

CRP vs ESR

*Assessing & Measuring
the Inflammatory
Response*



Prepared by bpac^{nz}
Level 8, 10 George Street
PO Box 6032
Dunedin

Phone 03 477 5418
Fax 03 477 2622
www.bpac.org.nz

Acknowledgement

bpac^{nz} would like to thank Professor John Highton, Professor John Campbell, Dr Bert White and Dr Neil Whittaker for their help and advice on the development of this resource.

July 2005
©bpac^{nz}

All information is intended for use by component health care professionals and should be utilised in conjunction with pertinent clinical data.

ESR and CRP are some of the most commonly requested tests by New Zealand general practitioners. ESR is being performed about twice as often as CRP, but it is now recognised that in most situations CRP provides more valuable information to the clinician.

What do we recommend?

1. Choose CRP first on most occasions
2. Seldom request ESR and CRP simultaneously

Why do we make these recommendations?

- CRP shows a rapid response to infection and inflammation: increasing within hours of stimulus, and returning rapidly to normal following resolution.
- There are distinct ranges of normal and abnormal in CRP reference ranges, without variations for age or gender.
- CRP is not affected by conditions such as pregnancy, anaemia and plasma protein variations.
- There is seldom any value in requesting ESR and CRP simultaneously.

What is the best test to use in different situations?

There are few studies that compare the use of ESR and CRP, hence there are only a few conditions for which there are clear recommendations. As a result, the best approach is to consider the various clinical questions that may be posed during the course of the consultation, refer Table 1.

Table 1: Choosing CRP or ESR

Question	CRP	ESR	Comments
Screening asymptomatic patients?			Unlikely to be useful
I know this patient is ill but I don't know why.	✓		Actual level of CRP helpful
Could this patient have a significant bacterial infection?	✓		CRP good, ESR slow response
Could the patient have post-op infection?	✓		CRP good, ESR slow response
Has the infection responded to this antibiotic?	✓		CRP good, ESR slow response
Is this RTI more serious than it seems?	✓		Level of CRP useful
Is this patient responding to a trial of steroid therapy?	✓		CRP good, ESR slow response
Does this patient have PMR?	✓	✓	PMR with a normal ESR occasionally occurs
Monitoring PMR	✓		CRP more sensitive indicator of activity
Does this patient have temporal arteritis/GCA?	✓	✓	GCA with a normal ESR occasionally occurs
Monitoring temporal arteritis/GCA?	✓		CRP more sensitive indicator of activity
What is the cause of this/these inflamed joints?	Little use	?	Must be interpreted in clinical context
Monitoring Rheumatoid arthritis	✓		CRP better measure of the disease activity
Monitoring SLE?	✓	✓	CRP usually normal during flare, but elevated in infection
Why is the platelet count elevated?	✓	✓	Many different causes which may include inflammation
Prediction of cardiovascular disease	?		Role not yet established

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. Historically, both ESR and CRP have often been requested as part of a “well-person check”, or in patients presenting with non-specific symptoms such as “feeling tired”. When there is no strong evidence of disease, the tests are of little value.

Polymyalgia rheumatica

There has been some interest in using CRP as a diagnostic criterion for the diagnosis of PMR,¹ however there is little evidence of how to use it in practice. Criteria that include an ESR > 40 mm/hour have been recently demonstrated to have high sensitivity in detecting PMR,² although it is reported that 4 to 13% of PMR patients will have a normal ESR at diagnosis.³ As a result it is recommended both ESR and CRP are requested when considering PMR as a diagnosis.

CRP is recommended for the monitoring of PMR. The initial CRP level should be used as the baseline when monitoring treatment, therefore an absence of a clinical response and improvement of the CRP within one to two weeks of therapy, should suggest reconsideration of the diagnosis.⁴

Temporal (giant cell) arteritis

While it is reported that overall there is good correlation between CRP and ESR at diagnosis of temporal arteritis, cases with normal ESR and elevated CRP are reported.³ It is therefore recommended that CRP and ESR should be tested simultaneously, which will result in a higher sensitivity for diagnosis.⁵ Although there are no reported values to define CRP use for diagnosis,⁵ a CRP of more than 1-2 times the upper limit of normal, in conjunction with clinical symptoms should increase suspicion. CRP is recommended for monitoring temporal arteritis, and appropriate treatment results in an improvement in the CRP level.

Infection

CRP is a useful test when considering an atypical infection, as it can be helpful in differentiating between bacterial and viral infections. As the CRP increases above 100 mg/L, the likelihood of a bacterial infection becomes greater than a viral infection.⁶ CRP may also be useful in determining response to antibiotics, as a persistent elevation after 1 week suggests either treatment failure (e.g. incorrect antibiotic treatment, additional infection, abscess formation) or other alternative diagnosis.⁷

Rheumatoid arthritis

Neither CRP or ESR are of use when diagnosing rheumatoid arthritis, as there are other defined diagnostic criteria.⁸ When monitoring rheumatoid arthritis, it has been difficult to compare CRP to ESR because a discordance rate (28 to 55%) has been demonstrated between the two tests.⁹ It is assumed that most of the lack of correlation is due to the effect of immunoglobulins, rheumatoid factor, and haemoglobin on the ESR result. 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.⁹

Systemic lupus erythematosus (SLE)

The correlation of CRP with disease activity in SLE has been clinically unhelpful. Some patients with severe active disease have been found to have normal CRP levels.¹⁰ A more useful role of CRP is to distinguish between a lupus flare and infection: it usually remains normal in a flare but is elevated in infection, while the ESR is often elevated in both.¹¹

Malignancy

Most malignant tumours, especially when they are extensive and metastatic, induce an acute phase response. This is particularly so with neoplasms which cause systemic symptoms such as fever and weight loss, for example, lymphomas and renal cell carcinoma. However, 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 intercurrent infection has not yet been established. Neither CRP nor ESR should be used as a screening test for malignancy in the general population, since any increase in these is non-specific. An ongoing prospective cohort study has already determined that elevated CRP has no predictive value for cancer.¹²

CRP as a cardiovascular disease risk factor

High Sensitivity-CRP (Hs-CRP) has been reported as predictor for cardiovascular disease, although when compared with major established risk factors (such as elevated cholesterol and smoking status) the Hs-CRP added only marginally to the predictive value of the risk factors.¹³ At this stage it does not have a definitive role in the management of cardiovascular disease.

CRP as an indicator of Severity

When a patient is ill but the diagnosis is not known, the level of CRP may provide additional information to assist in reaching a diagnosis. The level of CRP may provide an indication as to the severity (table 2) of the condition - a mildly elevated level of CRP may give some cause for concern, but as the CRP rises significantly higher, more urgent review of the patient becomes necessary.

Table 2: CRP as an indicator of severity

CRP (mg/L)	
10 – 40	Mild inflammation, viral or bacterial infection
40 – 100	Moderate inflammation, viral or bacterial infection
100 – 200	Marked inflammation, bacterial infection
>200	Severe bacterial infection, vasculitis, severe arthritis

Result interpretation

Table 3: CRP and ESR reference ranges¹⁴

CRP (mg/L)	<5	
ESR (mm/hour)	Female	Male
Child 1 -10	1 – 10	1 – 10
Adult <50 years	1 – 20	1 – 15
>50 years	1 – 30	1 - 20

How do CRP and ESR differ?

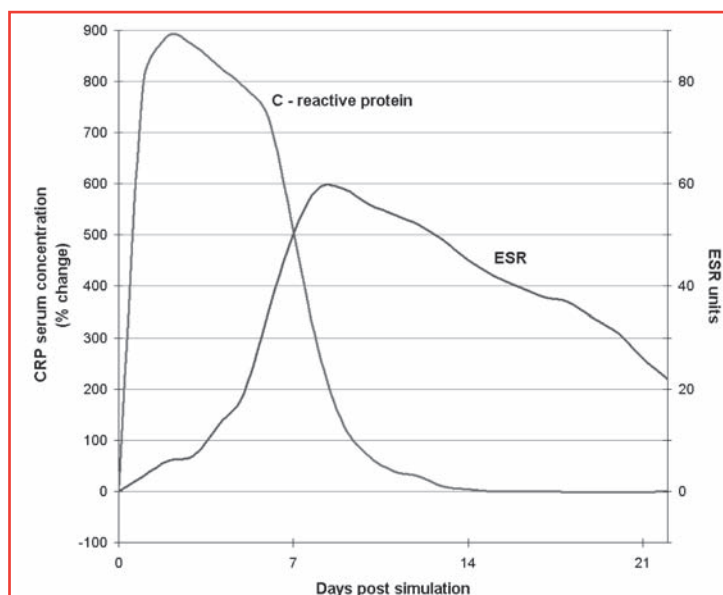
The CRP methods used in the laboratory are a more direct measure of the inflammatory process, because only CRP is measured, by contrast ESR is a more indirect measure. ESR reflects the concentration of several plasma proteins including fibrinogen, α -globulins, β -globulins, immunoglobulins and albumin. Therefore, any condition (pathological or non-pathological) that affects any of the contributing proteins can alter the ESR (table 4).

Table 4: Comparison of ESR and CRP¹⁵

	ESR	CRP
Results affected by Gender	Yes	No
Age	Yes	No
Pregnancy	Yes	No
Temperature	Yes	No
Drugs (eg. steroids, salicylates)	Yes	No
Smoking	Yes	No

Both CRP and ESR have characteristic patterns of response (Figure 1). CRP begins to rise within 4-6 hours of stimulus, peaks within 36-50 hours, and returns to normal 3-7 days following resolution. ESR shows a much slower response, taking up to a week to peak, and up to several weeks to return to normal.¹⁰

Figure 1: CRP and ESR patterns of response

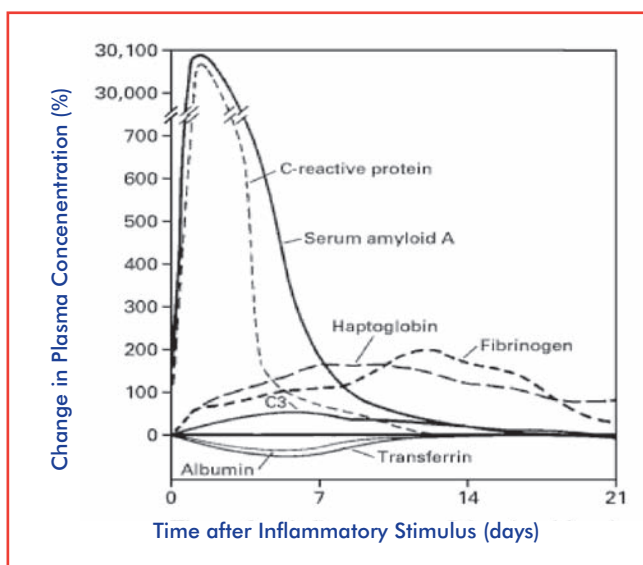


The acute phase response

Following injury, trauma or infection of a tissue, a complex series of reactions occur in an effort to prevent ongoing tissue damage, and activate the repair processes. This cumulative homeostatic process is known as inflammation, and the early series of reactions are known as the acute phase response (APR).

The cells that most commonly initiate the APR are tissue macrophages and blood monocytes. These cells release cytokines such as IL-1 and TNF that control the migration of leukocytes into tissue and orchestrate the inflammatory response. Fever and leucocytosis are among the most obvious consequences. The biosynthetic activity of the liver is profoundly affected. The pro-inflammatory cytokines IL-1 and TNF act on hepatocytes to greatly increase production of acute phase proteins such as CRP and serum amyloid A protein (Figure 2). These proteins are particularly useful for reflecting inflammation because of the increase of up to 1000 fold from resting levels. There are more moderate increases in the level of other proteins such as ferritin which may affect assessment of iron status in the presence of inflammation. There is a corresponding decrease in the synthesis of some other proteins, most notably albumin which may reach low levels in the presence of sustained inflammation.

Figure 2: The acute phase proteins



The phenomenon now recognised as the erythrocyte sedimentation rate was first observed by ancient Greeks. They observed the relationship between the sedimentation of red blood cells and fibrinogen (or “phlegma”), and used it as a means of detecting bad bodily “humors”.¹⁶ The test used today was introduced in 1918 by Robin Fahraeus, when he recorded the erythrocytes of pregnant women settled more quickly than the erythrocytes of non pregnant women.

Normally, erythrocytes settle quite slowly, as the gravitational force of the erythrocyte’s mass is counteracted by the buoyant force of the erythrocyte’s volume. In normal circumstances erythrocytes have a net negative charge and therefore they repel each other. Many plasma proteins are positively charged, thereby reducing the repulsive forces and promoting red cell aggregation, which in turn creates a higher mass and therefore the cells settle much more quickly. Fibrinogen and α - and β -globulins are major contributors to the ESR¹⁷, and immunoglobulins to a lesser extent. These proteins all have half-lives of days to weeks, and there is a significant lag time between changes at the clinical level and variations in the ESR.

If the haematocrit is reduced, as in anaemia for example, the velocity of upward flowing plasma is altered, resulting in the red cells aggregating and therefore falling faster. As a result, in conditions associated with moderate or severe anaemia, the ESR is of limited use. In conditions such as myeloma, the increase in the level of immunoglobulins causes an increase in red cell aggregability, resulting in an elevated ESR.

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.

Plasma levels begin increasing within 4-6 hours following acute inflammatory stimulus and the half-life of CRP is 5-7 hours, therefore the level of CRP in the blood is regulated solely by its own synthesis.

CRP is reported to have several main functions¹⁸:

- **Anti-infective:** CRP can opsonise particles for phagocytosis, and activate complement via the classical pathway.
- **Anti-inflammatory actions:** CRP helps in preventing systemic inflammation. CRP aids in the release of neutrophils from blood vessels, while preventing white cell adhesion to vessels in non-inflamed tissues. It is also able to stimulate the release of anti-inflammatory molecules from monocytes.
- **Scavenging actions:** Although CRP does not bind to normal cell membranes, it can bind avidly to cells that are undergoing apoptosis or necrosis, possibly because it recognises particular receptors that appear on the surface of dying cells. This in turn binds and activates complement, initiating an inflammatory reaction that attracts neutrophils and monocytes to the site.

Tests should supplement clinical skills

When requesting any laboratory tests, the tests should supplement rather than substitute for clinical skills. The quality of any test is improved by limiting the test to those patients who, on clinical assessment, are likely to have the disease in question.

This discretionary approach to testing acknowledges some of the limitations of laboratory tests.

Sensitivity – the percentage of people in a tested population with a disease, and who are correctly identified by a positive test.

High sensitivity = few people who have the disease
are falsely identified as normal

Specificity – the percentage of people in a population without a disease, that are correctly identified by a negative test.

High specificity = few people who don't have the disease are falsely
identified as having the disease

Reference ranges – Most reference ranges include 95% of the healthy population; therefore the probability of a normal person having a result outside the reference range is 5%. As more tests are requested, the probability increases of an incidental out-of range result. Once 20 tests are requested (ie FBE and liver function tests), there is a 64% probability that one of these results will fall outside the reference range.

References

1. Cantini F, Salvarani C, Olivieri I. Letter: Erythrocyte Sedimentation Rate and C-Reactive Protein in the Diagnosis of Polymyalgia Rheumatica. *Ann Intern Med* 1998;128:873-4
2. Bird H A et al. A comparison of the sensitivity of diagnostic criteria for polymyalgia rheumatica. *Ann Rheum Dis* 2005;64:626-9
3. Epperly T et al. Polymyalgia Rheumatica and Temporal Arteritis. *Am Fam Physician* 2000;62:789-96
4. Dharmanand B, Dasgupta B. Guide to polymyalgia rheumatica and giant cell arteritis. *Prescriber* 2004;15:35-40
5. Qureshi J, Wilke W. Giant Cell Arteritis: Diagnosis and Management. *Hosp Physician* 2003;39:48-58
6. Hunter Area Pathology Service (HAPS), Education Information, C-reactive protein. November 1998. <http://www.haps.nsw.gov.au/edrsrch/edinfo/crp.html> (Accessed 23 May 2005)
7. Ng T. Erythrocyte sedimentation rate, plasma viscosity and C-reactive protein in clinical practice. *Br J Hosp Med* 1997;58:521-3
8. Arnett F C et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24
9. Wolfe F. Comparative Usefulness of C-Reactive Protein and Erythrocyte Sedimentation Rate in Patients with Rheumatoid Arthritis. *J Rheumatol* 1997;24:1477-85.
10. Deodhare SG. C-Reactive Protein: Clinical Applications. <http://www.embeediagnosics.com/features/crp.htm> (Accessed 23 May 2005)
11. Hay EM, Snaith ML. ABC of Rheumatology: Systemic Lupus Erythematosus and Lupus-like Syndromes. *BMJ* 1995;310:1257-61
12. Rifai N et al. Is C-Reactive Protein Specific for Vascular Disease in Women? *Ann Intern Med* 2002;136:529-33
13. Danesh J et al. C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease. *NEJM* 2004;350:1387-97
14. Gill M. A handbook for the Interpretation of Laboratory Tests. Diagnostic Medlab, Auckland, August 2000.
15. Husain T, Kim D. C-Reactive Protein and Erythrocyte Sedimentation Rate in Orthopaedics. *The University of Pennsylvania Orthopaedic Journal* 2002;15:13-16
16. Bedell SE, Bush BT. Erythrocyte Sedimentation Rate. From Folklore to Facts. *Am J Med* 1985;78:1001-9
17. Pizzorno, Murraray. Erythrocyte Sedimentation Rate, A Textbook of Natural Medicine 1986,1992. (<http://www.healthy.net/library/books/textbook/Section2/esr.pdf>) (Assessed 23 May 2005)
18. Munford R. C-Reactive Protein and Cardiovascular Risk: The Eyes of the Hippopotamus. Internal Medicine Grand Rounds, Louisiana State University Medical Center, October 19, 2000. (<http://homepage.mac.com/juliofigueroa/docs/GRdocs/BobMunford2000/RobertMunford.html>) (Assessed 23 May 2005)

