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Erythrocyte sedimentation rate and C-reactive protein

SUMMARY

C-reactive protein is a better indicator of inflammation than the erythrocyte sedimentation rate. It is more sensitive and responds more quickly to changes in the clinical situation.

False negative and false positive results are more common when measuring the erythrocyte sedimentation rate. Renal disease, female sex and older age increase the erythrocyte sedimentation rate.

The erythrocyte sedimentation rate has value in detecting low-grade bone infection, and in monitoring some patients with systemic lupus erythematosus.

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Introduction

As well as the clinical evaluation of symptoms and signs indicating inflammation (pain, fever, and localised redness, swelling and tenderness), laboratory investigations are frequently used to support the diagnosis of inflammatory processes. Both acute and chronic inflammation cause cytokines, mainly interleukin-6, to be released into the bloodstream. The liver responds to this by producing acute phase reactants such as C-reactive protein (CRP). This is the most commonly used marker of an acute phase reaction and was first discovered in the serum of patients with pneumococcal pneumonia.[1]

Detecting the acute phase reaction

Although the erythrocyte sedimentation rate (ESR) is still used to assess inflammation, specific acute phase proteins are more commonly measured now. Markers of the acute phase reaction are C-reactive protein, serum amyloid A protein and procalcitonin. They increase 100-fold or more in patients with acute or chronic inflammatory processes. Many other serum proteins change during an acute phase reaction (shift up or down) but to a lesser extent.[1]

C-reactive protein

C-reactive protein has an important role in many parts of the inflammatory process. It is involved in the innate immune response by attaching to microorganisms and damaged cellular components via phosphocholine. This leads to complement activation and phagocytosis. Although C-reactive protein activation of complement increases inflammation and tissue damage, it also has some anti-inflammatory actions, thus it acts as a promoter and down-regulator of inflammation.

C-reactive protein is a useful marker of the acute phase reaction as it responds quickly to the inflammatory process, whether it is an infection, autoimmune disease or tissue necrosis.[2] C-reactive protein has a doubling time and a decay time of around six hours, and maximal concentrations are reached in less than two days. After the inflammation has resolved, concentrations fall rapidly. Once inflammation and its cause have been identified and treatment is started, there is usually no need for further C-reactive protein measurements.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate is a surrogate marker of the acute phase reaction. During an inflammatory reaction, the sedimentation rate is affected by increasing concentrations of fibrinogen, the main clotting protein, and alpha globulins. The test mainly measures the plasma viscosity by assessing the tendency for red blood cells to aggregate and 'fall' through the variably viscous plasma.

However, the sedimentation rate is often and significantly affected by many factors other than the acute phase reaction. Known influences include:

- plasma albumin concentration
- size, shape and number of red blood cells
- non-acute phase reaction proteins, in particular normal and abnormal immunoglobulins.

The non-specificity of the erythrocyte sedimentation rate means the test is more likely to be falsely positive (elevated in the absence of inflammation) than a C-reactive protein test. Also, the erythrocyte sedimentation rate's slow response to the acute phase reaction leads to false negatives early in an inflammatory process.[3] Normalisation of an

elevated erythrocyte sedimentation rate once an immunoglobulin response has occurred may take weeks to months.

Raised erythrocyte sedimentation rates are observed in patients without an acute phase reaction, for example when haematological disorders including anaemia are present. Renal failure, obesity, ageing and female sex are associated with higher erythrocyte sedimentation rates. C-reactive protein results are also higher with obesity but are not affected by renal failure.

C-reactive protein versus erythrocyte sedimentation rate

In laboratory-based studies examining consecutive patients with elevated C-reactive protein or erythrocyte sedimentation rate, C-reactive protein has been found to be a better marker of the acute phase reaction than the erythrocyte sedimentation rate.[1] It is a more sensitive test and rapidly detects changes in the acute phase reaction.

In a retrospective cohort study, discrepancies between C-reactive protein and erythrocyte sedimentation rate have been reported in 12.5% of patients.[4] Patients with raised C-reactive protein and a normal erythrocyte sedimentation rate usually have infection but some have other tissue damage (e.g. myocardial infarction or venous thromboembolism). These discrepancies may be due to timing, with the rise in C-reactive protein manifesting itself before the sedimentation rate elevates, or simply because the sedimentation rate does not change with minor inflammation.[3] Patients with a high erythrocyte sedimentation rate and normal C-reactive protein mostly have conditions without demonstrable systemic inflammation such as malignancy.

However, there are two circumstances when the sedimentation rate can be a better marker of an inflammatory process:

- some low-grade bone and joint infections (e.g. in joint prosthesis infections due to low-level pathogens such as coagulase negative staphylococci)
- autoimmune disease, in particular some people with systemic lupus erythematosus.

With systemic lupus erythematosus, a patient may have a normal C-reactive protein in the presence of significant tissue damage and inflammation. This is possibly due to high levels of type 1 interferons which inhibit the production of C-reactive protein in hepatocytes. Despite this, a C-reactive protein test is still useful as elevation will indicate concomitant bacterial infection, active serositis and chronic synovitis.

C-reactive protein is considered a better marker of disease activity in other autoimmune diseases such as polymyalgia rheumatica and giant cell arteritis, despite the erythrocyte sedimentation rate also being elevated in most of these conditions.[4] Patients with rheumatoid arthritis show considerable variation in erythrocyte sedimentation rate and C-reactive protein elevations during times of increased disease activity. A prudent approach may be to measure both initially in order to identify the best marker to use.

The erythrocyte sedimentation rate has been used as a surrogate marker for hypergammaglobulinaemia, especially myeloma protein. Where myeloma is suspected, a much better test is the protein electrophoresis and immunoglobulin measurements.

Conclusion

C-reactive protein should be used judiciously. It is not a screening test for wellness and should only be used in the diagnosis and monitoring of a patient who appears to have an inflammatory process.

Compared to the erythrocyte sedimentation rate, C-reactive protein is a more sensitive and specific marker of the acute phase reaction and is more responsive to changes in the patient's condition. There are only two circumstances where the erythrocyte sedimentation rate is superior – detecting low-grade bone and joint infections, and monitoring disease activity in systemic lupus erythematosus. ≺

Michael Harrison is chief executive officer of a private pathology laboratory that performs erythrocyte sedimentation rate and C-reactive protein tests. Although the laboratory receives Medicare funding for these tests, he does not directly benefit.

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