

The Erythrocyte Sedimentation Rate: Old and New Clinical Applications

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ABSTRACT

Background. The erythrocyte sedimentation rate (ESR) is a simple and inexpensive laboratory test. It is commonly used to assess the acute phase response.

Methods. A review of the recent literature was done to evaluate the role of the ESR and its importance in different clinical conditions both inflammatory and non-inflammatory.

Results. Despite the critical role cytokines have in inflammatory conditions, the ESR still maintains its important role in the diagnosis and follow-up of rheumatoid arthritis and temporal arteritis. Recently, ESR has been reported to be of clinical significance in sickle cell disease, osteomyelitis, and, surprisingly, in non-inflammatory conditions such as stroke, coronary artery disease, and prostate cancer. Erythrocyte sedimentation rate measured by the Westergren method is marginally affected by age, race, and blood storage.

Conclusion. Despite its importance in many clinical conditions, ESR should be used only as a clinical guide to aid the diagnosis, management, and follow-up of these different clinical situations.

THE ERYTHROCYTE SEDIMENTATION rate (ESR) is a simple and inexpensive laboratory test for assessing the inflammatory or acute response. The International Committee for Standardization in Hematology (ICSH) recommends the use of the Westergren method.^{1,2} While the role of acute phase reactants and cytokines in inflammatory responses is well-established,³ ESR measurement remains the method of choice in evaluating different clinical conditions.⁴ The ESR has also been found to be of clinical significance in the follow-up and prognosis of non-inflammatory conditions such as prostate cancer,⁵ coronary artery disease,⁶ and stroke.⁷ Therefore, the ESR is important in the diagnosis of inflammatory conditions and in the prognosis of non-inflammatory conditions,⁸ making this old test **far from obsolete in either the near or distant future.**

METHODS AND FACTORS AFFECTING THE TEST

Several reviews detail the method of measuring the ESR.^{2,4} The International Committee on Standardization in Hematology Reference Procedure accepts the Westergren method.²

Ethylenediaminetetraacetic acid (EDTA) anticoagulated blood sample is preferably diluted in a large bore tube before using the Westergren tube.² With this modified

Westergren's method,^{2,9} there is an excellent correlation with the ICSH reference. Blood samples can be stored for up to 24 hours at 4°C, but not at room temperature, without affecting the Westergren level.¹⁰ Erythrocyte aggregation is affected by two major factors: red cell surface charges and frictional forces around the red cell. The erythrocytes normally have net negative charges and, therefore, repel each other.⁴ High molecular weight proteins, especially when positively charged, increase viscosity and favor rouleaux formation and thus would raise the ESR.^{11,12} Fibrinogen, the most abundant acute phase reactant, has the greatest effect on the elevation of ESR when compared with other acute phase proteins.^{3,4,11} Paraproteins are positively charged molecules and when abundantly present as in multiple myeloma or Waldenstrom's macroglobulinemia will increase the ESR levels by enhancing rouleaux formation and elevating plasma viscosity.^{3,4,11} For this reason, plasma viscosity measurement correlates with the ESR, but it is not as reliable as that of ESR since it is marginally affected by short-term changes in acute phase responses.³ In vitro systems, when erythrocytes from healthy volunteers were isolated, the ESR increased when albumin was added to a mixture of fibrinogen and immunoglobulin; however, in the same system and in hypoalbuminemic plasma, the addition of albumin decreased the ESR. Thus, in clinical situations in which the albumin is normal, the ESR will only be affected by the level of acute phase reactants such as fibrinogen, whereas in hypoalbuminemic inflammatory states the ESR may be more elevated than if the serum albumin was normal.¹³

On the other hand, a change in the frictional forces around the red blood cell can affect the ESR. A drop in the red cell number, as in anemia, slightly elevates the ESR since this also physically interferes with rouleaux formation.^{4,11} Macrocytosis with a small surface-to-volume ratio have charge relative to their mass and thus sediment more rapidly.⁴ In general, normal values are 15 mm/hr or less for men and 20 mm/hr or less for women.^{4,11}

EFFECT OF AGE AND RACE

Normal ESR values increase with age³ and a formula for calculating the maximal normal ESR at any age has been proposed.⁴ A study by Caswell et al¹⁴ showed that the highest normal ESR values are among those aged 65 years to 74 years. Using the same reference range for old and young, however, has also been suggested.³ The probability of disease at any age increases with increased ESR and becomes more significant when the ESR exceeds 50 mm/hr.^{3,15} It appears that age alone has only a marginal effect, if any, on the ESR. In blacks, normal values of the ESR are at least 2 mm/hr to 13 mm/hr higher even after correcting for age, hemoglobin concentration, and certain chronic diseases.^{16,17}

INDICATORS OF INFLAMMATORY RESPONSE OTHER THAN ESR

There are tests other than ESR that measure acute phase responses, but these tests have limitations. These include the following:

Plasma Viscosity. This is a readily available test but with a limited role in the measurement of acute phase response. It is significantly affected by long-term changes of

chronic disease and has a weaker response to acute inflammatory conditions than the ESR.³

C-reactive Protein (CRP). This test is comparable to the ESR when used for screening elderly patients, but it is more expensive. In a prospective trial from the Netherlands, general practitioners found no diagnostic gain from CRP measurements as compared with the ESR.¹⁸ The CRP, however, may complement the ESR in the monitoring of chronic inflammation as in rheumatoid arthritis.³

Cytokines. Cytokines are glycoproteins produced by different cells involved in the immune response. They enhance or regulate inflammation by acting on different cells of the immune system. Some of these cytokines are pro-inflammatory and may be a measure of the inflammatory response. Their measurement, however, is more tedious than the ESR, takes longer time, and is more expensive.¹⁹ Some of these cytokines are interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-alpha). In a double-blind, randomized study involving 267 patients with rheumatoid arthritis treated with naproxen versus prinomide, elevated baseline levels of IL-6 did not change with treatment. The ESR and the CRP, however, decreased significantly in the prinomide treated patients.¹⁹ Interleukin-6 is also a more cumbersome and expensive test. Similarly, IL-1 alpha surface expression in active rheumatoid arthritis synovium correlated with the ESR in vitro.²⁰ In another controlled prospective study of 40 patients with juvenile chronic arthritis, soluble levels of TNF receptors were useful in monitoring disease flare-up.²¹ The future role of these glycoproteins in monitoring inflammatory conditions is uncertain, but appears to be promising. **At present, the ESR is still the easiest and most convenient way to monitor such activity.**

Others. Other proteins such as serum amyloid A and alpha-1 antitrypsin rise within 6 hours to 10 hours and 24 hours to 48 hours, respectively, in inflammation. These are expensive tests and their levels rarely rise above twofold, making them of very limited use in clinical practice.^{3,11}

THE ESR IN CLINICAL PRACTICE

Established Clinical Uses

Rheumatoid Arthritis (RA) and Other Autoimmune Conditions. Rheumatoid arthritis is a chronic inflammatory condition of unknown etiology whereby autoimmune destruction of the joints occurs usually in a symmetric fashion. The American College of Rheumatology has established criteria for the diagnosis of RA.⁴ ESR can aid in the diagnosis of RA, but it cannot be used solely for diagnosing RA. It is very useful when used with other parameters as outlined in the American College of Rheumatology guidelines, in the diagnosis and follow-up of RA patients.⁴ Wolfe and Michaud²² showed that the ESR can be elevated when RA is quiescent clinically and vice versa. The authors concluded that the ESR role in the diagnosis and follow-up of RA patients may not be accurate. An editorial comment on the study²³ emphasized that the ESR should not be used as an isolated test, but as part of a group of clinical criteria to diagnose and follow

patients with RA and inflammatory arthritis. The ESR is also helpful in the follow-up of systemic lupus erythematosus, but of questionable value, if any, in inflammatory myopathy or spondyloarthropathy.¹¹

Temporal Arteritis and Polymyalgia Rheumatica. Traditionally, the ESR is almost always elevated in both temporal arteritis and polymyalgia rheumatica. In temporal arteritis it may exceed 100 mm/hr.¹¹ However, recently it was emphasized that a normal ESR in patients with symptoms suggestive of either temporal arteritis or polymyalgia rheumatica or both should not rule out the diagnosis.²⁴ Fortunately, only a minority of patients have normal ESR.^{4,24,25} This does not diminish the value of ESR in the diagnosis and follow-up of these patients.⁴ It is important, however, to emphasize that if clinical features of temporal arteritis are present, such as headache with jaw claudication, a temporal artery biopsy is highly recommended even if the ESR is not elevated.²⁶

Multiple Myeloma and Other Paraproteins. The importance of ESR parallels that of plasma viscosity in these conditions.⁹ While an increased ESR is helpful in suspecting these conditions, the diagnosis depends on criteria such as monoclonal spike or serum electrophoresis, marrow plasmacytosis, and lytic bone lesions.²⁷ While data on ESR in benign monoclonal gammopathy are not well studied, it appears that in one recent study involving 684 patients with monoclonal gammopathy, the ESR was one of several parameters in which benign monoclonal gammopathy was separated from malignant multiple myeloma in those patients (mean ESR of 47 in the latter group and 28 in the former group with a $P < .001$). However, in this study the ESR was not the main distinguishing feature, but the proportion of plasma cells in the bone marrow. A bone marrow plasmacytosis of 20% or more was more predictive of multiple myeloma than the ESR.²⁸

USE IN ASYMPTOMATIC PATIENTS

The ESR should never be used as a screening test in asymptomatic patients.⁴ Normal ESR in general practice is more reassuring to the patient with minor and unrelated complaints.²⁹ A review of the literature on the diagnosis of low back pain using ESR revealed that ESR has a limited value in ankylosing spondylitis but significant in vertebral cancer when coupled with the history and physical examination.⁸ In another prospective trial, the ESR when normal was more reassuring to the patient and doctor when no pathology was suspected rather than in confirming the presence of inflammatory disease and malignancy.³⁰ The same study noted pathology in 68% (36 patients with pathology; ⁵³ patients with suspected pathology) of the time before the ESR was known to the doctor, and the ESR value when known confirmed the doctor's expectations. This is in agreement with previous findings that the ESR should serve only as a guide and not as a screen, and only in symptomatic patients.⁴ Current evidence also suggests that the ESR when elevated remains high until the primary inflammatory process is resolved.³¹ Therefore, an ESR ³ 100 even in asymptomatic patients should prompt the clinician to search for occult infection such as infectious mononucleosis, metastasis, or early temporal arteritis.³²

POTENTIAL NEW APPLICATIONS OF THE ESR

It may be difficult to conceive that an old test that has been used since ancient Greek times may have new potential uses in modern medicine. We will summarize some of the current literature data on the relevance of the ESR in some clinical conditions whereby both infection and inflammation is predominant and in few non-inflammatory conditions. These were only a few studies but they illustrate that the ESR may have uses in clinical practice more than what is expected from a simple, old test.

Bacterial Otitis Media. The ESR or CRP has been shown to be elevated in 55% of 31 patients with otitis media. The infection was documented by culturing the microorganism via tympanocentesis. These children were otherwise healthy. Most of them were afebrile (90%) and none of them was seriously ill or had signs of other bacterial infection during the study. Those with elevated ESR or CRP have a much higher risk for recurrence.³³ Since this study was small, a larger study is needed before confirming this data. These data, however, may indicate a unique systemic inflammatory response in some children with uncomplicated otitis media.

Acute Hematogenous Osteomyelitis in Children. In a prospective study of 48 children with acute hematogenous osteomyelitis, the ESR and CRP were both elevated (³ 20 mm/hr and > 19 mg/L, respectively) in 92% and 98%, respectively. Both declined rapidly with treatment. The decline in CRP was faster than that of the ESR. The white blood cell count was a poor predictor of recovery.³⁴ Although the authors favor CRP over ESR in the diagnosis and monitoring of osteomyelitis in children, in this study, the ESR still appears to be of major significance in this disease process. The ESR was elevated in all 44 patients and the CRP was elevated in all but one patient. Obviously, the ESR is of little value in the diagnosis of osteomyelitis, but when elevated in the presence of osteomyelitis, it can be of clinical significance to monitor the response to therapy.³⁵

Sickle Cell Disease (SCD). In sickle cell anemia, the ESR is usually low in the absence of a painful crisis.³⁶ In fact, a low ESR is an intrinsic property of the sickle red blood cell rheology.^{37,38} During a severely painful crisis that requires hospitalization and that is not complicated by infection, the ESR is moderately increased during the 4th and last stage of the crisis known as the resolving phase. This phase occurs approximately one week into the crisis.³⁶ In another recent study, in patients with fever, SCD, and hospitalization, an elevated ESR raises the suspicion of bacterial infection. In 32 children with SCD and an elevated ESR (> 21 mm/hr), 72% had documented bacterial infection in contrast with 23% of 31 children with SCD whose ESR at admission was < 20 mm/hr.³⁹ Both groups had similar levels of mean hemoglobin to control for the anemia effect on ESR levels. In this study in contrast to uncomplicated painful crisis, the ESR was elevated at presentation.

Acquired Immune Deficiency Syndrome (AIDS). The ESR determination in a prospective study of 447 human immunodeficiency virus (HIV) infected patients was a predictor of the development of AIDS, but only when coupled with a CD4 count of < 500 x 10⁶/mL and an elevated b2-microglobulin. In this study, an ESR ³ 9 mm/hr was

considered clinically significant.⁴⁰ The authors suggest that the elevated ESR may be a reflection of advanced immune deficiency and the resultant increase in severe opportunistic infections. A major critique of this study is that an abnormal ESR of 9 is still within the normal range. In addition, the ESR is only of additional, perhaps minor, value in predicting the progressing to AIDS.

Pelvic Inflammatory Disease. In 72 women with pelvic inflammatory disease, 35 had severe disease. The ESR and CRP were both elevated with a positive predictive value of 70%. An ESR ³ 40 mm/hr or a CRP of ³ 60 mg/L had high sensitivity and specificity for severe disease.⁴¹ Although this is a small study, the ESR and CRP levels were found to be of significantly logistic regression analysis.

Febrile Intravenous Drug Users. In 106 intravenous drug users who were febrile, an ESR ³ 100 mm/hr was found to be the only variable associated with severe illness requiring intensive care unit monitoring or even hospitalization.⁴² In this study, however, it was also noted that a normal ESR may still be associated with serious infection. Thus, a high ESR in these patients is a strong positive predictor for a serious infection, but the reverse may be true.

Prostate Cancer. In a prospective follow-up of 300 population-based, consecutive patients, an ESR ³ 37 mm/hr was associated with a higher incidence of disease progression and death. These findings were synergistic with other factors such as M and T categories, grade, performance status, hemoglobin level and age.⁵ Whether this finding will continue to hold true will need to be determined in larger population-based studies.

Coronary Artery Disease. In the National Health and Nutrition Examination Survey I, a slight rise in the ESR in white men aged 45 years to 64 years was found to be a high risk for coronary artery disease after 15 years of follow-up. This finding was independent of other risk factors. The risk was highest when the ESR was > 22. It was hypothesized that an elevated ESR when present is associated with elevated blood fibrinogen levels, which might facilitate atherogenesis.⁶ This is a large-based population study and this finding is interesting and may be significant.

Early Predication of Stroke Severity. A prospective evaluation of 208 patients with ischemic stroke revealed that infarct size and clinical severity on admission were strong predictors of short-term functional outcome. However, the ESR was also an independent predictor of short-term stroke outcome. An ESR ³ 28 was associated with a poorer prognosis.⁷ This study is a preliminary study; nevertheless, the statistical analysis was excellent and the findings on the ESR role on prognosis in stroke poses an interesting finding.

CONCLUSION

The ESR is an old, inexpensive, yet still widely used test. Since the review by Sox and Liang,⁴ there has not been a general review on the guidelines for the use of this test. The test has a role in rheumatoid arthritis, temporal arteritis, polymyalgia rheumatica, and

myeloma. It may have an additional role in follow-up of patients with otitis media, osteomyelitis, sickle cell disease, HIV, pelvic inflammatory disease, intravenous drug users, prostate cancer, coronary artery disease, and stroke. The ESR can be helpful in patients with symptoms. The ESR, however, should only be used as a guide. The clinician, when ordering an ESR, should realize that this test is only one parameter that could be helpful in the diagnosis and follow-up of certain inflammatory conditions. The ESR can also have an important prognostic role in noninflammatory conditions such as prostate cancer, stroke, and coronary artery disease. Thus, we continue to learn about this old yet still important test even today. We present a summary of the clinical usefulness of the ESR in the Table.

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