintrusive best practice advisory for appropriate ordering of ESR and/or CRP for specialties who frequently order inappropriate simultaneous ESR and CRP. Additional alert parameters can be added to refine as relevant, such as triggering only after the first order of ESR and CRP, when no rheumatology or other relevant specialty referral is placed, or no relevant diagnosis is listed.

INTERVENTION ANALYSIS

The total number of individual and concurrent ESR and CRP orders can be compared prior to and after implementation of the intervention(s) selected. The number of appropriate concurrent ESR and CRP orders among the total orders can be determined by review of provided clinical indication. Chart review for clinical scenarios and laboratory data can also be performed for further information, as needed. Inappropriate testing can be further evaluated by various filters, such as ordering providers, provider specialties or order indications, to provide targeted education. Lastly, given the burden of EHR alerts, clinician time and satisfaction with the intervention can be assessed and refined, as necessary.

1. Perform a pre-intervention assessment of appropriate concurrent ESR and CRP orders.
2. Implement interventions as suggested above or those developed by your institution.
3. Perform a post-intervention assessment of appropriate concurrent ESR and CRP orders.
4. Compare the change in appropriate concurrent ESR and CRP orders for your laboratory's pre-intervention and post-intervention performance.
5. Repeat as needed for each major intervention or guideline update.

APPENDIX A: CALCULATING THE INTERVENTION IMPACT

Laboratory Test Volume Outcomes and Opportunities				
Description	**Pre-Intervention**	**Post-Intervention**	**Pre - Post Volume Change**	**Percent Volume Change Impact (%)**
Frequency of ESR ordered per 1000 patient-days or outpatient/ED visits	A1	A2	A1 - A2 = A3	A3/A1 x 100% = A4%
Frequency of CRP ordered per 1000 patient-days or outpatient/ED visits	B1	B2	B1 - B2 = B3	B3/B1 x 100% = B4%
Frequency of ESR and CRP ordered simultaneously per 1000 patient-days or outpatient/ED visits	C1	C2	C1 - C2 = C3	C3/C1 x 100% = C4%

QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Describe the pathophysiology and test methodology of ESR and CRP in the acute inflammatory response.

QUESTION 1

Which of the following is TRUE regarding CRP?

A. CRP demonstrates slow kinetics during acute inflammation, gradually rising and falling after an inciting event.
B. CRP is not influenced by age or gender.
C. CRP is an indirect marker of acute inflammation.
D. CRP elevations are highly sensitive to acute inflammation.
E. CRP is a specific but not sensitive biomarker of inflammation due to infection.

The correct answer is D. CRP increases in response to pro-inflammatory cytokines, primarily driven by interleukin 6 (IL-6), and is highly sensitive for acute inflammation.
A is incorrect. CRP has well-defined kinetics, rising and falling quickly following an inciting inflammatory event, in contrast to ESR which slowly rises and falls with inflammation.
B is incorrect. While ESR is generally more significantly impacted by age and sex, CRP levels also rise to a lesser extent with age and may also be higher in women.
C is incorrect. CRP is an acute phase reactant produced by the liver in the acute phase response, in contrast to ESR which is due to plasma proteins increasing the rate of rouleaux formation of erythrocytes.
E is incorrect. CRP is a highly sensitive biomarker of acute inflammation stimulated by acute phase cytokines in the innate immune response.

REFERENCE

Markanday A. Acute Phase Reactants in infections: evidence-based review and a guide for clinicians. *Open Forum Infect Dis.* 2015;2(3):ofv098. doi:10.1093/ofid/ofv098

QUESTION 2 OBJECTIVE
State the recommended indications for ESR and CRP ordering in the evaluation of acute inflammation.

QUESTION 2
Which of the following indications is most appropriate for ESR and/or CRP?
A. Concurrent ESR and CRP are recommended in the initial evaluation of all types of acute inflammation.
B. CRP alone is recommended in the initial evaluation of acute inflammation.
C. CRP alone is included in diagnostic guidelines for certain rheumatologic conditions.
D. ESR is recommended to evaluate early acute inflammation.
E. ESR is useful to monitor therapeutic response in acute inflammatory conditions.

The correct answer is B. CRP is far more sensitive and specific than ESR in the workup of acute inflammation and is recommended as the sole test in the initial evaluation of acute inflammation.
A is incorrect. Concurrent ESR and CRP is unnecessary, with a few specific exceptions, as CRP is more sensitive and specific than ESR, while routine ordering of both ESR and CRP increases unnecessary test risks of discrepant results.
C is incorrect. While indirect and nonspecific, ESR is a better biomarker of chronic inflammation, whereas CRP is a highly sensitive biomarker of acute inflammation. ESR, rather than CRP, is therefore included in diagnostic guidelines for certain chronic rheumatologic conditions.
D is incorrect. ESR demonstrates slow kinetics, slowing rising and falling in response to inflammation, in contrast to CRP which is sensitive to even mild changes in inflammation.
E is incorrect. Because ESR remains elevated for an extended period of time following inflammation, it is not useful to monitor clinical or therapeutic response of acute inflammatory conditions. In contrast, CRP quickly decreases with resolution of inflammation and is a better biomarker to monitor acute inflammation.

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Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation Rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ*. 2016;115(6):317-321.

QUESTION 3 OBJECTIVE
Discern the unique clinical situations in which concurrent ESR and CRP ordering is useful and how to interpret discrepant results.

QUESTION 3
Which of the following conditions can best benefit from concurrent ESR and CRP?
A. To distinguish between viral and bacterial infection.
B. To distinguish between SLE disease activity and acute infection in patients with SLE.
C. To screen for acute inflammatory conditions.
D. To exclude orthopedic infection in a clinical scenario with a high-pretest probability of infection.
E. To predict primary cardiovascular disease risk.

The correct answer is B. Routine ESR and CRP testing in patients with SLE is challenging due to chronic active inflammation. Concurrent ESR and CRP testing is, however, useful in the evaluation of a fever in patients with SLE, in which each unit increase in the ratio of ESR:CRP is associated with a 17% increase in the odds of the fever being attributable to SLE flare versus active infection.
A is incorrect. ESR and CRP increase in response to inflammation and cannot distinguish between viral or bacterial infection as either infection would stimulate inflammation and increase both ESR and CRP.
C is incorrect. CRP alone is recommended in screening for acute inflammatory conditions as it is more sensitive and specific than ESR, reduces unnecessary testing and potential discrepant results.
D is incorrect. Simultaneous ESR and CRP can improve diagnostic accuracy and reduce false positive rates in clinical scenarios with a low, not high, pretest probability of orthopedic infection.
E is incorrect. High sensitivity CRP (hs-CRP) testing can detect very low levels of CRP and is used in the prediction of primary and stratification of secondary cardiovascular events. ESR is not sensitive enough to be used for low-level screening.

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Littlejohn E, Marder W, Lewis E, et al. The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever. *Lupus*. 2018;27(7):1123-1129. doi:10.1177/0961203318763732

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