

# Feature Article

Application

## CRP (C reactive protein) Basics and Clinical Application of CRP



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Accurate identification of infected organs, an infecting organism, the necessity of an antimicrobial and the degree of severity is important for the treatment of infection, for which it is essential to understand accurately the severity of inflammation. However, even if doctors perform careful evaluations, we occasionally come across the cases in which it is difficult to understand exactly the inflammation. These situations require a simple and accurate inflammatory marker. Although many inflammatory markers have been developed, there is no biomarker useful by itself for all of diagnosis, prognostic prediction, response evaluation and healing evaluation. CRP is considered to be useful in the treatment of infection as a biomarker that reflects the clinical course rapidly, at a low cost and in a balanced manner. Moreover, if we understand the mechanism of CRP production and its weak point, it has a great deal of potential in the daily medical practice.

### Introduction

Accurate identification of the severity of inflammation is very important to decide a policy of infection treatment, for which it is essential to confirm vital signs, such as the body temperature, respiratory rate, pulse, blood pressure, and consciousness level, in addition to careful examination of the locally infected site. Various modalities, such as ultrasonography and computed tomography, have recently been frequently used and may have improved the diagnosis rate. However, at actual clinical sites, some cases physically diagnosed as relatively mild are severer than expected, or it sometimes becomes a problem to overlook abnormalities on imaging diagnosis. This situations show a simple and accurate inflammatory marker as a tool to identify the “severity of inflammation” is needed. Out of the many inflammatory markers, in this report, we focus on CRP and enlighten its usefulness for the treatment of infection.

### What is CRP?

CRP is an acute-phase reactive substance discovered in the serum of patients with pneumococcal infection, and it was named so because it reacts and forms a precipitate with pneumococcal C polysaccharide.<sup>[1]</sup> It exists as a pentamer comprised of 5 non-covalently bound identical subunits.<sup>[2]</sup> (Figure 1) In Japan, it is widely used as an important biomarker to define infection treatment. The baseline range of CRP was reviewed as the measurement

sensitivity increased, and it has been reported to be 0.2 mg/dL or lower.<sup>[3]</sup> In Japan, ‘mg/dL’ is used as a common unit of CRP measurement, but the SI unit (mg/L) is recommended internationally, and ‘mg/L’ is used overseas. Regarding the CRP production mechanism, monocytes and macrophages are mainly activated in response to the ‘causative microorganism’ and ‘tissue injury’, and inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , are produced. These cytokines act on and induce IL-6 production in Kupffer cells in the liver, then CRP is

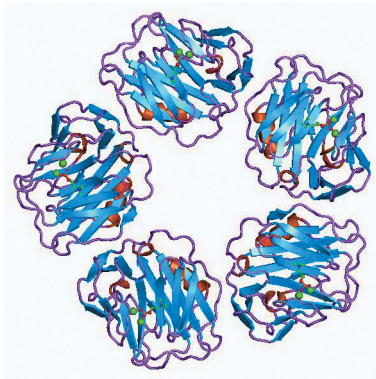


Figure 1 Structure of CRP<sup>[2]</sup>

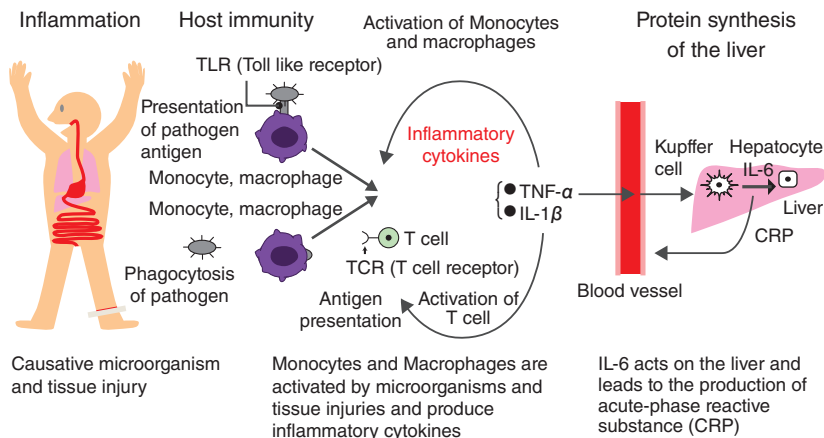


Figure 2 Process of CRP production

finally synthesized and secreted by hepatocytes. Accordingly, CRP production is modified by the following factors. (Figure 2)

- (1) Severity of inflammation
- (2) Host immunity
- (3) Ability of protein synthesis

### Significance of CRP production

CRP binds to phosphoryl choline present on the surfaces of ‘microorganisms, mainly bacteria’ and ‘cells of injured tissues’, which then bind to the first complement component of the classic pathway, C1. As a result, complement system is activated, which finally plays important roles in the following processes.<sup>[4, 5]</sup> (Figure 3)

- (1) Further induction of inflammation
- (2) Lysis of microorganisms by forming a Membrane Attack Complex (MAC)
- (3) Elimination of foreign bodies, necrotized cells, and apoptotic cells by opsonization and phagocytosis

CRP is an important protein for the maintenance of homeostasis of the human body involved in ‘host defense’ as a part of natural immunity. MAC described above represents the C5b6789 complex comprised of C5b bound by B C6, C7, C8, and C9, and this is the final product of the complement system. MAC has a cylindrical structure, and it is incorporated into the cell membrane by making a hole. Water and ions influx through this hole, inducing cell swelling and rupture. This series of actions is termed immune bacteriolysis.

### CRP Production

CRP starts to increase about 6-8 hours after the onset of inflammation, peaks at 48-72 hours, and slowly decreases. Since CRP production delays in the early phase of inflammation, a low CRP level is often encountered, despite clinical symptoms being severe. However, the course thereafter may relatively sensitively reflect the clinical course. Considering that CRP is produced as a ‘host defense reaction’ to inflammation, the CRP level basically reflects the severity of inflammation. However, since it is influenced by ‘host immunity (administration of steroids and immunosuppressors, complication of hematological disorders and HIV/AIDS) and the ‘ability of protein synthesis (fulminant hepatitis)’ as described above, comparison of the CRP level among individuals is not clinically useful, and it is important to observe the trend within each individual.

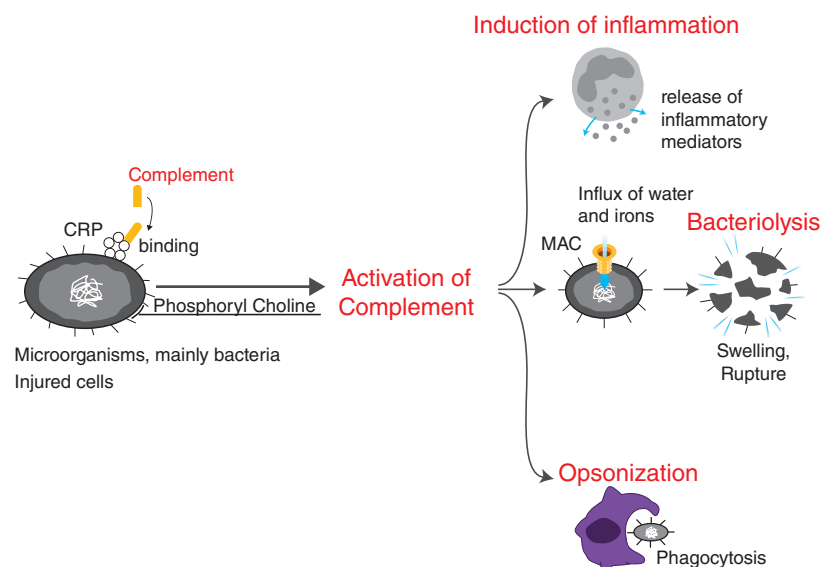


Figure 3 Role of CRP in human body

Table 1 Main causes of false-positive and -negative results of PCT measurement. (cited from ref. [9])

<p>Common causes of false-negative and false-positive results:</p> <p>False-positive (i.e., falsely high levels in the absence of a bacterial infection):</p> <ul style="list-style-type: none"> <li>· Newborns (physiologically) during first days of life</li> <li>· Acute respiratory distress syndrome acute attacks of plasmodium falciparum malaria systemic fungal</li> <li>· Infections (e.g., candidiasis, aspergillosis)</li> <li>· Severe mechanical trauma</li> <li>· Following surgical trauma</li> <li>· Administration of monoclonal or polyclonal anti-thymocyte globulin in the treatment of care</li> <li>· Rejection after transplantation</li> <li>· Chemical pneumonitis</li> <li>· Severe burns and heat strokes</li> <li>· Patients with medullary thyroid cancer, small cell cancer of the lung, carcinoid tumours with</li> <li>· Paraneoplastic hormone production</li> <li>· Inflammation associated with "cytokine storms", e.g., IL <math>\beta</math>, in familial Mediterranean fever, therapeutic</li> <li>· Infusions of TNF <math>\alpha</math> for melanoma</li> </ul> <p>False-negative (i.e., falsely low levels in the presence of a bacterial infection):</p> <ul style="list-style-type: none"> <li>· Early course of infections</li> <li>· Localized infections</li> <li>· Subacute endocarditis</li> </ul>
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In addition, CRP reflects not only infection but also tissue injury and necrosis. Therefore, it should be kept in mind that the CRP level also rises in allergy, collagen disease (rheumatoid arthritis, systemic lupus erythematosus, rheumatic fever), malignant tumor, fracture, trauma, and myocardial infarction.

### Other Inflammatory Markers

#### Procalcitonin (PCT)

PCT is synthesized as a precursor of calcitonin by thyroid c cells in healthy individuals,<sup>[6]</sup> but it is secreted mainly by the liver, kidney, adipocytes, and muscle in response to various cytokine stimulations in severe infection.<sup>[7]</sup> Reportedly, PCT production is not influenced by steroids,<sup>[8]</sup> and PCT was previously reported to be superior to CRP in the differential diagnosis of bacterial sepsis and severity judgment. However, false negativity in acute-phase and local infections and false positivity in severe trauma, surgical invasion, and cytokine storm have been reported in some later studies.<sup>[9]</sup> (Table 1) Currently, PCT is considered appropriate as an index for the withdrawal of antibacterial agents, but not for judgment of the severity of infection in some reports.<sup>[10]</sup> At present, it is unlikely that PCT is able to substitute other inflammatory markers because only limited medical institutions can measure it at their own facilities, and the cost of the test remains an issue.

#### Erythrocyte sedimentation rate (ESR)

ESR was originally measured as the speed of red blood cell sedimentation in a specific time in citric acid-added whole blood in a vertically stood glass tube (Westergren

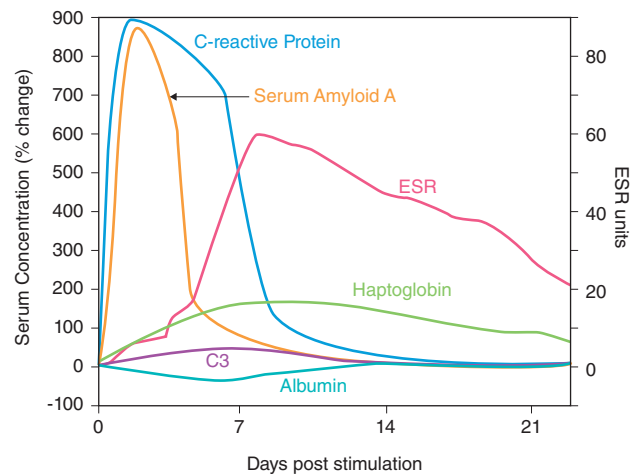


Figure 4 Time-course changes in acute inflammatory markers. (cited from ref. [11])

tube). When inflammation occurs, the negative charge of the red blood cell surface is neutralized by positively charged fibrinogen and immunoglobulin, and red blood cells come to readily form rouleaux with each other. Since the test is simple and the cost is low, it is commonly used as a nonspecific inflammatory marker. However, errors due to pathologies other than inflammation are likely to occur because the test does not directly measure acute-phase protein. Therefore, attention should be particularly paid to the influences of fibrinogen and immunoglobulin, which are blood coagulation factors, and the red blood cell volume and morphology. For example, ESR rises in multiple myeloma and anemia, and decreases in disseminated intravascular coagulation in many cases. Since the onset of change in ESR is not as rapid as CRP, and ESR alters slowly compared to CRP,<sup>[11]</sup> (Figure 4) its clinical application for acute inflammation is not appropriate. Mary et al. stated in their book that CRP is more sensitive than ESR.<sup>[12]</sup> In addition, Colombet et al. assessed the agreement between ESR and CRP in all patients measured both markers at the same time in their hospital during a 1 year period, and a disagreement was observed in 33% of the patients (elevated ESR / normal CRP in 28%, normal ESR / elevated CRP in 5%). Then, 99 patients were randomly selected from the patients with discordant results and their medical charts were reviewed. It showed that 25 patients with elevated CRP and normal ESR had an active inflammatory disease (false-negative ESR) and among 74 patients with elevated ESR and normal CRP, 32% of the patients had resolving inflammatory disorders, 28% disclosed a variable interfering with the ESR measure (false-positive ESR), 32% had unexplained discrepancies, and 8% had an active inflammatory disease (false-negative CRP). As a result, they finally concluded that priority should be given to CRP measure when an inflammatory disorder is

suspected.<sup>[13]</sup> Therefore, the significance of ESR measurement for acute inflammation is currently low because CRP can be measured at a relatively low cost. Its use may be more appropriate for the exclusion of temporal arteritis and polymyalgia rheumatica, screening of inflammatory diseases, and as an index of chronic inflammation.

### White blood cells (WBC)

When inflammation occurs, a sharp increase in the white blood cell count results, and neutrophils normally stored in the spleen, liver, and lung are mobilized in bacterial infection through the actions of various cytokines, mainly granulocyte Colony-Stimulating Factor (G-CSF). Since this reaction occurs within several hours after infection, WBC measurement is used to diagnose the early phase of infection. However, the count increases in various diseases, such as hematological disorders, malignant tumor, cerebral infarction, gout, myocardial infarction, and trauma, showing very poor disease specificity. Therefore, it cannot be used alone to diagnose bacterial infection or as a prognostic factor. To appropriately use the early reactivity of WBC, it may be necessary to use it in combination with an inflammatory marker playing a supplemental role, such as CRP. Regarding the differentiation of bacterial and viral infections, the former is accompanied by a WBC increase mainly constituted of neutrophils, whereas WBC induction is relatively poor in the latter, and lymphocytes increase in many cases when the count rises. Utilizing these characteristics, WBC may be functional to differentiate between bacterial and viral infections, although there are some exceptions. Here, we introduce data showing time-course changes in the CRP, ESR, and values. Markus et al. followed these in children with bone marrow and joint infections for one year after discharge.<sup>[15]</sup> (Figure 5). As described above, their time-course changes on infection showed individual characteristics. CRP showed a slightly poor response in the hyperacute phase compared to WBC, but it sensitively reflected inflammation in the acute through chronic phase, showing the usefulness for judgment of the treatment effect for not only acute but also chronic infection. WBC cannot be used for evaluation after the acute phase because it did not markedly change after day 5 of the illness, but it may be appropriate to use it in the early treatment phase to supplement for the low sensitivity of CRP and ESR in the hyperacute phase. ESR is inappropriate to judge the effect of early treatment of chronic infection because it slowly changes in the acute through chronic phase, and it is desirable to use it for judgment of the effect of long-term treatment in the same manner as before.

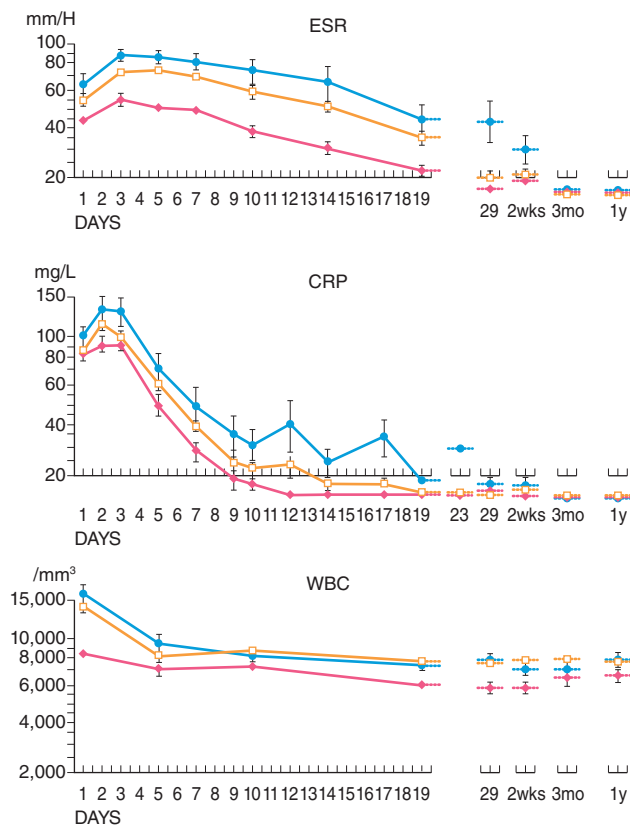


Figure 5 Time-course changes in ESR, CRP, and WBC in children with bone marrow and joint infections. (cited from ref. [14])

## Conclusions

Basic features of CRP, such as the mechanism and significance of production and comparison with other inflammatory markers, were mainly outlined in this section.

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