C-reactive protein (CRP) is a highly conserved acute phase protein involved in innate inflammatory response. This vital arm of the immune response is the first line of defence, working parallel to the adaptive immune system to clear invading pathogens or microbes. CRP is released from hepatocytes under the stimulation of the cytokines, interleukin 6 (IL-6) or the tumour necrosis factor (TNF) under control of IL-6. These cytokines commonly originate at the site of pathology. Following release, CRP will bind to the offending antigen, via a calcium-dependent mechanism, where it can aid the process of phagocytic binding.

The serum concentration of CRP increases rapidly within hours upon immunological insult, microbial infection or tissue damage. De novo hepatic synthesis is stimulated promptly and serum levels can reach pathological concentrations (above 5mg/l) within six hours, reaching the maximum within 48–72 hours. This can be up to 1,000-fold that of basal levels and implies that it is solely the rate of release that is indicative of a persistent stimulus or immunological challenge. When the stimulus for production ceases, CRP concentration decreases at a rate similar to that of plasma clearance. CRP is thus regarded as a useful diagnostic tool to monitor the acute phase of inflammation.

CRP - A Successful Tool for Clinical Diagnostics

In recent years the increasing validity of data from CRP investigations has supported its use as a widely accepted and wholly appropriate marker of systemic inflammation. CRP can be used to screen or monitor infection and non-infectious inflammatory diseases and to direct therapy. Thus it can replace or complement more traditional tests such as white blood cell count (WBC) and erythrocyte sedimentation rate (ESR). Recent observations have shown that CRP, when compared with ESR and WBC count, may be the most useful and versatile marker of inflammation. ESR is an established diagnostic test that indirectly reflects the acute phase response to inflammatory disease. The sedimentation is accelerated by the increased plasma concentration of acute phase proteins. It is simple and inexpensive but does have some limitations. There are clear advantages associated with CRP analysis during the acute phase response in comparison with other laboratory tests, such as ESR, as the circulating levels are more accurately representative of infection/disease progression. The response time for CRP following the onset of inflammation is hours, not days or weeks as for ESR, and the test time is much shorter, compared with ESR (see Figure 1).

Additionally, CRP’s reliability is supported by the fact that the serum concentration and secretory levels remain unaltered by eating and display little or no interference by most drug administration unless, of course, they alter the inflammatory stimulus. Alternatively, ESR can be influenced by sex, inflammation, oestrogen status, immunoglobulin levels, hyperlipidaemia, hypo-albuminemia, severe anaemia and the number and morphology of red blood cells present.2,3 Nevertheless, as with all laboratory tests, CRP and ESR must always be interpreted in the full light of the patient’s clinical information.

CRP, ESR and WBC, including automated differential count, all have sufficient analytical characteristics using modern laboratory equipment. However, in the case of manual microscopic analysis of WBC and differential count, care should be taken and they should only be used for specific cases as there is an increased risk of human error. To discriminate between bacterial or viral infection it is evident, in most cases, that determination of CRP better supports clinical decision. For the diagnosis, prognosis and treatment management of patients with non-infectious acute inflammatory diseases, CRP works better than ESR in the majority of cases, yet for the diagnosis and follow-up of chronic inflammatory diseases, or conditions where inflammation and stimulation of the immune system occur in parallel, the simultaneous use of CRP and ESR can be useful, especially in general practice.2
Clinical Applications of CRP – Diagnosis, Prognosis and Therapy Management

CRP is one of many standard diagnostic tests used within centralised hospital laboratories to monitor a series of inflammatory conditions. At present CRP analysis is predominantly employed to monitor the extent or activity of disease and the effect of treatment. CRP analysis is also a useful test for supporting the diagnosis of infections and has proven to be a valuable tool in differential diagnosis. Such examples include bacterial versus viral infections, pneumonia versus bronchitis and phylonephritis versus cystitis. High levels of CRP are associated with bacterial infection, but low-level elevations are, in most cases, indicative of viral infection. CRP can enable the comprehensive monitoring of bacterial complications to disease and post-operative infection complications. CRP measurement can contribute greatly to the detection of intercurrent infection in immuno-compromised individuals. One key characteristic is that increased levels of CRP mimic temperature fluctuations during fever. Therefore, such close monitoring of the patient can allow not only acute diagnosis and prognosis, but also dynamic analysis of infection progression. Consequently, it is suitable for use with a number of conditions such as tuberculosis, rheumatoid arthritis, Crohn’s disease, myocardial infarction (MI) and trauma following surgery, burns or fractures. Additionally, CRP can aid the monitoring of malignant conditions such as lymphomas, carcinomas and sarcomas.

With such a broad spectrum of diagnostic applications, CRP has a lot to offer as a point-of-care (POC) test. Relocating the test closer to the patient’s bedside or to the local general practitioner (GP’s) surgery could provide a plethora of advantages for both the patient and the healthcare service.

Clinical and Economical Advantages of CRP POC Testing

There are distinct advantages, both clinical and economical, to POC testing CRP analysis compared with the laboratory-based counterparts. The use of CRP testing in general practice could be beneficial both to the healthcare sector and the patients. With such reliable diagnostic tests in place, patients may be discharged from the hospital earlier and receive regular checks and treatment from the GP’s surgery, thus reducing the workload and costs attached to an already stretched hospital network. In general practice settings, tests such as ESR and WBC count, including WBC differential count, can be carried out on site. However, this can be a time-consuming process with such interpersonal variation that the accuracy of results can be compromised, thus they are usually limited to specific conditions or cases such as malignant blood disorders. Serum concentration of CRP can provide a more useful variable. Axis-Shield provides rapid, quantitative and easy-to-use systems for CRP POC testing (http://www.axis-shield-poc.com). The well established NycoCard® Reader II (see Figure 1) and recently introduced Afinion™ AS100 Analyzer (see Figure 2) both have applications for CRP POC testing. Using just one small drop of whole blood, a reliable CRP result, comparable with those produced in hospital laboratories, is obtained within a few minutes. The CRP tests do not require centrifugation or the use of additional instrumentation, and so are suitable for use on hospital wards, at the patient’s bedside and in the GP’s consulting office.

CRP POC testing is of special value for the detection of an inflammatory response in respiratory or urinary tract infections. Up to 40% of patients visiting GP surgeries can exhibit the symptoms indicative of these types of infections. The CRP test in a POC setting can be a useful tool to differentiate between pneumonia, acute bronchitis and obstructive lung disease or heart failure and can assist in the diagnosis of bacterial versus viral upper respiratory tract infections. CRP POC testing also has diagnostic applications for acute pyelonephritis and cystitis, and can be extremely efficient when used to monitor the effect of antibacterial treatment. Additionally, for women under GP supervision for antenatal monitoring, results achieved using the CRP test at the POC may aid and speed the diagnosis of infections during pregnancy. In the cases of acute inflammatory disorders or fevers of unknown aetiology it is believed that on-the-spot CRP tests

![Typical Changes of CRP, Fibrinogen, ESR and Albumin During the Acute Phase.](image-url)
could provide quick and accurate results within the consultation period that could support diagnosis and direct therapy or, more urgently, a speedy referral to the appropriate medical facility.

The NycoCard and Afinion POC CRP tests are also suitable for hospital use in the emergency room (ER), the intensive care unit (ICU) and haematology, oncology, rheumatology and paediatric units. Both in the hospital and in the GP’s surgery the rapid results achieved from CRP POC testing can save time for the physician and patient through faster and fewer consultations, in addition to reducing the demand on staff resources. An increased turnaround of results allows the physician to, on the basis of the test information at hand, initiate, stop or modify treatment during one patient consultation. In the case of infection, for example, a rapid, quantitative CRP test can be used to support the diagnosis of infection or monitor the infection profile. CRP POC testing enables the dynamic analysis of infection progression that can lead to a more appropriate or prompt administration of antibiotic therapy or withdrawal if required. CRP levels reflect inflammatory activity during treatment, remission and recurrence of the disease. With follow-up CRP testing, the course of the illness and the efficacy of any antibiotic treatment can therefore be monitored. In the present climate, where the incidence of antibiotic resistance seems on the increase, one of the major benefits of CRP POC tests is to rule out patients that do not require immediate, if any, antibiotic treatment. This is highly applicable when dealing with virus infections or self-limiting bacterial upper respiratory tract infections, acute bronchitis and influenza. These measures would enable a more targeted therapeutic approach reducing the risk of acquiring antibiotic resistance.

POC testing enhances evidence-based medical decision-making, improving patient diagnosis, prognosis and treatment with the added benefit of potentially reducing the costs associated with prolonged hospital stays or unnecessary treatment.

**High Sensitivity CRP for POC testing**

Work to increase the sensitivities of CRP assays has meant that in the near future POC testing can be applied to discrete target groups where serum fluctuations are minor. High sensitive CRP (hs-CRP) analysis has been developed for the detection of low levels of CRP and has been applied to monitor neonatal infection and patients at risk of future cardiovascular events.

Serum CRP analysis in neonates could have profound effects on diagnosis and subsequent treatment. Neonatal levels of CRP are lower than adults, and the increases in the pathological state are not so pronounced, therefore hs-CRP tests show great potential for CRP analysis in neonates. Prompt and accurate measurements of neonatal serum CRP, using a highly sensitive POC test system, in the six to 12 hours following infection, may be crucial for effective and optimal treatment. The treatment window for neonates remains extremely small due to the rapid progression of infection, meaning that early initiation and sometimes unnecessary administration of antibiotic therapy frequently occurs. However, with rapid hs-CRP analysis and result delivery, inappropriate antibiotic treatment could be prevented. This can therefore reduce the risks associated with antibiotic treatment, recovery time and the subsequent costs attached.

Additionally, these highly sensitive methodologies have also been developed to accompany a panel of markers including high cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL), and homocysteine levels. Elevated concentrations of these molecules are thought to be
indicative of an individual’s increased risk for cardiovascular (CV) disease and MI and there is evidence to support the association between inflammatory markers such as CRP, coronary heart disease (CHD) and stroke.10 These minor elevations in serum CRP associated with low grade inflammation may be involved in the pathogenesis of atherosclerosis and therefore indicative of the future occurrence of CV events.11 The use of CRP POC testing as a prognostic tool, means that long-term preventative treatment plans can be developed.12,13

Conclusion

In summary, the use of CRP as a diagnostic tool has increased steadily over the last few years. The plethora of clinical applications and easy detection has meant that CRP is an extremely versatile and robust marker of inflammation and disease. The more recent move to use CRP for POC testing has increased its potential for use across the healthcare sector and the rational for doing so is both clear and supported. The NycoCard and Afinion CRP POC test systems, produced by Axis-Shield, can provide improved patient diagnosis, prognosis and therapy management. As part of a cost control plan, CRP POC testing can aid both staff and patients within the clinical diagnostic environment.

NycoCard and Afinion are trademarks for in vitro diagnostic POC test systems manufactured by Axis-Shield.

References