C-Reactive Protein*
A Clinical Marker in Community-Acquired Pneumonia

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Study objective: To assess the range of plasma C-reactive protein (CRP) in patients presenting with community-acquired pneumonia and to compare the serial changes of this acute-phase protein with clinical outcome.

Design: Prospective hospital-based study, including separate retrospective case series.

Patients: Twenty-eight consecutive patients (mean age, 60 years) admitted to our hospital with community-acquired pneumonia were studied. Serial daily plasma samples were taken and assayed for CRP, tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6). Clinical parameters, laboratory data, and response to treatment were recorded. Four other patients considered to be antibiotic failures (three empyemas, one death) were studied separately.

Results: Two patients died. Of those who survived, mean ± SD CRP values for days 1, 2, 3, 4, and 5 were as follows: 136 ± 43, 96 ± 44, 53 ± 36, 54 ± 43, and 44 ± 31 mg/L. CRP levels on day 1 in patients who had received antibiotics prior to hospital admission were significantly lower than those who had not, 107 ± 42 and 152 ± 44 mg/L (p<0.05). CRP levels did not correlate with other laboratory parameters or with recognized predictors of mortality. A CRP value that continued to rise despite antibiotic treatment was associated with infective complications or death. Only 52% of patients had detectable TNF-α and 24% detectable IL-6 at some point during their hospital stay.

Conclusions: CRP is a sensitive marker of pneumonia. A persistently high or rising CRP level suggests antibiotic treatment failure or the development of an infective complication. These results suggest that CRP, rather than TNF-α or IL-6, may have a role as a clinical marker in pneumonia.

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Key words: C-reactive protein; cytokines; pneumonia

Community-acquired pneumonia continues to be a major clinical problem in terms of morbidity, mortality, and use of hospital resources. It is well recognized that a delay in making the diagnosis and instituting appropriate antibiotic treatment is associated with an increased mortality.1 A diagnosis of pneumonia is easily made in the presence of typical symptoms, physical signs, and radiographic features. However, the clinical picture may not be so well defined in the presence of coexisting lung disease or if the patient presents in the early stages of pneumonia before consolidation has become radiologically apparent. In addition, other traditional markers of infection, such as body temperature or WBC count, may not be elevated. If making the diagnosis has not been easy, then assessing treatment response is likely to be difficult.

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver in response to a number of stimuli that involve tissue damage. Interleukin 6 (IL-6) is thought to be the main mediator of CRP production,2 though other cytokines such as tumor necrosis factor (TNF), IL-1, and transforming growth factor-α are also involved.3 Bacterial infection is a particularly potent stimulus with marked elevation in serum CRP levels occurring within a few hours.4 Pneumonia elicits a powerful inflammatory response, both locally and systemically, with chemotactic cytokine release into the peripheral circulation. Limited studies of cytokines in the peripheral circulation have not suggested a use for them in assessing severity of pneumonia or treatment response.5,6 A previous retrospective study of uncomplicated community-acquired pneumonia demonstrated that it was possible to distinguish between pneumonia and infective bronchitis without pneumonia on the basis of serum CRP levels.7 However, there is little in the published literature regarding the serial

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behavior of CRP levels in pneumonia and its relation to clinical outcome.

The main aim of this study was therefore to prospectively evaluate the serial changes of CRP levels in the peripheral circulation of patients with community-acquired pneumonia and to assess the relationship of such changes with clinical outcome.

METHODS

Patients

Twenty-eight consecutive patients admitted to our hospital with community-acquired pneumonia were prospectively studied. Pneumonia was defined as the presence of new shadowing on a chest radiograph in association with an appropriate clinical history and physical signs for which no other cause was found. Informed consent was obtained and the study was approved by the Tayside Ethical Committee. The average age was 60.5 years (range, 25 to 88 years), 18 were male, and 10 had preexisting lung disease (8 COPD, 1 asthma, and 1 bronchial carcinoma). Nine patients had received antibiotics prior to hospital admission and ten patients were identified as being in the poor prognosis category as defined by the British Thoracic Society (BTS) (exhibiting two of three of a respiratory rate >30/min on admission, a diastolic BP <60 mm Hg on admission, and a urea level >7 mmol/L on admission). However, only 2 of the 28 patients died in hospital: 1 died of his pneumonia after 3 days, the other died of bronchial carcinoma 4 weeks after an initial clinical recovery. An etiologic agent was established in only nine patients: seven had Streptococcus pneumoniae infection (five blood culture, two sputum culture), one had Staphylococcus aureus (sputum culture), and one had influenza B virus infection (serology). The clinical data collected for each patient included temperature, respiratory rate, BP, chest radiograph appearance, and the presence or absence of confusion. Each patient had WBC count, lymphocyte subsets, and renal and liver function test measured on the day of hospital admission. In addition, daily plasma samples were taken for CRP measurement in all patients, for TNF-α assay in 25 patients, and for IL-6 assay in 23 patients.

Four patients with community-acquired pneumonia who were considered to be antibiotic treatment failures were also identified and retrospectively studied (one death—Legionella pneumophila antigen identified in urine; three empyemas—culture of pleural fluid yielded S pneumoniae in one case, combined infection with Haemophilus parainfluenzae and Eikenella corrodens in the second case, and no identifiable organism in the third case). CRP values were obtained from the case notes and from retrospective analysis of stored serum samples. The serial CRP profile was then compared with the clinical course in each case.

CRP and Cytokine Assays

Plasma CRP levels were estimated by a single radial immunodiffusion method using a commercially available kit (Behring; Marburg, Germany). Assays for IL-6 and TNF-α were performed by enzyme-linked immunosorbent assay. IL-6 levels were measured using a commercially available kit (Medgenix Diagnostics; Fleurus, Belgium) and unbound TNF-α was measured by an enzyme-linked immunoassay system developed by Engelberts et al.8

Data Analysis

The mean, SD, and upper/lower quartiles were calculated using a software package (Statgraphics). Comparison of CRP levels between the specified subgroups was made by analysis of the variance (ANOVA) and comparison between sequential days was made with ANOVA multiple range testing. Least squares linear regression analysis was used to examine the relationship between CRP levels and the various other clinical and laboratory parameters measured on day 1 of hospital admission.

RESULTS

Plasma CRP levels were elevated above 50 mg/L in all and above 100 mg/L in 75% of patients on the day of hospital admission. However, only 67% of patients had a pyrexia (axillary temperature >37°C) and only 62% an elevated WBC count (>10x109/L) at time of presentation. With antibiotic treatment, CRP levels fell rapidly as demonstrated by the data for the first 5 days (Table 1). Missing CRP data for days 2 to 5 were due to patient discharge from hospital or loss of samples. One patient developed antibiotic-related colitis on day 4 producing a marked elevation in the CRP level that had otherwise been coming down with treatment. This resulted in a higher than expected mean CRP value for day 4 (Table 1), but demonstrated how plasma CRP level can rise with infective complications. In those patients who had an uncomplicated survival, serial CRP levels fell progressively in every instance (Fig 1). In the patient who died of pneumonia, there was a progressive rise in plasma CRP level prior to death, whereas in the patient who died of disseminated bronchial carcinoma 4 weeks after hospital admission, the plasma CRP level fell in association with the initial clinical recovery. The data from this latter patient are therefore grouped with those of the survivors. There was a significant difference in CRP levels on admission between those who had received antibiotics prior to admission and those who had not: mean ± SD were 107±42 and 152±44 mg/L, respectively (p=0.023) (Fig 2). However, there was neither a relationship between CRP levels and the presence or absence of raised WBC count, pyrexia, preexisting lung disease, or the poor prognosis criteria as defined by the BTS (Ta-
Fig. 1. Serial CRP levels in pneumonia patients (survivors).

Table 2—Day 1 Mean (SD) CRP Levels (mg/L) Within Patient Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised WBC count, &gt;10 x 10^9/L (n=17)</td>
<td>139 (41)</td>
<td>127 (43)</td>
<td>0.720</td>
</tr>
<tr>
<td>Pyrexia, &gt;37°C (n=18)</td>
<td>141 (44)</td>
<td>131 (42)</td>
<td>0.619</td>
</tr>
<tr>
<td>Pneumonia (n=10)</td>
<td>118 (43)</td>
<td>144 (42)</td>
<td>0.205</td>
</tr>
<tr>
<td>Preadmission antibiotics (n=9)</td>
<td>107 (43)</td>
<td>152 (44)</td>
<td>0.023*</td>
</tr>
<tr>
<td>2 of 3 BTS risk factors (n=10)</td>
<td>128 (41)</td>
<td>138 (11)</td>
<td>0.660</td>
</tr>
<tr>
<td>S. pneumoniae culture positive (n=7)</td>
<td>143 (46)</td>
<td>132 (39)</td>
<td>0.601</td>
</tr>
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*p<0.05.

Fig. 2. CRP levels on day 1 in patients who had received antibiotics prior to hospital admission (n=9) and those who had not (n=19) (p<0.05 ANOVA).

Fig. 3. Serial CRP levels in four cases of pneumonia considered to be antibiotic treatment failures (three empyema, one death).

Discussion

In our study, all patients admitted to hospital with community-acquired pneumonia had an elevated CRP level at the time of hospital admission. Although small, our study did suggest that plasma CRP level is a sensitive marker of pneumonia unlike other more commonly used clinical markers of sepsis such as body temperature and WBC count which were not elevated in a significant proportion of our pneumonia patients. This is supported by similar findings in other studies of community-acquired pneumonia.4,5

There was no significant difference in CRP between those patients in whom a causative organism was identified and those in whom none was found. Other studies have demonstrated differences in CRP levels between bacterial and viral pneumonia9 and between Mycoplasma pneumoniae infection and other bacterial causes of pneumonia.10 However, the numbers in whom a cause was established in our cohort were too small to establish any relationship between CRP level and individual organisms. Likewise, the number of deaths was too small to draw any conclusions regarding the use of CRP level as a predictor of mortality. There was no correlation between recognized mortality risk factors and plasma CRP levels; however, levels were higher in those patients who had not received antibiotics prior to hospital admission (Fig 3). It is well recognized that early treatment reduces pneumonia...
mortality and that patients who have received antibiotics prior to hospitalization are less likely to die. Further studies involving much larger numbers are needed to evaluate the behavior of CRP levels in patients who die of pneumonia and other forms of respiratory sepsis.

We believe that monitoring the treatment response is the most useful role for CRP assay in the management of pneumonia. High CRP levels were present in all patients at presentation and subsequently fell rapidly in accordance with clinical recovery. The clinician can therefore be reassured by a falling CRP level that treatment is working. A persistently high or rising CRP level suggests either treatment failure, as demonstrated by the patient who died 3 days after hospital admission and the fatal case that was retrospectively studied, or development of a complication, as in the three patients who developed empyema or the patient who developed antibiotic colitis. TNF-α and IL-6 did not show any correlation with the development of complications and were detectable only in the circulation in a minority of patients with pneumonia, not necessarily at the time of presentation. As a consequence, these two cytokines are unsuitable as clinical markers in pneumonia.

In all our patients, the diagnosis and treatment response were established by traditional clinical and radiologic means. Measuring CRP levels in these patients, therefore, did not assist in their treatment. This study was designed to evaluate the serial behavior of this acute-phase protein during pneumonia and its relationship with clinical parameters. Our results suggest that CRP is a sensitive marker of pneumonia that falls rapidly and significantly with successful treatment. In our own clinical practice, we have found CRP to be a useful diagnostic tool at presentation where the chest radiograph is equivocal in the presence of a normal body temperature and WBC count. The time course characteristics of CRP, unlike other cytokines, make it ideally suited for use as a peripheral marker in pneumonia. Further prospective studies are needed to evaluate the clinical usefulness of CRP levels in those patients in whom the diagnosis is in doubt at presentation and also in those who have coexisting conditions known to elevate CRP levels.

There are various commercially available assays for serum or plasma CRP that are relatively quick to perform. We do not advocate assaying CRP in all cases of suspected pneumonia; however, we do suggest that the provision of a service that reports CRP levels within 24 h may be of clinical use in the treatment of those patients in whom the diagnosis is in doubt. In our hospital, we have found such a service to be particularly useful. We also propose that a serum or plasma sample should be taken and stored from all patients with pneumonia at time of hospital admission. If the diagnosis is in doubt or a patient fails to respond to treatment, this baseline sample can be retrospectively assayed for CRP and compared with current levels. Thus, in the group of pneumonia patients in whom the response to treatment is not clinically obvious, serial CRP levels may be useful to the clinician as a marker of infection.

REFERENCES

3 Sim JE, March CD, Cosman D, et al. cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin superfam-ily. Science 1988; 241:585-89
7 Smith RP, Lipworth BJ. C-reactive protein in simple community acquired pneumonia Chest 1995; 107:1028-31

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