EDUCATIONAL COMMENTARY – THE ERYTHROCYTE SEDIMENTATION RATE AND ITS CLINICAL UTILITY

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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- Describe the principles and performance of the erythrocyte sedimentation rate (ESR) test.
- Discuss the importance and clinical utility of the ESR.
- Discuss different methods of ESR measurement and factors affecting ESR measurements.

The erythrocyte sedimentation rate (ESR) is the rate at which erythrocytes settle in a vertical column of anticoagulated blood in 60 minutes. The ESR is also called the sed rate or sedimentation rate. The ESR was invented in 1897 by the Polish physician Edmund Biernicki and modified and popularized by Farhraeus, Westergren, Wintrobe, and others. It is one of the oldest laboratory tests still in wide use, despite being nonspecific. It is simple, inexpensive, and has a time-honored role, although its usefulness is decreasing with the advent of new laboratory tests and other diagnostic modalities.

Test Principle

The basic principle of the ESR is that when anticoagulated blood is placed in a vertical column the RBCs normally settle quite slowly. This occurs for 2 main reasons: (1) RBCs repel each other due to the negative charges on their surfaces, or zeta potential, and (2) the large surface-area-to-volume ratio of normal RBCs resists settling. The aggregation of RBCs into rouleaux, which happens slowly under normal conditions, markedly accelerates sedimentation by decreasing the surface-area-to-volume ratio. Conditions that promote the formation of rouleaux produce an elevated ESR.

The most common promoter of rouleaux is increased plasma fibrinogen. Fibrinogen's positive charge decreases the RBCs' zeta potential, leading to increased rouleaux and an increased ESR. In fact, the clinical utility of the ESR is largely attributable to increased fibrinogen in acute-phase reactions and chronic inflammatory conditions.

The ESR may be elevated by other conditions that decrease the zeta potential or the RBC surface-area-to-volume ratio. The zeta potential is reduced by other plasma proteins, including immunoglobulins, as well as cholesterol, phospholipids, and some medications. By creating more space between RBCs, anemia reduces the effect of the zeta potential to slow sedimentation. Decreases in the surface-area-to-volume ratio, as in macrocytosis, also increase the ESR.

The ESR may be decreased by conditions that interfere with the formation of rouleaux or increase the RBC surface-area-to-volume ratio. Rouleaux formation is hindered by spherocytosis, sickle cell disease, microcytosis, marked variation in RBC size (anisocytosis), and some drugs. Polycythemia decreases the compactness of rouleaux formation. The surface-area-to-volume ratio is increased in some thalassemias and hemoglobinopathies.

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Technical factors also influence the ESR. RBCs settle more quickly in nonvertical tubes and with vibration. RBCs become more spherical as specimens age, decreasing the ESR.

Some causes of increased and decreased ESRs are listed in the **Table** below.

TABLE. ***Factors Affecting the Erythrocyte Sedimentation Rate (ESR).***

Category	***Increased ESR***	***Decreased ESR***
Blood proteins & lipids	Hypercholesterolemia Hyperfibrinogenemia Hypergammaglobulinemia Hypoalbuminemia	Hyperalbuminemia Hyperglycemia Hypofibrinogenemia Hypogammaglobulinemia Increased bile salts Increased phospholipids
RBCs	Anemia Macrocytosis	Acanthocytosis Anisocytosis (marked) Hemoglobin C Microcytosis Polycythemia Sickle cells Spherocytosis Thalassemia
WBCs	Leukemia	Leukocytosis (marked)
Drugs	Dextran Heparin Penicillamine Procainamide Theophylline Vitamin A	ACTH Corticotropin Cortisone Ethambutol Quinine Salicyclates
Clinical conditions	Acute heavy metal poisoning Acute bacterial infections Collagen vascular diseases Diabetes mellitus End-stage renal failure Gout Malignancy Menstruation Multiple myeloma Myocardial infarction Pregnancy Rheumatic fever Rheumatoid arthritis Syphilis Temporal arteritis	Cachexia Congestive heart failure Newborn
Specimens	Refrigerated sample not returned to room temperature	Clotted blood sample Delay in testing
Technique	High room temperature Tilted ESR tube Vibration	Bubbles in ESR column Low room temperature Narrow ESR column diameter

Clinical Use of the ESR

As a nonspecific test, the ESR has inherent limitations in its clinical utility; however, in some clinical contexts the ESR may provide valuable information for screening, diagnosis, and monitoring disease activity or therapeutic response.

Screening

Asymptomatic Patients

Although the ESR has been used in the past as a general screening test, clinical trials have not demonstrated any value of the ESR for screening asymptomatic individuals. Not only is the number of abnormal results low, but also the abnormal results in most cases return to normal over several months without any significant diagnosis being made. A complete history and physical examination is a much better screen than an ESR.

Nonspecific Symptoms

An elevated ESR in the presence of nonspecific symptoms may help justify or direct further evaluation because moderate elevations of the ESR are common in infections, inflammatory diseases, and neoplasia. A normal ESR, however, does not exclude active disease.

Diagnosis

The ESR is a useful aid in establishing the diagnosis of several diseases.

Temporal Arteritis and Giant Cell Arteritis

Temporal arteritis, a giant cell arteritis involving the temporal arteries, is a medical emergency. Unless treatment is instituted within a few hours, there is a high risk of ophthalmic arterial thrombosis, leading to blindness. The definitive diagnosis is made by histologic examination of a temporal artery biopsy, but this examination cannot generally be performed quickly enough to guide initial therapy. In patients with temporal arteritis, the average ESR is >90 mm/h (Westergren method) and exceeds 30 mm/h in 99%. When symptoms of temporal arteritis are present, an elevated ESR—particularly a highly elevated ESR—indicates that corticosteroid therapy should be started immediately.

Giant cell arteritis may affect a variety of arteries other than the temporal artery, often with vague symptoms. A very high ESR may be an important clue to the diagnosis.

Polymyalgia Rheumatica

Polymyalgia rheumatica and giant cell arteritis are thought to represent a spectrum of one disease, but the signs and symptoms of polymyalgia rheumatica—stiffness and pain in the shoulders, hips, and lower back, with malaise, anemia, and an elevated ESR—may occur without giant cell arteritis. Polymyalgia rheumatica is a clinical diagnosis made after excluding other rheumatic diseases, systemic vasculitides, malignancies, and chronic infections.

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Other Inflammatory Diseases

The ESR is used in the emergency department setting in the evaluation of suspected appendicitis, pelvic inflammatory disease, septic arthritis, and other inflammatory diseases.

Monitoring

The ESR continues to be used as an aid in monitoring the activity of selected inflammatory diseases.

Temporal Arteritis and Polymyalgia Rheumatica

The ESR is usually highly elevated in these patients. A significant decrease in the ESR, in combination with improved clinical status, is indicative of a therapeutic response. Sustained elevation of the ESR, even with symptomatic improvement, suggests a poor response to therapy.

Rheumatoid Arthritis

Only 5% to 10% of patients with rheumatoid arthritis have a normal ESR. The ESR generally parallels disease activity and mirrors other symptoms. A sustained elevation of the ESR is associated with a poor prognosis.

Other Collagen Vascular Diseases

As with rheumatoid arthritis, the ESR generally parallels disease activity with other collagen vascular diseases.

Neoplastic Diseases

A high ESR has been found to correlate with an 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. In patients with solid tumors, an ESR >100 mm/h usually indicates metastatic disease, but for most tumors this relatively nonspecific finding has been supplanted by more precise diagnostic tests.

ESR Test Methods

Many test methods and supplies are commercially available for performing the ESR. Each method has its own characteristics, and the results from different ESR methods should generally not be considered interchangeable. Most testing is done with so-called “standard” Westergren or Wintrobe methods, while some is performed by alternate methods.

“Standard” Methods

Two classical methods, Westergren and Wintrobe, originally included strict specifications for specimen anticoagulants as well as column heights and diameters. Over the years, a variety of modifications have been introduced in specimen requirements and column dimensions, but most vendors have continued to use the names Westergren or Wintrobe somewhere in their naming conventions, usually to identify the height of the column, with Westergren being longer and Wintrobe being shorter, rather than to imply that the testing

method is classical Westergren or Wintrobe. It is important to gather information about the comparability of a commercial ESR method with a reference method. (See the Clinical and Laboratory Standards Institute document listed in the bibliography.)

Modified Westergren Method

The most commonly used method today is a modified Westergren method. EDTA-anticoagulated blood is diluted 4:1 with sodium citrate or sodium chloride solutions and placed in a 200-mm column with an internal diameter of 2.55 mm or greater. Sometimes this is referred to simply as the Westergren method. Favorable attributes of the modified Westergren method include: (1) convenience of using EDTA blood, as for other hematology testing, (2) highly elevated ESRs can be detected due to the tall column height, and (3) this method is recommended by the International Council for Standardization in Hematology (Expert Panel on Blood Rheology) and the Clinical and Laboratory Standards Institute.

Wintrobe Method

Another commonly used method is the Wintrobe method. Originally, the Wintrobe method utilized oxalate-anticoagulated whole blood placed into a 100-mm column. Today "Wintrobe" generally means only that a shorter column is used than in the Westergren method. EDTA or citrated whole blood are often used. The Wintrobe method is considered to have increased sensitivity for detecting mildly elevated ESRs, but marked elevations are hard to detect due to the short column height. The reference range for the Wintrobe method is lower than for the modified Westergren method.

Alternate Test Methods

The desire for alternate methods is driven primarily by 2 characteristics of the standard methods: (1) long analytical time (60 minutes sedimentation time plus setup and reading times), and (2) requirements for relatively large specimen volumes (1.0-2.0 mL). Additional considerations are the need for diluting specimens and the elevation of the ESR by anemia.

Zeta Sedimentation Ratio (ZSR)

A centrifugal device (Zetafuge [Coulter Electronics, Hialeah, FL]) spins capillary tubes filled with blood in a vertical position in four 45-second cycles, accelerating the formation of rouleaux and RBC sedimentation. The capillary tube is then read as a microhematocrit, giving a value called the zetacrit. The true hematocrit is divided by zetacrit, and the result is the ZSR. The ZSR method can be completed in a few minutes, requires only 100 μL of blood, is not affected by anemia, and correlates reasonably well with the Westergren method when the ESR is only mildly or moderately elevated. Its drawbacks are the requirement for special equipment (which is no longer produced) and the "drop-off" of results at high values in comparison with the Westergren method.

VES-matic ESR

The VES-matic family of systems contains several modifications of the Westergren method. One mL of whole blood is collected into a special tube containing enough sodium citrate to both anticoagulate and dilute

the blood in the 4:1 modified Westergren ratio. The tube is placed on a reader where it is held at an angle of 18º off vertical to accelerate sedimentation. An infrared reader determines the endpoint after 20 minutes. The VES-matic ESR results correlate well with the modified Westergren results and offer advantages of improved timeliness and less specimen handling. Drawbacks include the need for specialized equipment and specimen tubes.

Micro-ESR

The basis of the micro-ESR method is the reduction of the required specimen volume by using a column with an internal diameter of only 1 mm rather than the 2.5 mm or more of a standard method. One micro-ESR method uses a column 230 mm long while another uses a 75-mm column. Both methods are targeted for pediatric use, where a reduction in specimen volumes is highly desirable. Correlation studies versus standard methods have produced mixed results.

Other Alternatives

New methods are continually being introduced commercially. The primary aim is to shorten the test time, but simplifying the test procedure and reducing specimen volumes are additional considerations. Before a laboratory introduces a new method, its benefits, limitations, and comparability with standard methods should be understood.

Summary

The ESR is one of the oldest and simplest laboratory tests still in common use. Its clinical value is derived primarily from its elevation by increased concentrations of fibrinogen and immunoglobulins, but the utility is limited by its clinical nonspecificity and its being affected by a large number of technical and physiological variables. The ESR is useful in the evaluation and monitoring of temporal arteritis, polymyalgia rheumatica, and other inflammatory conditions, and in the evaluation of nonspecific symptomatology. Many methods are available for measuring the ESR, but with different performance characteristics and different levels of comparability with recommended methods.

Suggested Reading

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