Leading article

Why measure C reactive protein?

Some of the most important questions clinicians ask can be phrased in very simple terms:

Is this patient getting better?

Is he or she getting worse?

Are complications arising? And even

Is there anything wrong with this person?

Measurement of circulating levels of C reactive protein (CRP) has emerged as a robust and useful tool that can help answer these questions.

A raised serum CRP concentration is one measure of the combination of events known as the 'acute phase response'. In its fully developed form, the acute phase response is *illness* – fever, malaise, anorexia, leukocytosis, negative nitrogen balance – which forms a cardinal response of the body to infection and trauma, and may be the result of many immunological reactions and inflammatory processes. The acute phase response also involves changes in the plasma concentrations of a number of liver synthesised proteins. These range from small increases in weak acute phase proteins such as C3 complement, and a two to fourfold rise in proteins such as α_1 -acid glycoprotein (serum orosomucoid for the traditionalist), fibrinogen, and α_1 -antitrypsin, to spectacular rises in a few proteins such as CRP and amyloid A-associated protein. The levels of these may be increased up to a thousandfold over basal. The increases in these acute phase proteins are accompanied by transient, modest reductions in the concentrations of the negative acute phase proteins, of which albumin and transferrin are typical examples.¹⁻³

Measurement of the existence of these changes in the plasma profile, of course, underlies one of the traditional approaches to quantifying the acute phase response, measuring the erythrocyte sedimentation rate (ESR). The ESR reflects these changes in the various acute phase proteins, but it is affected by factors such as anaemia and hyperglobulinaemia, which may be irrelevant to the acute phase response in some people. As the ESR reflects changes in many serum proteins, some of which have long half lives, it is often slow to alter when there are major clinical changes. In safety and cost conscious laboratories, the manipulations of the blood sample involved in measurement of this non-specific test may outweigh the apparent simplicity of the technique. The alternative approach of accurately quantitating a single rapidly responding acute phase protein such as CRP has much to commend it.⁴

CRP, so called because of the proteinic nature of the C-reactive substance was first discovered when a precipitate was formed where pneumococcal C-polysaccharide was added to the sera of ill patients.⁵ It is about 105 000 in molecular weight, coded on chromosome 1 with an intriguing pentagonal shape.⁶ The functions now being attributed to it are appropriate to a non-specific defence protein generated during inflammation and trauma. CRP accumulates at sites of cell injury, and is selectively deposited on necrotic cells that have exposed damaged membrane phospholipid: CRP can also complex with free DNA released from lysed cells.^{7,8} There is evidence of a variety of other functions, as the protein can bind to platelets, polymorphonuclear leukocytes, and macrophages, and can modulate some lymphocyte functions.⁹⁻¹²

CRP is synthesised in the liver, and during the onset of an

inflammatory response a progressively greater number of hepatocytes are recruited to its synthesis.¹³ This recruitment has been shown in experimental systems to be extremely rapid, the early increase in mRNA in the liver translates into raised circulating levels of the protein approximately six hours after tissue injury.¹⁴ Within 24–48 hours the increase may be a thousandfold. The reduction in the plasma CRP concentration as the acute phase response subsides may be similarly rapid, with a fall from peak with a half time of 48 hours, as hepatocyte production of CRP rapidly decreases.^{15,16} The biological half life of the circulating protein itself is 19 hours.¹⁷

The liver is stimulated to produce CRP by soluble cytokines, produced notably by cells of the macrophage series, but also by other leukocytes and other tissues such as endothelium. The cytokines IL (interleukin)-1, IL-6, and IL-11; tumour necrosis factor- α (TNF- α); and transforming growth factor- β (TGF- β) all have a role in stimulating transcription of the genes controlling hepatic acute phase production.¹⁸⁻²³ The generation of these cytokines by macrophages is an extremely early event in the response to infection or trauma – for example one of the strongest stimuli to macrophage production is bacterial lipopolysaccharide. By measuring CRP in the plasma, the clinician has access to direct evidence that the body has started to mobilise its non-specific defences.

Where is this useful to the gastroenterologist? Recent publications indicate a variety of settings – the assessment of inflammatory bowel disease, detection of sepsis, and prognosis of acute pancreatitis being the most prominent.

Inflammatory bowel disease

The assessment of patients with inflammatory bowel disease is often complex, requiring a combination of clinical, laboratory, and endoscopic, radiological, or scanning techniques. This is particularly so in Crohn's disease, which lacks the relatively uniform symptoms, and direct access to rectal inflammation, characteristic of ulcerative colitis.²⁴ In clinical trials of Crohn's disease, objective criteria of gut inflammation are desirable, particularly if quantifiable. In the individual patient, separating symptoms attributable to an active inflammatory process from those of chronic fibrotic strictures may determine whether surgery is appropriate.

The CRP value is particularly helpful in Crohn's disease, both in trials and in individual patient management.²⁵ Pepys²⁶ pointed out that, while the CRP concentration rises in both active ulcerative colitis and Crohn's disease, for comparable degrees of severity the increases in CRP are much greater in Crohn's disease. Recent work has suggested a greater production of CRP stimulating cytokines from mononuclear leukocytes in Crohn's disease patients.²⁷

There is a good overall correlation between the clinical symptoms in Crohn's disease (the 'activity indices') and the circulating CRP concentration²⁸; but the important fact is that the correlation is not perfect. If it were, why bother the laboratory? Consider a patient with pain, diarrhoea, and malaise – raised CRP is a clear indication that there is active inflammation present that may reflect the intrinsic inflammatory processes of Crohn's disease; a low CRP implies the absence of an active inflammatory process. CRP estimation is

thus an objective guide to assessing the potential value of corticosteroid or other anti-inflammatory regimens. It is also a useful parameter with which to monitor the success of treatment; the CRP value falls rapidly as inflammation comes under control.^{24,28} A high serum CRP value can, of course, occur in a patient with Crohn's disease for reasons other than active Crohn's disease, but this too can be clinically helpful. Crohn's disease complicated by an indolent abscess may have its presence heralded by a high CRP value.

In the initial outpatient assessment of patients with abdominal discomfort or diarrhoea, a normal CRP estimation is helpful in supporting a diagnosis of irritable rather than inflammatory bowel disease.²⁹

Detection of sepsis

A CRP response also occurs with other intra-abdominal pathology. CRP is a rapid and sensitive aid to the diagnosis of appendicitis. The increase in CRP is related to the time elapsed since the onset of symptoms, and is dependent on the amount of appendicular infiltration and inflammation present. Its diagnostic efficiency in acute appendicitis is higher than the ESR. The CRP concentration is also a better indicator of acute appendicitis than the white blood cell count. When both of these parameters and the number of segmented leukocytes are within the normal range the diagnosis of acute appendicitis is highly unlikely.³⁰⁻³²

After surgery

Surgical procedures may trigger a transient rise in serum CRP as a response to cytokines which are secreted in response to trauma. Serum CRP showed no detectable increase after minor surgery for example, lumpectomy. In patients who underwent uncomplicated major surgery, however, CRP rose above baseline eight to 12 hours after incision, and reached a maximum in 48 to 72 hours, before levelling off towards normal over five to 14 days.³³⁻³⁶ Interruption of the rapid decline in CRP by a second rise or persisting elevation is therefore a helpful clue to postoperative infection or another complication.

Acute pancreatitis

In the management of acute pancreatitis it is important to distinguish between interstitial oedematous pancreatitis and necrotising pancreatitis. While contrast enhanced computed tomography has an established role, measurement of markers such as CRP, polymorphonuclear elastase (PMN elastase), and antiproteases are useful in detecting pancreatic necrosis.³⁷

A raised serum CRP has been explored as a prognostic index to define high risk patients and predict the course of the disease. These studies now suggest that CRP is the best single serum parameter for distinguishing between mild and severe acute pancreatitis.^{38,39} Büchler⁴⁰ reported that CRP showed an overall accuracy of 93% in the detection of pancreatic necrosis; a serum CRP concentration of $>$ or <100 mg/l distinguished between patients with a better or worse prognosis with 100% sensitivity and 86% specificity. Severe complications of acute pancreatitis and duration of ileus were also related to the CRP.⁴¹

Since CRP is induced in response to cytokines, it is not surprising that estimations of cytokines themselves may provide an even earlier clue to detecting and measuring the acute phase response. Recently interleukin-6 was suggested as an even better early parameter for the assessment of the severity of acute pancreatitis than CRP.⁴² However, CRP is now available as a standard laboratory assay, whereas cytokine assays are largely confined to research laboratories

and it will probably be sometime before the even earlier warnings provided by cytokine estimations become generally available.

Liver diseases

Patients with alcoholic liver disease exhibit many biochemical abnormalities and clinical complications that may be cytokine mediated such as fever, neutrophilia, hypergammaglobulinaemia, and increased production of acute phase reactants including CRP.^{43,44} However, in acute viral hepatitis, in spite of the presence of inflammatory changes in the liver, there is no accompanying systemic acute phase response, and only small changes in serum CRP concentrations occur. Similarly, there are mild disturbances only of acute phase reactants in chronic viral hepatitis. One recent report suggests that hepatocellular carcinoma may be associated with increased CRP, noted in 78% of 104 patients with this disorder.⁴⁵

Other diseases

Some predominantly immune-driven diseases such as rheumatoid arthritis, and vasculitides such as Behçet's or Wegener's granulomatosis also show high serum CRP values, and as with Crohn's disease these may be used to monitor the response to treatment. Some neoplasms of the reticulo-endothelial system, including lymphoma and Castleman's disease, may also be associated with high CRP values reflecting cytokine release from either neoplastic tissue or in response to the presence of neoplasia.

CRP assays

Several quantitative immunoassays for monitoring changes in CRP are currently available. The assay technology has reached an advanced state of development and rapid analysis can be provided using automated analysers which are also efficient and cost effective in handling large number of samples. The cost of performing a screening test for CRP in the UK is currently £0.50–0.60 per test.

Automated methods include immunoturbidimetric assays based on the reaction between an antibody and sample CRP in a dilute solution. This method is capable of quantitative measurements between 2.0–200.0 mg/l (Beecham J, personal communication). Values less than 6.0 mg/l are considered normal and those exceeding 6.0 mg/l are regarded as evidence of a raised CRP in serum. Rocket immunoelectrophoresis and radial immunodiffusion procedures, although time consuming and requiring expertise, may be required for analysing samples which contain interfering material such as lipaemic and icteric samples.

Conclusion

In requesting an estimate of the circulating CRP concentration, the clinician is seeking objective evidence that the body has initiated an acute phase response. The CRP value is a surrogate for direct assessment of cytokine generation, and is valuable in confirming the presence of inflammation, assessing its severity, and monitoring the response to treatment and the development of complications.

M Z MAZLAM
H J F HODGSON

Gastroenterology Unit,
Department of Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
150 Ducane Road,
London W12 0NN

Correspondence to: Professor H J F Hodgson

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