

Review

Clinical utility of the erythrocyte sedimentation rate

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The erythrocyte sedimentation rate (ESR) determination is a commonly performed simple and inexpensive laboratory test with various acclaimed diagnostic implications. While the test remains helpful in the specific diagnosis of a few conditions, there is diverse opinion on the exact significance and implications of an elevated ESR. This paper examines the physiological basis, the diagnostic significance, the emerging alternatives of monitoring disease activity, various factors and determinants of this simple and inexpensive laboratory tool. Literature on the subject was reviewed using manual library search, electronic books such as CD-ROMS and journals articles published by various authors on the subject; it also included internet search on relevant aspects of the topic. The ESR is helpful in the specific diagnosis of a few conditions, notably temporal arteritis, polymyalgia rheumatica and possibly rheumatoid arthritis. It may predict relapse in patients with Hodgkin's disease. An extreme elevation of the ESR is strongly associated with serious underlying disease. When an increased ESR is encountered with no obvious clinical explanation, the physician should repeat the test after an appropriate interval rather than pursue an exhaustive search for occult disease. The usefulness of the ESR is becoming limited as a result of low sensitivity and specificity and emergence of new methods of evaluating disease. Nevertheless, it still remains a key diagnostic criterion for a few conditions.

Key words: Clinical, utility, erythrocyte, sedimentation, rate.

INTRODUCTION

The erythrocyte sedimentation rate (ESR) determination is a simple and inexpensive laboratory test that is frequently ordered in clinical medicine (Saadeh, 1998; Dacie and Lewis, 1994; Brigden, 1998). The test measures the distance that erythrocytes have fallen after one hour in a vertical column of anticoagulated blood under the influence of gravity.

PHYSIOLOGIC BASIS FOR ERYTHROCYTE SEDIMENTATION RATE (ESR)

The phenomenon of erythrocyte sedimentation and the basic factors influencing it have been exhaustively investigated by many scholars (Brigden, 1998; Bull, 1981; Hardwick and Squire, 1982); the amount of fibrinogen in the blood directly correlates with the ESR. Other factors which affect erythrocyte sedimentation include the difference in specific gravity between red cells and plasma, ratio of red cells to plasma, that is, the packed cell volume, the plasma viscosity, the verticality or otherwise of the sedimentation tube, the bore of the tube and the dilution, if any, of the blood. The most

satisfactory method of performing the test was introduced by Westergren in 1921 (Saadeh, 1998; Dacie and Lewis, 1994). Although, there is an enormous body of literature concerning the ESR, an elevated value remains a non-specific finding (Sox and Liang, 1986). Reference ranges for the ESR are stated in Table 1 (Bottiger and Svedberg, 1967). As with other laboratory tests, the actual reference range used for the ESR should be established by the laboratory performing the test. Women tend to have higher ESR values, as do the elderly (Brigden, 1998). The higher values in females correlate with sex differences in fibrinogen levels. In women, the ESR is specifically influenced by the stage of the menstrual cycle. For unknown reasons, obese people have also been noted to have slightly elevated ESRs, although this is not thought to have clinical significance (Sox and Liang, 1986).

Other factors that may influence the ESR are detailed in Table 2. Any condition that elevates fibrinogen (e.g., pregnancy, diabetes mellitus, end-stage renal failure, heart disease, collagen vascular diseases, malignancy) may also elevate the ESR (Brigden, 1998). Anaemia and macrocytosis increase the ESR. In anaemia, with the

Table 1. Reference ranges for the ESR in healthy adults.

Adults	Upper limit of reference range (mm/hr)
Age < 50 years	
Men	0 - 15
Women	0 - 20
Age > 50 years	
Men	0 - 20
Women	0 - 30

ESR=Erythrocyte sedimentation rate (Adapted after Bottiger, 1967).

Table 2. Factors that may influence ESR.

Factors that increase ESR	Factors that decrease ESR	Factors with no clinically significant or questionable effect
Old age	Extreme leucocytosis	Obesity
Female	Polycythaemia	Body temperature
Pregnancy	Spherocytosis	Recent meal
Anaemia	Acanthocytosis	Aspirin
Macrocytosis	Microcytosis	NSAIDs
Technical factors	Technical factors	
Dilutional problem-overdilution	Dilutional problem-underdilution	
Increased temperature of specimen	Inadequate mixing clotting of blood sample	
Tilted ESR tube	Short ESR tube	
Elevated fibrinogen level	Vibration during testing	
Infection	Hypofibrinogenaemia	
Inflammation	Hypogammaglobulinaemia	
Malignancy	Dysproteinaemia	

NSAID = Non steroidal anti-inflammatory drugs, ESR= Erythrocyte sedimentation rate (Adapted after Hardwick and Squire, 1982).

haematocrit reduced, the velocity of the upward flow of plasma is altered so that red blood cells sediment faster. Macrocytic red cells with a smaller surface-to-volume ratio also settle more rapidly. A decreased ESR is associated with a number of blood diseases in which red blood cells have an irregular or smaller shape that causes slower settling (Saadeh, 1998; Brigden, 1998). In patients with polycythaemia, too many red blood cells decrease the compactness of the Rouleau network and artifactually lower the ESR. An extreme elevation of the white blood cell count as observed in chronic myeloid leukaemia has also been reported to lower the ESR (Stuart and Whicher, 1988). Hypofibrinogenemia, hypergammaglobulinemia associated with dysproteinemia, and hyperviscosity may cause a marked decrease in the ESR. Although, it has been reported that drug therapy with aspirin or other nonsteroidal anti-inflammatory agents may decrease the ESR, this has been disputed (Sox and Liang, 1986).

Precaution must be taken when performing ESR to avoid factors that may produce erroneous values (Table 2). A tilted ESR tube will cause an artifactual elevation, whereas inadequate anticoagulation with clotting of the blood sample will consume fibrinogen and may artifactually lower the ESR (Saadeh, 1998). Researchers have wondered whether other tests, such as measurement of C-reactive protein, may perform better than the ESR (Miettinen et al., 1993; Katz et al., 1990). Repeatedly, the ESR and plasma viscosity determinations have been shown to be the most satisfactory monitors of acute phase response to disease after the first 24 h (Katz et al., 1990). During the first 24 h in an inflammatory process, C-reactive protein may be a better indicator of the acute phase response (Miettinen et al., 1993). However, C-reactive protein tests are more expensive, less widely available and more time-consuming to perform than the ESR (Katz et al., 1990). Advantages and disadvantages of these three tests are

Table 3. Comparison of the ESR, C - reactive protein and plasma viscosity tests.

Test	Advantages	Disadvantages
ESR	Inexpensive, quick, simple to perform	Affected by a variety of factors including anaemia and red cell size, not sensitive enough for screening.
C-reactive protein	Most rapid response to inflammation (complementary to ESR in this regard)	Wide reference range may necessitate sequential recording of values, expensive, batch processing may delay individual results.
Plasma viscosity	Unaffected by anaemia or red blood cell size	Expensive, not widely available, technically cumbersome to perform.

summarized in Table 3.

DIAGNOSTIC USE OF THE ERYTHROCYTE SEDIMENTATION RATE (ESR)

The ESR remains an important diagnostic criterion for polymyalgia rheumatica and temporal arteritis (Wise et al., 1991; Fauchald et al., 1972; Goodman, 1979). Nearly all patients who have temporal arteritis will have an elevated ESR; however, an occasional patient may present with a normal value (Wise et al., 1991). One study found that the average ESR was greater than 90 mm per hour in patients who had temporal arteritis, with values exceeding 30 mm per hour in 99% of the cases (Huston et al., 1978). However, if there is solid clinical evidence of temporal arteritis, a normal ESR value should be disregarded and the patient should undergo a temporal artery biopsy or an empiric trial of corticosteroid therapy (Wise et al., 1991).

The ESR traditionally has been a diagnostic parameter for rheumatoid arthritis, but it is used as a means of staging the disease rather than as one of the major diagnostic criteria (Weinstein, 1994). The American Rheumatism Association criteria include an elevated ESR as one of 20 findings that may be present (Sox and Liang, 1986). Most rheumatologists believe that careful joint examination confirming synovitis constitutes a more important diagnostic criterion. However, the ESR may still be useful if the diagnosis is questionable and definite evidence of inflammation might affect therapeutic decisions (Weinstein, 1994). In tuberculosis, the ESR provides an index of progress of the disease and it is also useful as a screening test in the routine examination of patients. An elevated ESR occurs as an early feature in myocardial infarction (Froom et al., 1984). Although, a normal ESR can not be taken to exclude the presence of an organic disease, the fact remains that the vast majority of acute and chronic infections and most neoplastic and degenerative diseases are associated with changes in plasma proteins, which leads to an acceleration of erythrocyte sedimentation.

ERYTHROCYTE SEDIMENTATION RATE IN SPECIFIC CLINICAL SETTINGS

Oncology diseases

In oncology, a high ESR has been found to correlate with overall poor prognosis for various types of cancer, including Hodgkin's disease, gastric carcinoma, renal cell carcinoma, chronic lymphocytic leukemia, breast cancer, colorectal cancer and prostate cancer (Ljungberg et al., 1995; Johansson et al., 1992; Henry-Amar et al., 1991). In patients with solid tumors, a sedimentation rate greater than 100 mm per hour usually indicates metastatic disease, but for most tumors this relatively nonspecific finding has been supplanted by more precise diagnostic tests. However, studies of patients with Hodgkin's disease have suggested that an elevated ESR may still be an excellent predictor of early relapse, especially if the value remains elevated after chemotherapy or fails to drop to a normal level within six months after therapy (Henry-Amar et al., 1991). Certainly, an increased ESR should never be used as the sole criterion for diagnosing relapsed Hodgkin's disease.

Chronic inflammatory conditions

The ESR may be useful in differentiating iron deficiency from anaemia of chronic disease in patients with a background chronic inflammatory condition such as rheumatoid arthritis (Brigden, 1993; Witte et al., 1988). Iron deficiency anaemia and anaemia of chronic disease are hyporegenerative and characterized by a low reticulocyte count. Because both may have a transferrin saturation of around 15%, simply evaluating the serum iron level and percent saturation will not differentiate between the two conditions. Similarly, an individual serum ferritin level may not be helpful when inflammation is present because ferritin is an acute phase reactant and may be artifactually elevated (Brigden, 1993). In the past, the final arbitrator in this situation has been bone marrow

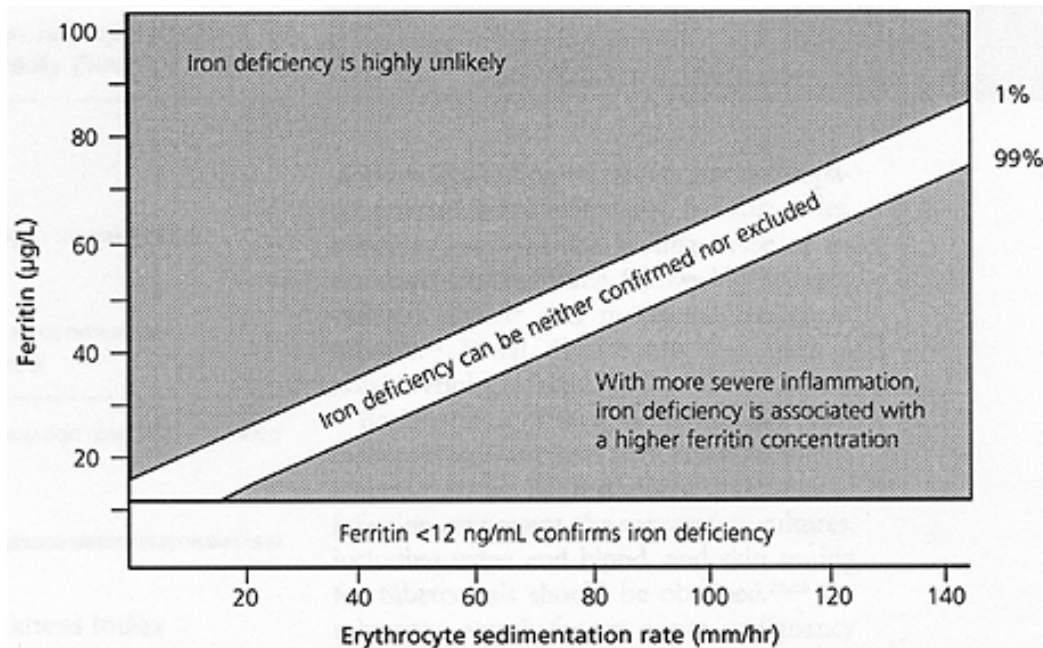


Figure 1. A nomogram to verify the presence or absence of iron deficiency coexistent with an underlying inflammatory condition by correlating serum ferritin level with degree of inflammation as evidenced by the erythrocyte sedimentation rate (Froom et al., 1984).

aspiration with Prussian blue staining to determine the presence of iron. The probability of iron deficiency can usually be established by correcting an individual ferritin value for the degree of coexistent inflammation as indicated by the ESR (Witte et al., 1988). A nomogram for this purpose is provided in Figure 1 (Froom et al., 1984).

Screening for systemic disease or neoplasia

Unfortunately, the ESR is neither sensitive nor specific when used as a general screening test (Smith and Samadian, 1994). For instance, the ESR may be elevated in the presence of infectious disease, other inflammatory or destructive processes, collagen vascular disease or malignancy (Sox and Liang, 1986), but it may not be increased in a number of infectious diseases (e.g., typhoid fever, malaria, mononucleosis), allergic processes, angina (as opposed to myocardial infarction) or peptic ulcer disease (as opposed to active inflammatory bowel disease).

An elevated ESR may occur in so many different clinical settings; hence, this finding is meaningless as an isolated laboratory value. In addition, some patients who have malignant tumors, infections or other inflammatory disorders will have normal ESR values. Most unexplained ESR elevations are short-lived and not associated with any specific underlying process. In those instances where disease is present, it will usually be obvious after completion of history taking, physical examination and

collection of routine laboratory data (Sox and Liang, 1986).

Although, an elevated ESR may occur with many types of cancer, it rarely indicates an occult tumor because most of these patients have widely metastatic disease (Henry-Amar et al., 1991). For this reason, when a mild to moderate elevation of the ESR (less than 100 mm per hour) is encountered in an asymptomatic patient, simply repeating the test at some future time should be considered in the absence of other clinical findings (Sox and Liang, 1986). No diagnostic evidence exist that suggests that an elevated ESR that is unsubstantiated by history, physical examination or other findings should trigger an extensive laboratory or radiographic work-up or invasive diagnostic procedures (Sox and Liang, 1986).

Screening for infection in specific clinical settings

Recent studies have evaluated the ESR as a screening test for infection in specific clinical instances such as infection associated with orthopedic prostheses, pediatric bacterial infection and gynecologic inflammatory disease (Thoren and Wigren, 1991). Although, frequently abnormal in patients who have an infected prosthesis, the ESR value is not as sensitive or specific an indicator of infection as joint aspiration (Thoren and Wigren, 1991). Elevation of the ESR has been proposed as a clue to the presence of an invasive bacterial infection in children after the first 48 h of symptoms (Stuart and Whicher, 1988). In one investigation (Miettinen et al., 1993), the

ESR more accurately indicated the severity of acute pelvic inflammatory disease than did the physical examination, thus helping to evaluate patients who required antimicrobial therapy. The appropriateness of the ESR as a screening test for infection, even in these well-defined clinical settings, requires further evaluation.

Usefulness as a sickness index in the elderly

Some authors have proposed that the ESR be used as an inexpensive "sickness index" in the elderly (Tinetti et al., 1986). In a study of 142 residents of a long-term care hospital who had a nonspecific change in health status or developed new musculoskeletal complaints, the post-test probability of new disease rose from 7% in those with an ESR of less than 20 mm per hour to 66% in those with an ESR of more than 50 mm per hour. However, this investigation specifically excluded patients known to have an ESR-elevating disease and those in whom no disease was suspected (Tinetti et al., 1986). The authors concluded that combining clinical evaluation with an individual ESR value allowed the identification of groups of patients in whom the likelihood of disease was quite low or reasonably high, possibly limiting unnecessary investigations.

Extreme elevation of the erythrocyte sedimentation rate

An extreme elevation of the ESR (defined as greater than 100 mm per hour) is associated with a low false-positive rate for a serious underlying disease (Fincher, 1986; Lluberas-Acosta, 1996). The conditions found in this situation have varied in individual populations, depending on patient age and inpatient versus outpatient status. In most series, infection has been the leading cause of an extremely elevated value, followed by collagen vascular disease and metastatic malignant tumors (Fincher and Page, 1986). Renal disease has also been a notable aetiological factor (Sox and Liang, 1986). Since most of these conditions are clinically apparent, any tests performed should be clinically driven.

For instance, if symptoms of infection are present, the appropriate cultures, including urine and blood, and skin testing for tuberculosis should be obtained (Lluberas-Acosta and Schumacher, 1996). An exhaustive search for an occult malignancy should not be undertaken because, if cancer is present, it is almost always metastatic (Saadeh, 1998). No obvious cause is apparent in fewer than 2% of patients with a markedly elevated ESR. In such patients, the history and physical examination coupled with readily available tests (Table 4) will usually establish the aetiology. Because a notable number of patients with an ESR greater than 100 mm per hour have myeloma or some other type of dysproteinemia, urine and serum protein electrophoretic studies should be

included in the testing (Brigden, 1998).

CONCLUSION

The ESR is a simple and inexpensive test of chronic inflammatory activity, whose usefulness is becoming limited as a result of low sensitivity and specificity and emergence of new methods of evaluating disease. Nevertheless, it still remains a key diagnostic criterion and monitoring test for a few conditions. Outside this, and despite the enormosity of body of literature concerning ESR, an elevated ESR remains a non specific finding, if not meaningless, as an isolated laboratory finding. In developing countries like ours, emphasis is still placed on ESR for obvious reasons. It is unfortunate that most of the new methods of disease evaluation that could replace the ESR are still far from our reach, at least for now. Be that as it may, while physicians continue to utilize the ESR as an ancillary/ supportive tool in diagnosis, they must not lose sight of its associated setbacks and limitations. Suffice to say that it is time to ensure the availability of new methods of disease evaluation in our environment.

Using the ESR to make diagnosis: Key considerations

1. The ESR is an inexpensive, simple test of chronic inflammatory activity.
2. Indications for the ESR have decreased as the sophistication of laboratory testing has increased.
3. The ESR rises with age, but this increase may simply reflect higher disease prevalence in the elderly.
4. The use of the ESR as a screening test in asymptomatic persons is limited by its low sensitivity and specificity.
5. An elevated ESR is a key diagnostic criterion for polymyalgia rheumatica and temporal arteritis, but normal values do not preclude these conditions.
6. When there is a moderate suspicion of disease, the ESR may have some value as a "sickness index."
7. An extremely elevated ESR (>100 mm/h) will usually have an apparent cause--most commonly infection, malignancy or temporal arteritis.
8. A mild to moderately elevated ESR without obvious etiology should prompt repeat testing after several months rather than an expensive search for occult disease.

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