C-reactive protein: a sensitive marker in the management of treatment response in parapneumonic empyema of children

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C-reactive protein (CRP) is one of the best indicators of the acute phase response to inflammation. The rapid kinetics of CRP metabolism appears to closely parallel the degree of inflammation. The purpose of this prospective study was to analyze the clinical value of CRP, erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) in the assessment response to treatment in children with parapneumonic empyema. Thirty-eight children were prospectively studied. CRP was elevated in all patients on the day of hospital admission. With antibiotic treatment, serum CRP levels fell rapidly within the first days, and in 32 patients who had uncomplicated course, serial CRP levels fell progressively at each measurement. All but four patients had normal CRP levels on the day of hospital discharge. ESR was also elevated in all patients on the day of hospital admission. Despite antibiotic treatment, ESR continued to increase in all patients in the first few days, with peak values reached on day 3. Only three patients had normal ESR levels on the day of hospital discharge. In six patients who had a complicated course, after an initial decrease, CRP levels began to rise earlier than ESR and WBC count. Plasma CRP level is a sensitive marker not only in the diagnosis of parapneumonic empyema, but also in the management of treatment response.

Key words: parapneumonic empyema, C-reactive protein, children.

Despite improvement in medical therapy, empyema thoracis remains a common problem in the pediatric age group[1-4]. The optimal management remains controversial, with advocates for a variety of treatment options[5]. Most children with empyema can be adequately treated with antibiotics and prompt drainage of the pleural fluid. Since the chest radiograph is usually unchanged within the first few days, and it may take up to months to completely resolve, duration of the antimicrobial treatment usually depends on the clinical response and acute phase reactants[2].

C-reactive protein (CRP) is one of the best indicators of the acute phase response to inflammation. This plasma protein is synthesized in the liver under the influence of interleukin-1, a product of macrophages, and is normally present in the serum in trace amounts[6,7]. Once stimulated, the CRP level increases rapidly, and several studies of acute phase protein responses have shown that the CRP level rises more rapidly than the level of other inflammatory proteins, and also returns more rapidly to normal value in response to therapy[6,8,9]. The CRP level can be measured accurately, so it has several advantages of being and ideal laboratory test to monitor acute inflammation.

This prospective study describes the time course of CRP, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) (count) in patients with parapneumonic empyema. The value of CRP levels in monitoring the progress of infection and response to therapy is discussed.

Material and Methods

Thirty-eight consecutive patients aged 6 months to 14 years (mean 4.5±3.5 years) admitted with parapneumonic empyema between 1 January

2001, and 31 June 2002 were prospectively studied (Table I). Informed consent was obtained and the study protocol was approved by the University Ethical Committee.

Table I. Symptoms, Physical Findings and Some Clinical Characteristics of the Patients

	No.	%
Number of patients	38	
Male	14	37
Female	24	63
Common symptoms		
Fever	34	89
Cough	28	74
Respiratory difficulty	21	55
Chest pain	11	30
Physical findings		
Decreased breath sounds	31	83
Dyspnea	26	68
Rales	13	34
Previous antimicrobial treatment	11	30
Bacteriologic isolations	16	42
S pneumonia	9	24
S aureus	7	18
Chest tube drainage	23	61
Decortication	3	8

The diagnosis of empyema required one of the following criteria: 1) grossly purulent pleural fluid or pleural fluid with WBC count ≥10x10^9/L with a predominance of segmented neutrophils documented by thoracentesis; 2) positive pleural fluid culture or Gram stain; or 3) pleural fluid pH<7.10 and lactate dehydrogenase >1.000 U/L with an appropriate clinical history and physical signs. Needle aspiration was performed in all patients for emptying pleural fluid and diagnostic studies were made. If the pleural fluid was not drained or reaccumulated, thoracostomy tube drainage was performed. Thirty-two patients had an uneventful course and were discharged from hospital on a mean of 16±5 days (range, 12-34 days). Of the six patients with complicated course, three had decortication.

The cultures were obtained from both the pleural space and blood. An etiologic agent was established in 16 patients: nine had Streptococcus pneumonia infection and seven had Staphylococcus aureus infection. All children received intravenous antibiotics, usually a broad spectrum penicillin and an aminoglycoside for the first seven days. With culture results, antibiotics were changed if indicated.

C-reactive protein was measured quantitatively by nephelometric method at the time of hospital admission and on days 3, 5 7, 10, 15, 20, 30, and 40. ESR was measured by the conventional Westergren tube method on the same days as CRP. A normal CRP value is less than 0.35 mg/dl, and for ESR, less than 20 mm/h. The WBC count was performed using a Coulter counter at the time of hospital admission and on days 5, 10, 15, 20, and 30. A normal WBC count is less than 12x10^9/L.

Results

All patients had pyrexia and 89% had elevated WBC (>12x10^9/L) at the time of presentation. On admission, the mean WBC count was 19.4±7.3x10^9/L (range 7.4x10^9/L to 35x10^9/L), and it returned to normal value in a median time of 10 days (range 5 to 15 days).

Plasma CRP levels were elevated in all patients on the day of hospital admission, with a mean value of 18.6±6.4 mg/dl (range 6 mg/dl to 30 mg/dl). There was no significant difference in CRP between those patients in whom a causative organism was or was not identified. With antimicrobial treatment, serum CRP levels fell rapidly within the first days, and in those patients with an uncomplicated course, serial CRP levels fell progressively at every check (Table II, Fig. 1). Plasma CRP levels returned to normal in 88% (34) of the patients (<0.35 mg/dl) on the day of hospital discharge. The other four patients also had CRP levels less than 2.04 mg/dl. The mean time required for CRP to reach normal value was 16±4 days (range 10 to 30 days).

Table II. Mean Value (±SD) of Serum C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and White Blood Cell (WBC) Counts in Parapneumonic Empyema in Children

Time	CRP (mg/dl)	ESR (mm/h)	WBC (x10^9)
1*	18.6±6.4	73±18	19.4±7.3
3	14.1±5.3	90±16	
5	9.3±4.5	79±15	13.8±4.8
7	5.9±3.9	68±13	
10	3.1±2.2	62±16	8.7±2.9
15	1.1±0.5	50±15	7.8±1.6
20	0.6±0.5	35±15	7.4±1.5
30	<0.35	20±11	7.3±1.2
40	<0.35	10±9	

* The day of admission is day 1.

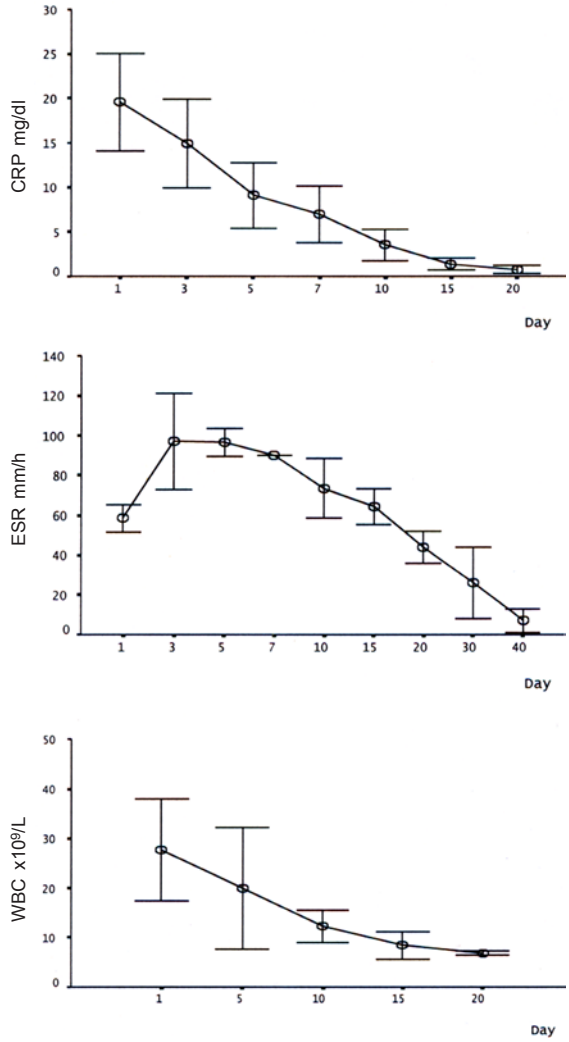

Fig. 1. Serial follow-up of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) (means ± SEM) in parapneumonic empyema in children.

Erythrocyte sedimentation rate was also initially elevated in all patients, with a mean value of 73±18 mm/h (range 50 mm/h to 119 mm/h). Despite antibiotic treatment, ESR continued to increase in all patients in the first three to five days, reaching a mean peak value of 90±16 mm/h (range 65 mm/h to 121 mm/h). In 68% of patients who had uncomplicated course it began to decrease on the fifth day and in 32% on the seventh day. Only three patients had normal ESR on the day of hospital discharge. At that time, the mean ESR was 42±1 mm/h (range 12 mm/h to 68 mm/h). The mean required for ESR to reach the value of 20 mm/h or less was 27±6 days (range 15 to 40 days).

In six patients who followed a complicated course, the plasma CRP level fell in association with the initial clinical recovery, then began to rise again. In all patients who had complicated course, CRP began to rise earlier than ESR and WBC. All these patients needed antibiotic change and three had decortication.

Discussion

Our study emphasizes the importance of sequential measurements of WBC count and CRP levels, especially in the management of parapneumonic empyema. Within two days of successful therapy, the CRP levels showed a marked reduction, which was interpreted as an indication that the inflammation was subsiding. Regular determination of CRP levels also proved useful in detecting complications by showing secondary elevation, which was earlier than with other inflammatory markers. Thus, a low CRP level may help in deciding on an early discharge from the hospital with confidence.

Serum CRP levels have been used in the management of other infections[10,11]. However, serial CRP level has not been previously studied in parapneumonic empyema. All patients admitted to hospital with parapneumonic empyema had an elevated CRP level at the time of hospital admission. In 88% of the patients who had an uncomplicated course it returned to normal on the day of hospital discharge. The clinician can therefore be assured by a falling CRP level that treatment is effective. In patients with a complicated course, an early fall in CRP levels was followed by a progressive increase, earlier than the rise seen in ESR. So, sequential CRP determinations were also helpful in early detection of impending complication. Although all patients also had elevated ESR on admission, only three of the 32 patients had normal ESR on the day of hospital discharge. Despite the appropriate antibiotic treatment, ESR continued to increase in all patients in the first three to five days. Thus, in the monitoring of the treatment response, ESR is not a suitable marker in parapneumonic empyema, as seen in previous studies[12,13].

Erythrocyte sedimentation rate is the most commonly used clinical laboratory test to measure the acute phase response[14]. However, it has several disadvantages that prevent it from being an ideal laboratory test to monitor acute

inflammation[9,14]. CRP is a simple test measured with currently available laboratory equipment, that requires only a finger-prick sample, not vein puncture, as for ESR. After the onset of inflammation, CRP synthesis increases within hours, and remains elevated during ongoing inflammation[7,9,16,17]. With resolution, it declines rapidly, because of a relatively short half-life. As the test result is available within an hour, the information reflects the current situation. The rapid kinetics of CRP metabolism appears to closely parallel the degree of inflammation, thereby supporting its value as an acute measure of disease activity, superior to other acute phase reactants whose rate of increase is much slower. As was suggested previously, CRP should be determined during the follow-up period, since a secondary rise is a warning sign of treatment failure or complication[17].

White blood cell count is another inflammatory marker that is assessed in almost all infectious and inflammatory diseases. In our study, 89% of the patients had elevated WBC count on admission. With antimicrobial treatment, it began to decrease at the second check, and in those patients who had uncomplicated course, it also fell progressively at every check thereafter.

Although the number of patients with a complicated course was small, there was no difference in initial CRP levels between those patients with or without an uncomplicated course. There was also no difference between patients in whom an etiologic agent was or was not established. In patients with a complicated course, an early fall in CRP levels was followed by a progressive increase, earlier than the rise seen in ESR and WBC counts.

Our study did suggest that plasma CRP level is a sensitive marker not only in the diagnosis of parapneumonic empyema, but also in the follow-up of treatment response. Serial determination proved useful in detecting complications by showing secondary elevation. A low CRP level may help in the decision of an early discharge from hospital with confidence.

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