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REVIEW

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C-reactive protein: a valuable marker of sepsis

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Introduction

The word sepsis originated from the old Greek word meaning "putrefaction". Nowadays, this term is used to describe the host systemic response to infectious stimuli that is characterised by clinical, haemodynamic, biochemical and inflammatory responses [1]. Sepsis is still one of the leading causes of death in the critically ill [2]. Despite all the research performed over the last two decades, few specific treatments have been shown to improve outcome.

In daily practice, clinicians are often faced with two dilemmas: whether a patient is infected or not, and whether the antibiotic therapy being given is effective. The distinction between infection and sepsis is frequently difficult to make. Infection without sepsis can occur if the process remains localised. A sepsis-like syndrome without infection is also a frequent finding in conditions such as trauma and pancreatitis [3]. The attention of the clinician must be directed towards the early diagnosis of infection [4]. However, bacteriological confirmation may be difficult to obtain and negative cultures do not exclude the presence of infection. In addition, manifestations of sepsis such as fever, leukocytosis and tachycardia are neither specific nor sensitive for infection, nor for monitoring the response to therapy [5]. Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection. C-reactive protein (CRP) is one such marker.

Physiology of C-reactive protein

C-reactive protein is a long-established marker of sepsis. In 1930, Tillet and Francis identified, in the sera of patients with pneumonia, the capacity to precipitate polysaccharide fractions, designated as fraction C, from *Streptococcus pneumoniae* [6]. This property quickly disappeared as patients recovered and was not identified in healthy volunteers. When the cause of this reaction was identified as a protein, it was named CRP. The "acute phase" designation was introduced to classify acutely ill patients with infection whose sera was CRP positive. Since then, several other acute phase proteins have been described.

C-reactive protein belongs to the pentraxin family of proteins, so called because they form a cyclic pentamer

composed of five identical non-glycosylated sub-units, non-covalently bound and organised in a very stable discoid-like structure [7]. Each monomer weighs 23027 Da and is highly resistant to proteolysis [8]. The other major member of this family is the serum amyloid P component. These proteins are conserved throughout vertebrate evolution, suggesting that CRP has a central role in the immune response [9, 10].

C-reactive protein binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi and parasites in the presence of calcium. These complexes activate the classical complement pathway, acting as opsonins and promoting phagocytosis [11]. Together with complement components, CRP is the only acute phase protein directly involved in the clearance of micro-organisms. In vitro, CRP stimulates cell-mediated cytotoxicity through activation of neutrophils, promoting platelet degranulation and enhancing NK cell activity [7, 9]. Under physiological conditions, CRP binds to small nuclear ribonucleoproteins, suggesting a direct role in the removal of necrotic tissue [12].

The potential role of CRP in eliminating bacteria has been recently demonstrated. Transgenic mice that express high levels of human CRP in serum in response to endotoxin are partially protected against lethal infection by *Streptococcus pneumoniae* [13]. This effect is probably mediated by CRP's ability to bind to phosphocoline moieties in the *Streptococcus pneumoniae* cell wall C-polysaccharide. CRP transgenic mice also exhibit increased resistance to lethal infection against the Gram-negative bacterium, *Salmonella typhimurium* [14].

The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples [7, 10]. Levels above these values are abnormal and indicate the presence of a disease process.

As with many other acute phase proteins, CRP is predominantly synthesised by the liver, mainly in response to interleukin 6 (IL-6) [5]. A good correlation exists between CRP and IL-6 levels [15]. Tumour necrosis factor α (TNFα) and IL-1β are also regulatory mediators of CRP synthesis [5]. The secretion of CRP begins within 4–6 h of the stimulus, doubling every 8 h and peaking at 36–50 h. With a very intense stimulus, the CRP concentration can rise above 500 mg/l, i.e. more than 1000 times the reference value [7, 10, 16, 17]. After disappearance or removal of the stimulus, CRP falls rapidly, as it has a half-life of 19 h [10]. However, CRP can remain elevated, even for very long periods, if the underlying cause of the elevation persists [7, 10]. With the exception of severe hepatic failure, CRP rises whenever an inflammatory process is present; its serum concentration only depends on the intensity of the stimulus and on the rate of synthesis [7, 10]. The CRP level is independent of the underlying pathology and is not modified by any therapy or intervention such as renal replacement therapy [10, 18]. Only those interventions affecting the inflammatory process responsible for the acute phase reaction can change the CRP level.

Table 1 Diseases associated with only minor elevations of C-reactive protein

Systemic lupus erythematosus
Systemic sclerosis
Dermatomyositis
Sjögren's disease
Ulcerative colitis
Leukaemia
Graft-versus-host disease

Elevations in serum CRP are seen with most invasive infections [17, 19]. Both acute systemic Gram-positive and Gram-negative bacterial infections, as well as systemic fungal infections cause marked CRP rises, even in immunodeficient patients. By contrast, CRP concentrations tend to be lower in most acute viral infections. Nevertheless, this rule is not absolute and uncomplicated infections with adenovirus, measles, mumps and influenza are sometimes associated with high CRP levels. Systemic viral infections caused by cytomegalovirus and Herpes simplex also induce marked changes in CRP concentrations. There is limited knowledge of CRP behaviour in parasitic infections, but some protozoan parasitic diseases such as malaria, pneumocystosis and toxoplasmosis are also able to cause marked rises in CRP. In chronic infections such as tuberculosis and leprosy, although abnormal, CRP levels are usually only modestly elevated.

In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentrations. These include trauma, surgery, burns, tissue necrosis, immunologically mediated inflammatory diseases, crystal-induced inflammatory diseases and advanced cancer [5, 10]. Other clinical situations such as vigorous exercise, heat stroke and even some psychiatric diseases are associated with mild CRP changes.

As shown in Table 1, there is a group of disease processes with an unequivocal presence of inflammation and/or tissue damage that are usually associated with normal or only slightly elevated CRP, even in the presence of severe disease [7, 10]. For reasons unknown, the acute phase response induced by these diseases is unable to raise the CRP, due to failure of synthesis rather than increase in clearance. However, in response to infection these patients are still able to mount a major CRP response. This property is used to distinguish infection from a flare-up of the underlying disease process.

Methods of C-reactive protein measurement

Since its identification, the quality of CRP measurement has greatly improved. Initially, the measurement was qualitative, which was useless in differential diagnosis as

Table 2 C-reactive protein cut-offs of different infectious situations, sensitivity and specificity

	n	CRP (mg/l)	Sensitivity	Specificity	Reference
Aspiration pneumonia	66	75	87	76	[54]
Infected pancreatitis	66	225	68	70	[43]
Infections post-cardiac surgery	97	50	84	40	[39]
Sepsis	66	40	100	85.4	[53]
Sepsis	23	50	98.5	75	[30]
Sepsis	190	79	71.8	66.6	[31]
Sepsis	101	100	71	78	[66]
Sepsis	101	100	74	74	[32]
Septic shock	60	100	93	40	[68]

it was positive in almost every disease state. Subsequently, a semi-quantitative latex agglutination test was developed but, even with this improvement, clinical interest remained scanty. After the biochemical characterisation of CRP it was possible to develop specific monoclonal antibodies and thus several immunological methods of measurement, such as enzyme immunoassay, immunoturbidimetry and nephelometry [20, 21]. The latter method is the most widely used since it is very accurate, stable and reproducible. It takes 15–30 min to obtain a result and its sensitivity is within 0.04 mg/l. Another advantage is its low cost [22].

Clinical applications of C-reactive protein

The CRP response is very non-specific and can never be used as a single diagnostic tool, however it is very helpful in several disease states. Its application in infectious diseases is unquestionable [5], not only in adults but also in paediatric patients [17]. Its application in cardiology, particularly coronary artery disease, is growing [23, 24, 25]. It is also currently used in rheumatology [26, 27] and transplantation [28, 29]. In this review, only the use of CRP in infection and sepsis will be considered.

Evaluation of a single C-reactive protein determination

Sepsis diagnosis

The value of a single CRP measurement in sepsis diagnosis has been investigated in different clinical situations. In two recently published studies in critically ill patients, the best cut-off for the diagnosis of sepsis was 50 mg/l (sensitivity 98.5% and specificity 75%) [30] and 79 mg/l (sensitivity 71.8%, specificity 66.6% with an area under the receiver operating characteristic (ROC) curve of 0.78) [31]. However, in both studies CRP was measured daily and each comparison performed subsequently against different methodologies. Table 2 summarises the findings of several CRP studies evaluating a single CRP measurement in different infectious situations. The most discriminatory CRP level has not yet been found and it may be different in diverse infections. However, published data point to a CRP value between 50 and 100 mg/l.

In conclusion, a single CRP measurement is reasonably useful in the diagnosis of sepsis.

Disease severity

The single determinant of CRP level is its rate of synthesis, which in turn depends on the inflammatory insult intensity. In a recent study, CRP levels from each septic patient were grouped according to the ACCP/SCCM Consensus Conference classification [1]. Mean values were 70 mg/l in systemic inflammatory response syndrome (SIRS) patients, 98 mg/l in sepsis, 145 mg/l in severe sepsis and 173 mg/l in septic shock, probably reflecting different degrees of inflammatory response [32]. Similar results have been found by others; for instance Ugarte reported median CRP levels of 66 mg/l, 108 mg/l and 126 mg/l, respectively for SIRS, sepsis and septic shock patients [31]. Therefore, the CRP concentration in each individual patient is likely to reflect the presence as well as the severity of sepsis.

Outcome prediction

Besides its use in the diagnosis of sepsis, CRP has also been evaluated as a prognostic marker. Non-survivors had a median CRP concentration on admission of 70 mg/l, significantly higher than that measured in survivors (18 mg/l) [33]. Peaks of CRP during their hospital stay were also higher in non-survivors [16]. In a recent study designed to evaluate outcome using several markers of inflammation on admission, CRP again performed very well, with an area under the ROC curve of 0.811 [34].

Evaluation of serial C-reactive protein determinations

There is a large body of literature dealing with clinical applications and the discriminative value of a single

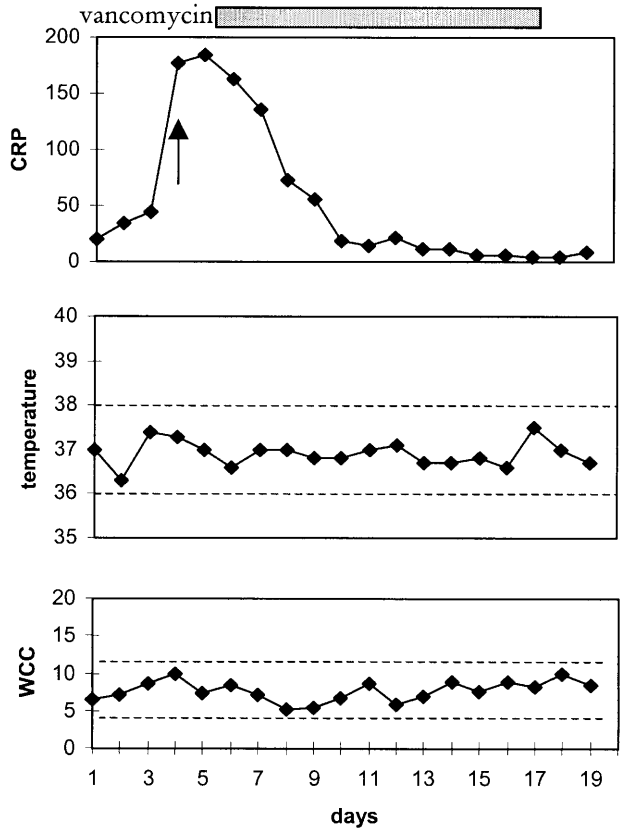

Fig. 1 Time course of C-reactive protein (CRP) concentrations (mg/l), temperature (°C) and white cell count (WCC, x10^3/ml). Note the CRP response in simple infection (see text). Case 1: methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in a kyphoscoliotic ventilated woman

CRP value. However, it is more important to follow its evolution over the duration of hospital stay. Changes are very helpful in diagnosis as well as in monitoring response to therapy, as CRP levels are only determined by the rate of synthesis. In contrast, other acute phase phenomena such as leukocytosis and fever are dependent on complex mechanisms involving several mediators. Therefore, these markers are not reliable markers of sepsis [5].

Sepsis diagnosis

Infection should always be suspected if there is a steady increase in CRP levels over 2–3 days in the absence of an intervention likely to mount an inflammatory response, e.g. surgery. The following case illustrates this point.

Case 1. (Fig. 1) A 53-year-old woman with kyphoscoliosis was admitted to the intensive care unit (ICU) with acute decompensation of her chronic respiratory failure necessitating mechanical ventilation. On the 3rd day CRP was 177 mg/l and the chest X-ray showed a right pulmonary consolidation. A bronchoalveolar lavage (BAL) (*arrow*) was performed from which a methicillin-resistant *Staphylococcus aureus* was identified. Vancomycin was started 2 days later. The CRP fell sharply, however temperature and white cell count (WCC) remained unchanged and within normal limits over the whole period.

Only a few publications have looked at the behaviour of CRP before the diagnosis of sepsis is made. In one study in critically ill patients, a 25% increase in plasma CRP over the previous day's level was highly suggestive of sepsis [35]. This study also emphasised that "normal" CRP levels in critically ill patients rarely lie within the normal range of a healthy population. However, they did not propose an upper cut-off for the "normal" range in the ICU patient. In a number of studies, rises in CRP were seen whenever patients became infected [28, 31, 33],CRP levels were higher in bacterial than in viral infections [28], CRP peaks were similar in Gram-positive and Gram-negative sepsis [31, 32, 36] and no differences were seen in CRP concentration between consecutive peaks in patients having multiple septic episodes [36]. In some papers, CRP time course evolutions similar to that shown in Fig. 1 were presented [16, 31, 33].

Knowledge of CRP patterns in response to an inflammatory insult, such as surgery, pancreatitis and trauma, is also helpful in the diagnosis of sepsis. CRP normally rises over 2–3 days, peaking at approximately 50 h after the stimulus. It then begins to decrease, though this depends upon the rate of disappearance of the inflammatory process. A failure to fall and a secondary rise in CRP level is highly suggestive of an infectious complication [33]. Case 2 exemplifies this CRP pattern.

Case 2. (Fig. 2) A 17-year-old man was admitted to the ICU after severe closed thoracic trauma with bilateral haemopneumothorax, pneumomediastinum and pulmonary contusions. He developed a severe acute respiratory distress syndrome (PaO_2/FIO_2 <50 mmHg). CRP rose initially as a consequence of the trauma, however it was still rising after 3–4 days. On the 5th day cultures were performed, but were negative (*arrow*). Meanwhile, he developed a pyrexia, though the WCC was decreasing. Antibiotics were started empirically on the 7th day. Initially, CRP diminished sharply followed by a slow decrease thereafter. Simultaneously, body temperature and WCC also normalised. Antibiotics were stopped on the 24th day and he was discharged on the 32nd day.

In a study performed in 104 surgical and trauma patients [37] the CRP level on day 1 did not discriminate between patients without infection and those that went on to develop nosocomial infection. However, on day 6 septic patients showed a CRP concentration significantly higher than patients without infection (216 versus 57 mg/l, $p<0.001$). On the 6th day a CRP level above

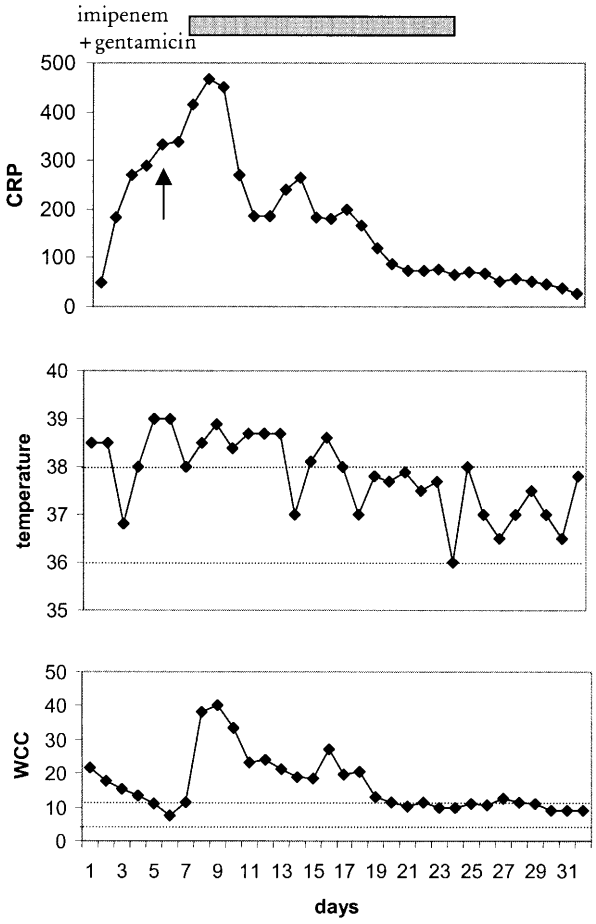

Fig. 2 Time course of C-reactive protein (CRP) concentrations (mg/l), temperature (°C) and white cell count (WCC, x10^3/ml). Note the CRP response in suppurative infection (see text). Case 2: severe chest trauma followed by a culture-negative sepsis

130 mg/l had a sensitivity of 85% and a specificity of 83% for the diagnosis of sepsis. In another large follow-up study with 151 consecutive patients who were submitted to pneumonectomy [38], CRP showed a peak between the 3rd and 6th post-operative days, and then declined progressively. By day 12 it was below 50 mg/l in all patients without complications, however those with infectious complications demonstrated a marked persistent elevation or a secondary rise in CRP. A CRP level above 100 mg/l after the 12th day showed a sensitivity of 100% and specificity of 94.8%. In cardiac surgery patients procalcitonin (PCT) performed better, however CRP was also found to be reasonably helpful in diagnosing infectious complications (CRP >50 mg/l; sensitivity 84%, specificity 40%, area under the ROC curve 0.68) [39]. Nevertheless, CRP was elevated in all septic patients, although PCT was below 1 ng/ml in five patients with mediastinitis, two with bacteraemia and one with pneumonia.

Pancreatitis is another situation were CRP monitoring can be useful. Apart from being a good prognostic indicator [40, 41], CRP is useful in the diagnosis of infected pancreatic necrosis, its most feared complication. The peaks in CRP concentration in patients with interstitial oedematous pancreatitis, sterile necrosis and in those who proceed to infected necrosis occur at the same time, between the 3rd and 5th day [42, 43]. However, the more severe the disease process, the higher the CRP peak level. These initial CRP peaks are the result of the acute phase response induced by the inflammatory pancreatic necrosis, since superadded infection is a late complication [44]. The CRP level will decrease in those making a good recovery. However, in patients developing infected necrosis, markedly high CRP levels persist throughout the follow-up period. In the second week of acute pancreatitis a CRP concentration exceeding 160 mg/l is suggestive of infected necrosis (sensitivity 77%, specificity 79% and area under the ROC curve 0.856) [43]. The persistence of high CRP levels or a secondary rise reflects a new stimulus inducing another acute phase response, this time usually associated with infection of the pancreatic necrosis. In contrast, PCT was almost normal in patients with interstitial oedematous pancreatitis and sterile necrosis, but was elevated from the 3rd day onward in patients who developed infected necrosis, a time point too early to be attributed to infection.

Response to therapy

After the diagnosis of infection and the start of therapy, serial determinations of CRP provide important information. There are four patterns of CRP response to therapy [33]. The pattern *simple infection* is found in patients with focal infections or with bacteraemia in whom CRP describes a sharp and exponential fall after antibiotic administration. The rate of CRP decline is related to its half-life. These patients usually make a full recovery from sepsis (Fig. 1). The pattern seen when CRP concentration does not fall promptly after the initiation of therapy is called *suppurative infection*. This situation is frequently associated with the presence of purulent collections, serious non-infectious diseases or inadequate antibiotic therapy (Fig. 2). This pattern should alert the clinician to search for persisting infection. The pattern with the worst prognosis, called *complicated infection*, is characterised by the failure of the CRP concentration to fall, or even increase further, despite therapy. This is usually associated with the use of inappropriate antibiotics, the presence of a surgical complication or the presence of a severe non-infectious disease. Finally, there is a fourth pattern, *recurrent infection*, which has a bimodal CRP time course. Firstly, there is a fall in CRP in response to the initial therapy followed by a secondary rise. The second elevation of

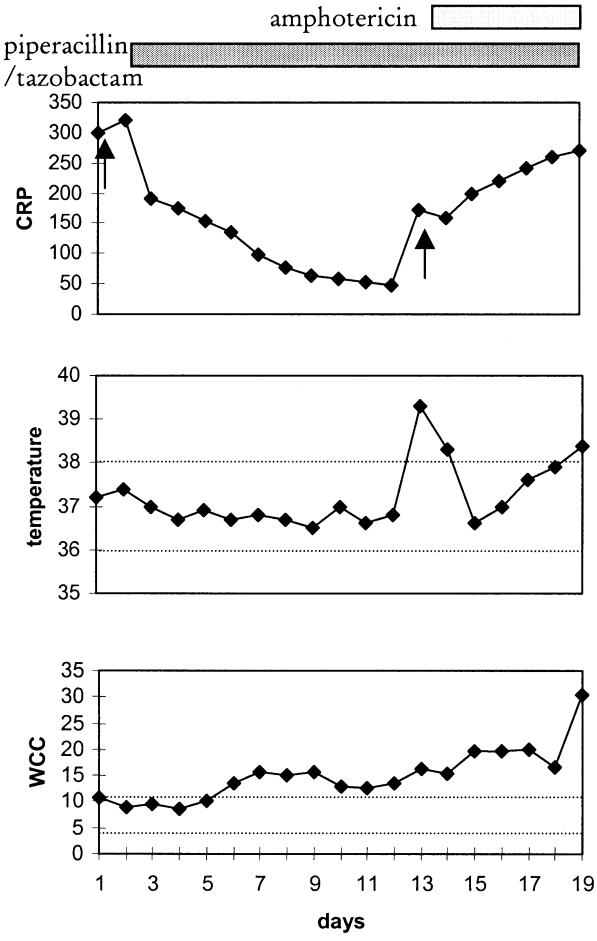

Fig. 3 Time course of C-reactive protein (CRP) concentrations (mg/l), temperature (°C) and white cell count (WCC, x10^3/ml). Note the CRP response in recurrent infection (see text). Case 3: *Klebsiella pneumonia* in a chronic obstructive pulmonary disease patient followed by catheter-related candidaemia with a poor outcome

CRP can be related to a recurrent infection of the same kind at the same site, but can also be due to a new infection. Prognosis depends on the response of the newly diagnosed sepsis to therapy. The following case is illustrative of this pattern.

Case 3. (Fig. 3) A 65-year-old man with a previous history of pulmonary tuberculosis and chronic obstructive pulmonary disease was admitted to the ICU with respiratory failure. He had fever, purulent sputum and radiological signs of pneumonia. C-reactive protein on day 1 was 299 mg/l. A BAL was performed (*arrow*), revealing *Klebsiella pneumoniae* for which antibiotic therapy was started. A fall in CRP levels was registered. On the 13th day, CRP increased sharply. *Candida albicans* was isolated from blood cultures and the central venous catheter (*arrow*). Amphotericin B was started, but the patient's condition deteriorated with development of multiple organ failure. The C-reactive protein kept on rising and he died on day 19. During his ICU stay temperature and WCC were not very helpful, either in diagnosis or in monitoring the response to therapy.

After the initiation of therapy, a CRP level that remains persistently elevated or continues to rise suggests either a wrong diagnosis or ineffective/inappropriate treatment. On the other hand, a fall in CRP indicates that the septic episode is resolving. In a study performed in critically ill patients with culture-positive sepsis, a decrease in CRP levels by 25% or more from the previous day's level was a good marker of sepsis resolution (sensitivity 97%, specificity 95%) [36]. In addition, a 25% decrease over two consecutive days further increased the specificity of CRP monitoring. The ROC curve for different changes in serial CRP determinations again showed that it is a good means of monitoring the response to therapy (area under the ROC curve 0.97). Another interesting finding was the observation that the decrease in CRP preceded the resolution of sepsis in 46% of the septic episodes.

The value of CRP changes over time has not yet been systematically investigated, but in several papers the authors recognised that decreases in CRP levels coincide with clinical improvements while, on the other hand, CRP increases suggest infectious complications [16, 31, 33, 38, 42, 43, 45, 46].

Initiation and suspension of antibiotics

The duration of antibiotic therapy is a matter of debate. CRP monitoring represents a possible means of stopping antibiotics safely, sparing patients from drug toxicity, probably decreasing the emergence of resistance and decreasing costs. This field of research has not yet been explored in critical care, but in paediatrics some interesting data already exist. Normalisation of CRP levels has been proposed as a guideline to stopping antibiotics [17, 47]. In 176 neonates with birth weights above 1500 g, a CRP level below 10 mg/l after 24 h correctly identified 99% of infants without sepsis [48]. The mean duration of antibiotic therapy was also shorter in infants whose CRP was monitored, namely 3.7 versus 5.5 days. In another study, antibiotics were also stopped when the CRP was below 10 mg/l; using this criteria 38% (162/425) of the infants had their therapy stopped after 48 h. None of the neonates discharged with a normal CRP were readmitted in the following month [49].

Data available in adults refer to the use of CRP in the primary care setting. The regular use of CRP monitoring was associated with a reduction in antibiotic prescribing [50, 51], though another study failed to show any difference [52].

Other markers of infection

The classic markers of infection are fever and leukocytosis. Although cheap and easy to measure, body temperature is a specific, but not sensitive, marker of infection [30, 53, 54]. Infection is frequently not the cause of fever in febrile critically ill patients [55]. On the other hand, there is no relation between fever and disease severity [56, 57]. High fever can be associated with minor infections such as streptococcal tonsillitis, while a normal temperature or even hypothermia is possible in very severe situations such as peritonitis. In addition, fever is influenced by many non-infectious factors, such as antipyretics and ambient temperature. Despite all these limitations, body temperature continues to be used as a criterion of sepsis diagnosis [1].

The WCC count is routinely performed in almost every ICU and is also a criterion of sepsis. It is influenced by many non-infectious factors, such as acute myocardial infarction, catecholamines, corticosteroids and acute bleeding [58]. Moreover, there are some infectious diseases that characteristically progress without leukocytosis such as typhoid fever, tuberculosis, chickenpox, measles and mumps. Thus, the value of leukocytosis in the diagnosis of infection and sepsis is very poor [30, 31, 53, 54].

Procalcitonin (PCT) has been proposed as a marker of infection [59, 60]. Its origin and role in sepsis remains unclear. The administration of *Escherichia coli* endotoxin to healthy volunteers induces a rapid and short-lived peak of TNFα and IL-6 followed by a rise in PCT [61]. After an inflammatory stimulus PCT is detectable 3–4 h later, peaks at 14 h, remains elevated for 24 h and has a half-life in serum of 22–35 h [62]. Localised bacterial infections as well as viral infections are responsible for minor PCT increases. By contrast, systemic bacterial infections cause marked elevations [59]. However, there are several non-infectious inflammatory diseases, such as trauma, burns and surgery, that are also associated with PCT elevations [63, 64, 65]. In the diagnosis of sepsis, several studies have shown that PCT is a reliable marker [31, 39, 42, 66]. Comparison between PCT and CRP in the diagnosis of sepsis has produced all manner of results, though sometimes the differences can be explained by looking at the biology of the two markers. In one comparative study, blood samples were collected until 8 h after the clinical onset of sepsis [67]. As CRP secretion only begins 4–6 h after the stimulus onset, it would be difficult to discern any differences between CRP levels in septic and SIRS patients.

Clinicians using PCT as a marker of infection should be aware of some important and potentially dangerous limitations. The behaviour of PCT in acute renal failure is still unknown [32]. In cardiac surgery patients complicated with mediastinitis, PCT concentrations were almost normal (0.8±0.58 ng/ml) in comparison with non-infected patients (0.41±0.36 ng/ml) [39]. In a study in critically ill patients, PCT was below 1.0 ng/ml in 12.5% and 62.5% of infected patients with and without septic shock, respectively [68]. Finally, in community-acquired pneumonia PCT can be normal or even undetectable (median 0.2 ng/ml, range 0.1–6.7 ng/ml, n=149) [69]. There is no obvious explanation for these unexpected findings.

With regard to cost, measurement of PCT is considerably more expensive than CRP. In a recent paper, a CRP determination cost $ 5 (US) whereas PCT costs were twice as high [22].

Conclusion

Determination of CRP is a cheap, consistent and reproducible test and is available in almost every hospital. Some authors prefer CRP to other markers such as PCT, since it is more reliable in sepsis diagnosis [32, 70]. Does the utilisation of a marker make any difference to the patient? In one study, the period in which CRP measurement was routinely performed was compared retrospectively with a preceding period of the same duration, involving 144 and 187 patients, respectively. Although not statistically significant, the routine determination of CRP was associated with a trend towards lower rates of mortality and morbidity [31]. However, this finding needs further confirmation.

In conclusion, serial CRP measurement, rather than a single determination at the time of admission, is a simple and valuable instrument in the diagnosis of sepsis and infection as well as in monitoring the response to therapy.

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