Erythrocyte Sedimentation Rate

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Disclosure Information
Tests I wish You Had Not Ordered

• I have no financial relationships to disclose.

• I will not discuss off label use or investigational use in my presentation.

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Objectives

• Learn how to stop doing this.
Case Presentation

- You are asked to consult on a 50-year-old female admitted with the weak and dizzies that started three weeks ago. Her exam is normal.
- A SED rate was obtained on admission and was noted to be 35 ml/hr.
- What does your consulting desired wish to convey?
Erythrocyte Sedimentation Rate

- Few laboratory tests are performed more frequently, yet none may be more difficult to interpret.
- Elevated levels lead to unnecessary testing.
  - No diagnosis can be made by an SED rate.
  - Mildly elevated ESR are typically ignored.
  - High levels attract attention, may not indicate serious disease.

Sigma ESR: an erythrocyte sedimentation rate adjusted for the hematocrit and hemoglobin concentration

CC: Elevated What?

Dear Donald T.

Did you know that the SED rate was 1\textsuperscript{st} discovered in 1866 by ______________. Your pleasant 50 year old woman states she developed the “weak and dizzies” from sitting on the couch in an awkward position during a meeting, that discussed the rating of a ”bad apprentice.” in the office.
Erythrocyte Sedimentation Rate

Edmund Faustyn Biemacki (1866 -1911)

Swedish hematologist, Robert Sanno Fåhraeus (1888-1968)

Swedish internist Alf Vilhelm Albertsson Westergren (1891-1968).
Studies of the Suspension Stability of the Blood in Pulmonary Tuberculosis

by

ALF WESTERGREN.

I. Introduction.

When a substance in a state of fine division is silted up in a liquid, we call this a suspension. The blood corpuscles, in this connection primarily the red ones, may thus be described as suspended in the plasma. A suspension is called stable, if the matter silted up for a long time keeps evenly distributed in the medium. The principal cause of a decrease of the stability is to be found, when the matter silted up has a
Erythrocyte Sedimentation Rate

It is the rate of downward descent of RBCs in a vertical column of blood.

**Principle:** If anti-coagulated blood is allowed to stand vertically in a narrow tube, the red cells will settle progressively to the bottom leaving clear plasma above.
Erythrocyte Sedimentation Rate

The cells settle due to:

- Density of RBCs is greater than that of plasma.
- RBCs tend to aggregate to form Rouleaux.

(Rouleaux differs from agglutination that agglutinated cells are irreversibly bound together and can not be separated.)

Westergren method for estimation of ESR:

Equipment:
- Westergren tube (straight glass tube 30 cm in length, 2.5 mm in diameter and graduated from 0 - 200 mm)
- Special stand.
- 3.8% Sodium Citrate.
- 5 ml disposable syringe.

Fig. 9.1: Steps showing Westergren method
The “Letter” to Holmgren

Title: [Letter] 1921-02-06 [to] Israel Frithiofsson Holmgren

Description:
- The Waller Manuscript Collection, Uppsala University Library
- Alf Vilhelm Albertsson Westergren 1891-1968

Westergren
Translanted: Don’t order this test
Your Consult

CC: Elevated What?

Dear Donald T.

Did you know that the SED rate was 1\textsuperscript{st} discovered in 1866 by \underline{Edmund Faustyn Biemacki}. Your patient’s “weak and dizzies” from sitting awkward on a couch in a meeting. The test appears to have been done by the historical method called the \underline{Westergen method}. It appears she has no history and is not anemic. However, despite the ‘news’ - comparisons in laboratory techniques don’t seem to change the test results. Her ESR test was found to be 35 mm/hr. This result is \underline{an uncorrected value}. 
What is a Normal ESR Value

Normal values:

In males:
- 1st hr: 3 - 5 mm
- 2nd hr: 6 - 10 mm

In females:
- 1st hr: 8 - 10 mm
- 2nd hr: 16 - 20 mm
Calculating Normal Erythrocyte Sedimentation Rate

• Measurement of the ESR requires adjustments.

• Westergren method in 27,912 adults (1,076 non pregnant woman) aged 20 – 65 years old during routine exams in 10 London teaching hospitals.
Calculating Normal Erythrocyte Sedimentation Rate

- ESR increases with age.
- 50% and 98% levels show that the results are skewed.
- Corrected valves thus adjusted to be within 2% of the population:
  - Adjustments needed:
    - ESR ♂ = \( \frac{\text{age} + 10}{2} \);
    - ESR ♀ = \( \frac{\text{age}}{2} \)

Clinical significance of ESR

- Because the ESR is changed in a great variety of conditions, its alteration is not specific and not diagnostic.

- It is a prognostic test:
  1. It detects the presence and severity of disease.
  2. It gives an idea about the activity of disease.
  3. Repeated ESR estimation may help in prognosis and follow up of disease.

Factors Effecting ESR Testing

Factors determining the rate of sedimentation of RBCs:

- **Plasma proteins**:
  - Albumin: If plasma albumin level is increased the ESR decreases.
  - Fibrinogen and globulins: If plasma fibrinogen or globulins level is increased the ESR increases.

- **Red cell count**:
  - If RBCs count is increased the ESR decreases.
Factors Effecting ESR Testing

Physiological factors:

ESR is increased in:
1. Old age.
2. Females.

ESR is decreased in:
1. Newborn.
2. Males.
3. High altitude.
Dear Donald T.

... It appears that her ESR test is actually fairly normal and not “fake” which is typically good for patients. We calculated her adjusted level to be ___30 mm/hr___, which is close to the 35 mm/hr test. However, since the symptoms started weeks ago – this may or may not be a “RED flag.”

Lucky for us, we can “tap” into the computer and see if a CRP was also drawn at the same time.
Case Presentation

- On the same 50-year-old female admitted with weakness and dizziness.
- A CRP was drawn and was noted to be 8 mg/L.
- What does your consulting desired wish to convey?
C Reactive Protein

- C-reactive protein (CRP) belongs to the pentraxin family of proteins, which has five identical subunits. It was named because it reacts with the somatic C polysaccharide of *Streptococcus pneumoniae*, and was first discovered in 1930 by Tillet and Francis.

CRP & ESR Patterns of Response

Days post simulation

CRP serum concentration

% change

ESR serum concentration

Units
CRP is reported to have several main functions

- CRP shows a rapid response to infection and inflammation: increasing within hours of stimulus, and returning rapidly to normal following resolution.

- CRP is not affected by conditions such as pregnancy, drug use, anemia and plasma protein variations.

- CRP reference ranges also have variations for age or gender.

What is a Normal CRP Value

Mean CRP (95% confidence interval)

Age in years

<24 25 - 31 36 - 44 45 - 59 60 - 74 >75

= Males

= Females

What is a Normal CRP Value

- US National Health & Nutrition Examination Survey
- 9,000 adults
- Mean level as 2.1 mg/L
- 90% had levels < 10 mg/L

- Corrected CRP
  - ♀ = (age + 6) / 5
  - ♂ = age in years / 5


# CRP as an Indication of Severity

**Table 2: CRP as an indication of severity**

<table>
<thead>
<tr>
<th>CRP (mg/L)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 40</td>
<td>Mild Inflammation, viral or bacterial infection</td>
</tr>
<tr>
<td>40 - 100</td>
<td>Moderate Inflammation, viral or bacterial infection</td>
</tr>
<tr>
<td>100 - 200</td>
<td>Marked inflammation, bacterial infection</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>Severe bacterial infection or extensive trauma</td>
</tr>
</tbody>
</table>
How do ESR and CRP differ

Table: Comparison of ESR and CRP

<table>
<thead>
<tr>
<th>Results affected by:</th>
<th>ESR</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Temperature</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drugs (eg. steroids, salicylates)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Comparison of ESR and CRP

<table>
<thead>
<tr>
<th></th>
<th>ESR</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Throughput time</strong></td>
<td>5 minutes to 2 hours</td>
<td>Typically less than 30 minutes</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td><em>Indirect measure of proteins</em></td>
<td><em>Direct protein measurement</em></td>
</tr>
<tr>
<td></td>
<td>Corresponds primarily with fibrinogen</td>
<td>Measures specific acute-phase protein</td>
</tr>
<tr>
<td></td>
<td>levels in acute inflammation</td>
<td></td>
</tr>
<tr>
<td><strong>Rises</strong></td>
<td>Days to weeks</td>
<td>Hours to days</td>
</tr>
<tr>
<td><strong>Peak level</strong></td>
<td>1–2 weeks</td>
<td>48 hours</td>
</tr>
<tr>
<td><strong>Declines</strong></td>
<td>Slowly (1–2 weeks)</td>
<td>Rapidly</td>
</tr>
<tr>
<td><strong>Age and gender</strong></td>
<td>Significant effect</td>
<td>Mild to moderate effect</td>
</tr>
<tr>
<td><strong>Accuracy for</strong></td>
<td>Frequent false positives</td>
<td>Rare false positives</td>
</tr>
<tr>
<td><strong>inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected by</strong></td>
<td>Often</td>
<td>Never/rarely</td>
</tr>
<tr>
<td><strong>multiple confounding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(eg, RBC abnormalities)</td>
<td></td>
</tr>
</tbody>
</table>

What is the best test to use in different situations?

There are few studies that compare the use of ESR and CRP.

The best approach is to consider the various clinical questions that may be posed during the course of the consultation.
When these test might help?

Screening Asymptomatic patients

- CRP and ESR are *not suitable* as a screen in asymptomatic patients.
- They should only be requested on patients in whom the clinical evaluation has given some indication of a disease process.

Polymyalgia rheumatica

- There is little evidence to suggest CRP is a suitable diagnostic test for the diagnosis of PMR.
- It is recommended both ESR and CRP are requested when considering PMR as a diagnosis, CRP is recommended for the monitoring of PMR.

Temporal (giant cell) arteritis

- It is recommended that CRP and ESR should be tested simultaneously, which will result in a higher sensitivity for diagnosis.

CRP as a cardiovascular disease risk factor

- At this stage, High Sensitivity-CRP (Hs-CRP) is defining its role as a cardiovascular disease risk factor.
When these test might help?

**Infection**
- CRP is useful when considering an atypical infection, as it can be helpful in differentiating between bacterial and viral infections.
- As the CRP increases above 100mg/L, the likelihood of a bacterial infection becomes greater than viral infection.

**Rheumatoid Arthritis**
- Neither CRP or ESR are of use when diagnosing rheumatoid arthritis, as there are other defined diagnostic criteria.
- CRP is considered a better measure of the disease activity and it is known that sustained high levels of CRP are associated with worse outcomes.

**Malignancy**
- Given the non-specific nature of the acute phase response, a definite role of CRP measurements in the management of cancer patients, other than in cases of current infection has not yet been established.
CC: Elevated inflammatory markers

Dear Donald T.

… we reviewed the literature but only the ones with “large crowds” and “SO many people” and it appears that her CRP test is actually normal.

Her clinical exam and consultation questions did not reveal anything “illegal” under oath. Thus, we recommend that close monitoring of the clinical condition can be done.

Sincerely,

Vad
Conclusions

- Recognize the ESR as an indirect measurement of acute phase protein that responds slowly.
- C-reactive protein test as a direct acute phase protein that responds quickly.
- ESR is affected by many factors whereas CRP is affected by degree of inflammation.
- Adjust factors are needed: ESR $\text{♀} = (\text{age } + 10)/2$; $\text{♂} = \text{age }/2$
- Adjusted factor are needed: CRP $\text{♀} = (\text{age } + 6) / 5$; $\text{♂}\text{age in year }/5$
- Use of these test for screening patient is not supported.
- ESR and CRP look at different processes of inflammation and data is mixed on the need for testing both.
- Both are incapable of making a diagnosis.
<table>
<thead>
<tr>
<th>Question</th>
<th>CRP</th>
<th>ESR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening asymptomatic patients?</td>
<td></td>
<td></td>
<td>Unlikely to be useful</td>
</tr>
<tr>
<td>I know this patient is ill but I don’t know why</td>
<td>✓</td>
<td></td>
<td>Actual level of CRP helpful</td>
</tr>
<tr>
<td>Could this patient have a significant bacterial infection</td>
<td>✓</td>
<td></td>
<td>CRP good, ESR slow response</td>
</tr>
<tr>
<td>Could the patient have post-op infection?</td>
<td>✓</td>
<td></td>
<td>CRP good, ESR slow response</td>
</tr>
<tr>
<td>Has the infection responded to this antibiotic</td>
<td>✓</td>
<td></td>
<td>CRP good, ESR slow response</td>
</tr>
<tr>
<td>Is this RTI more serious than it seems?</td>
<td>✓</td>
<td></td>
<td>Level of CRP useful</td>
</tr>
<tr>
<td>Is this patient responding to a trial of steroid therapy?</td>
<td>✓</td>
<td></td>
<td>CRP good, ESR slow response</td>
</tr>
<tr>
<td>Does this patient have PMR?</td>
<td>✓</td>
<td>✓</td>
<td>PMR with a normal ESR occasionally occurs</td>
</tr>
<tr>
<td>Question</td>
<td>CRP</td>
<td>ESR</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Monitoring PMR</td>
<td>✓</td>
<td></td>
<td>CRP more sensitive indicator of activity</td>
</tr>
<tr>
<td>Does this patient have temporal</td>
<td>✓</td>
<td>✓</td>
<td>GCA with a normal ESR occasionally occurs</td>
</tr>
<tr>
<td>arteritis/GCA?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring temporal arteritis/GCA</td>
<td>✓</td>
<td></td>
<td>CRP more sensitive indicator of activity</td>
</tr>
<tr>
<td>What is the cause of this/these</td>
<td>Little use</td>
<td>?</td>
<td>CRP more sensitive indicator of activity</td>
</tr>
<tr>
<td>inflamed joints?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring rheumatoid arthritis</td>
<td>✓</td>
<td></td>
<td>CRP better measure of the disease activity</td>
</tr>
<tr>
<td>Monitoring SLE?</td>
<td>✓</td>
<td>✓</td>
<td>CRP normal during flare, but elevated during infection</td>
</tr>
<tr>
<td>Why is the platelet count</td>
<td>✓</td>
<td>✓</td>
<td>Many different causes which may include inflammation</td>
</tr>
<tr>
<td>elevated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediction of cardiovascular</td>
<td>?</td>
<td></td>
<td>Role not yet established</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>