



Abnormal laboratory results

C-reactive protein

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Summary

C-reactive protein elevation is part of the acute-phase response to acute and chronic inflammation. It out-performs erythrocyte sedimentation rate in terms of responsiveness and specificity for inflammation. While C-reactive protein elevation is suggestive of inflammation or infection in the appropriate clinical context, it can also occur with obesity and renal dysfunction. Conversely, a lack of C-reactive protein elevation in inflammation may be seen with hepatic failure, as well as during flares of conditions such as systemic lupus erythematosus. Using C-reactive protein in refining cardiac risk assessment is not currently recommended outside of research settings.

Key words: acute-phase reaction, erythrocyte sedimentation rate, inflammation.

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Introduction

An elevated concentration of C-reactive protein in the blood is an indicator of inflammation. The bulk of C-reactive protein tests are requested for the detection of inflammatory responses associated with microbes, autoimmune diseases and drug allergies (especially to antibiotics).

The inflammatory response

Inflammation is a protective reaction of vascular connective tissue to damaging stimuli. The inflammatory response is associated with vasodilatation, increased vascular permeability, recruitment of inflammatory cells (especially neutrophils in acute inflammation), and the release of inflammatory mediators from these cells, including vasoactive amines, prostanoids, reactive oxygen intermediates and cytokines. Cytokines derived from macrophages and monocytes include tumour necrosis factor alpha (TNF- α), interleukin-1 and interleukin-6. These cytokines are primarily responsible for mediating the 'acute-phase response'.¹ They cause a change in the production of

various plasma proteins by hepatocytes, including an increase in C-reactive protein. The effects of inflammation on some of the more important acute-phase proteins are shown in Table 1.

C-reactive protein

C-reactive protein plays a key role in the host's defence against infection.² It was so named because it reacts with the C-polysaccharide of *Streptococcus pneumoniae*. In the presence of calcium, C-reactive protein specifically binds to polysaccharides such as phosphocholine moieties present on the cell surface of many pathogenic microbes. C-reactive protein binding activates the classical complement pathway and opsonises (prepares) ligands for phagocytosis. It also neutralises the pro-inflammatory platelet-activating factor and down-regulates polymorphs.

C-reactive protein is predominantly made in the liver and is secreted in increased amounts within six hours of an acute inflammatory stimulus.³ The plasma concentration can double at least every eight hours, reaching a peak after about 50 hours. After effective treatment or removal of the inflammatory stimulus, concentrations can fall almost as rapidly as the 5–7 hour plasma half-life of labelled exogenous C-reactive protein. C-reactive protein responses may be reduced by severe hepatocellular impairment, but renal dysfunction can elevate concentrations of C-reactive protein.

Normal ranges

The median normal concentration of C-reactive protein is 0.8 mg/L, with 90% of apparently healthy individuals having a value less than 3 mg/L and 99% less than 12 mg/L. Elevated values are abnormal and suggest the presence of organic disease, although minimal C-reactive protein rises can be seen with obesity.

C-reactive protein test results can vary between laboratories. It is therefore recommended that serial C-reactive protein assessments be undertaken through a single laboratory if possible, to minimise error.

'Ultra-sensitive' or 'highly-sensitive' C-reactive protein refers to the measurement of small changes in C-reactive protein concentrations occurring below the 'normal' cut-off used to define significant infection and inflammation.

Table 1

Acute-phase proteins

	Increased concentrations	Decreased concentrations
Protease inhibitors	alpha ₁ -antitrypsin antichymotrypsin	
Coagulation proteins	fibrinogen prothrombin factor VIII plasminogen	
Complement proteins	C1s, C2, C3, C4, C5 factor B C1 esterase inhibitor plasminogen	
Transport and storage proteins	haptoglobin haemopexin caeruloplasmin ferritin	transferrin
Miscellaneous	C-reactive protein procalcitonin serum amyloid protein fibronectin alpha ₁ -acid glycoprotein	albumin pre-albumin

Clinical utility of C-reactive protein

While an elevated C-reactive protein value is not specific for any condition, it is a fairly sensitive marker of inflammation (greater than 90%), and so provides a valuable adjunct to a careful clinical assessment. There is often no clear correlation between C-reactive protein concentrations and disease severity. The commonest conditions associated with major elevations of C-reactive protein concentrations are shown in Table 2. Despite unequivocal evidence of active inflammatory disease and/or tissue damage, some conditions are often associated with only minor (or no) elevation of C-reactive protein concentrations (see Table 2). In many of these conditions C-reactive protein remains normal in some patients despite severe disease. The mechanism of this 'selective' failure of the acute-phase C-reactive protein response is currently uncertain.

Monitoring the extent and activity of disease

In inflammatory conditions, C-reactive protein may be used to monitor the patient's response to therapy. For instance in rheumatoid arthritis, C-reactive protein concentrations correspond well to disease activity and treatment efficacy.

Screening for infection

As an adjunct to clinical assessment, a C-reactive protein test may be useful in differentiating between bacterial and viral

infections. A very high C-reactive protein (greater than 100 mg/L) is more likely to occur in bacterial rather than viral infection, and a normal C-reactive protein is unlikely in the presence of significant bacterial infection. However, intermediate C-reactive protein concentrations (10–50 mg/L) may be seen in both bacterial and viral conditions. Measurement of another acute-phase reactant, procalcitonin, has been advocated as an alternative marker in these circumstances, but data are too preliminary to recommend its universal adoption.

Detection and management of intercurrent infection

The possibility of intercurrent infection must always be kept in mind, especially when immunosuppressants are being administered. Bacterial infections usefully monitored by C-reactive protein concentrations include pyelonephritis, pelvic infections, meningitis and endocarditis. Serial C-reactive protein measurements are important adjuncts to the use of temperature charts in clinical practice, as C-reactive protein concentrations are not affected by antipyretic drug therapy or thermoregulatory factors.

In conditions such as systemic lupus erythematosus and ulcerative colitis, a major diagnostic dilemma is often posed between a disease flare and superinfection. Elevation of the C-reactive protein above usual baseline concentrations for a particular patient may provide a valuable clue to the presence of infection.

Table 2

Conditions causing elevation of C-reactive protein

Major elevations

Bacterial infections	pyelonephritis pelvic infections meningitis endocarditis
Hypersensitivity complications of infections	rheumatic fever erythema nodosum
Inflammatory disease	rheumatoid arthritis juvenile chronic arthritis ankylosing spondylitis psoriatic arthritis systemic vasculitis polymyalgia rheumatica Reiter's disease Crohn's disease familial Mediterranean fever
Transplantation	renal transplantation
Cancer	lymphoma sarcoma
Necrosis	myocardial infarction tumour embolisation acute pancreatitis
Trauma	burns fractures

Minor or no elevations

Inflammatory disease	systemic lupus erythematosus systemic sclerosis dermatomyositis ulcerative colitis Sjogren's syndrome
Transplantation	graft versus host disease
Cancer	leukaemia

The 'metabolic syndrome'

The metabolic syndrome refers to a constellation of risk factors for cardiovascular disease and type 2 diabetes, which are generally associated with obesity and insulin resistance. The role of inflammation in the pathogenesis of metabolic syndrome is increasingly being recognised. While an association between ultra-sensitive C-reactive protein and vascular risk exists at a population level⁴, data suggesting a role for ultra-sensitive C-reactive protein in assessing an individual's cardiovascular risk and offering interventions are conflicting and inconclusive.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) also provides a measure of inflammation. It reflects concentrations of fibrinogen and alpha-globulins.⁵ However, ESR is also influenced by immunoglobulins that are not acute-phase proteins. 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. This, plus the influence of various other factors on the ESR such as diurnal variation, anaemia, food intake and red cell morphology, makes it an imprecise guide to disease activity in most cases.

C-reactive protein or ESR?

C-reactive protein is superior to ESR in terms of rapidity of response and specificity for inflammation. Measuring C-reactive protein is also more precise and reproducible and a quicker test to perform. However, ESR measurements remain helpful in certain clinical situations such as the detection of paraproteinaemias, which often do not elicit an acute phase response.

Conclusion

When used in conjunction with clinical assessment, C-reactive protein measurement is a useful tool for evaluating possible infective or inflammatory disease. However, as with any diagnostic test, false positives and false negatives can occur, and no test represents a replacement for thorough clinical review.

References

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