

MEMO TO USERS OF MEDLAB CENTRAL SERVICES FROM:

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Re: ESR testing

Although the Erythrocyte Sedimentation Rate (ESR) has a long tradition of use in clinical medicine, we have become increasingly concerned about the validity of using the results of ESR testing to guide clinical management. Many clinicians will be familiar with the physiological variables and diseases that can affect this measurement, summarized in the attached document entitled *Laboratory Testing for Inflammation*. However, they are probably not aware of:

- the considerable variation between results obtained with different methods
- the very poor precision of this test
- the lack of any suitable material for quality assurance.

Because of these issues we do not have confidence in the reliability of the results reported for this test, making the ESR unique among the tests that we currently perform in the haematology laboratory.

Traditionally, the ESR has been used in two broad clinical contexts:

1. *Screening for the presence of paraproteins when a diagnosis of multiple myeloma, Waldenstrom macroglobulinaemia or monoclonal gammopathy of uncertain significance is suspected.* The laboratory tests of choice in these circumstances are serum protein electrophoresis and a serum free light chain assay. The ESR is not an appropriate test in these circumstances because of its lack of specificity and quality assurance problems outlined above.
2. *Assessing the acute phase response, when inflammatory disease is suspected.* The laboratory test of choice for assessing the acute phase response is the C-reactive protein (CRP). It is acknowledged that, in a few clinical circumstances, the ESR may provide additional information, provided that the limitations of the test are borne in mind.

Because of this, from 5 April 2010 Medlab Central will only process a request for an ESR if the request has been discussed with a haematologist, or if one of the following indications is documented legibly on the request form:

- SLE
- Rheumatoid arthritis
- Kawasaki disease
- Rheumatic fever
- Hodgkin lymphoma

A CRP will be substituted when an ESR has been requested without these criteria being met, provided that an appropriate sample has been received.

LABORATORY TESTING FOR INFLAMMATION

Acute phase reactants are proteins whose concentration changes by >25% in the presence of inflammation (acute or chronic). Positive acute phase proteins increase in inflammation and include CRP, fibrinogen, serum amyloid A, alpha-1 antitrypsin, haptoglobins and ferritin. Negative acute phase proteins decrease in inflammation and include albumin, transferrin and transthyretin.

CRP is part of the innate immune system and levels rise with 4-6 hours of an inflammatory stimulus, returning to normal 3-7 days after the stimulus is withdrawn. It is a **direct** measure of the acute phase response.

ESR is the rate at which erythrocytes settle when placed in a vertical tube. This depends primarily on the concentration of fibrinogen, which is an acute phase reactant. The ESR is an **indirect** measure of the acute phase response. As listed below, a number of other factors, some physiological, some disease-related and some related to the test system can influence the rate at which red cells settle when placed in a vertical tube. Furthermore, the rate of rise following a stimulus is comparatively slow and the ESR may not return to normal for weeks, despite clinical improvement.

Table 1: Comparison of ESR and CRP

Characteristic	ESR	CRP
Specimen Requirement	Fresh Whole Blood	Serum or Plasma
Specimen Storage	Must be tested the day of collection	Stored specimens remain stable for up to 7 days
Method of measurement	Indirect measurement of fibrinogen elevation	Direct quantitation of acute phase response
Rate of Rise	Rises comparatively slowly, may not return to normal for weeks, despite clinical improvement	Elevations begin at 4-6 hours, peak at 36-59 hours and return to normal 3-7 days after stimulus is withdrawn
Assay	Variation between labs in method	Nephelometer
Assay reproducibility	Low/Moderate	High
Cost	\$10	\$12

Table 2: Examples of Physiological variables that can affect the ESR

Variable	Effect of ESR
Age*	Increase with age
Gender	Males higher than females
Obesity*	Increase with obesity
Plasma protein concentration	Altered by concentrations of albumin, fibrinogens, cholesterol, immunoglobulins
Pregnancy*	Increase
Red Cell Factors	Decrease with sickling, elliptocytes
Smoking	Increase

* a slight increase may be seen in CRP with these variables

Table 3: Examples of underlying Diseases that can affect validity of ESR values

May increase ESR	May decrease ESR
Cachexia (low albumin) Hypercholesterolaemia Hypergammaglobulinaemia Macroglobulinaemia Monoclonal gammopathy Anaemia	Agammaglobulinaemia Polycythaemia DIC Hypofibrinogenaemia Aspirin

Laboratory Testing Factors which alter the result of the ESR

A) Test Method

There are a number of methods available to determine the ESR. The 2 test systems used by Medlab Central are:

1. The automated test on the StaRRsed III analyzer which uses the ISTH-recommended Westergren method, undertaken on 2ml of EDTA blood
2. The manual method, undertaken on 1ml of EDTA blood

There is marked variation between the results obtained by these two methods.

B) Precision

There are little reliable data because of the large specimen volumes required to run duplicate testing. Estimates of uncertainty of measurement are listed below;

ESR result	Estimate of uncertainty of measurement
<21	80%
21-50	26%
>50	13%

C) Quality Control Material

Laboratory tests undergo regular quality control using both internal (in house) and external quality assurance material which requires stabilized controls. The ESR can only be carried out on fresh specimens. There is, therefore, no suitable material to undertake quality control on the ESR.

Performance of CRP and ESR for specific applications

1) Rheumatoid Arthritis

The ESR has been more widely used for the purpose of disease activity monitoring in RA. Elevations of both CRP and ESR are associated with radiographic progression.

2) Polymyalgia rheumatica and giant cell arteritis

Whilst these diseases are frequently accompanied by an increase in ESR, 7-20% of patients may have normal ESR. What constitutes a "normal" ESR level in the elderly can also hamper interpretation of this result. CRP and ESR are considered to be of approximately equal value in assessing disease activity.

3) Systemic Lupus Erythematosus

Many patients with active SLE do not have elevated CRP concentrations.

4) Chronic Infections

The slow rate of fall of the ESR makes the CRP more useful in assessing response.

5) Kawasaki disease

Both ESR and CRP are increased.

6) Rheumatic fever

Both ESR and CRP may be increased. CRP can rise nonspecifically with heart failure and, therefore, in some cases, an ESR may provide additional information.

References

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