

Acute Phase Reactants and Cytokine Levels in Unilateral Community-Acquired Pneumonia

Mustafa Kolsuz^a Sinan Erginel^b Ozkan Alataş^c Füsün Alataş^b
Muzaffer Metintaş^b İrfan Uçgun^b Emel Harmancı^b Omer Çolak^c

^aTuberculosis Control Dispensary, and Departments of ^bChest Disease and ^cBiochemistry, Osmangazi University Medical Faculty, Eskisehir, Turkey

Key Words

Bronchoalveolar lavage fluid · C-reactive protein · Pneumonia · Cytokine levels, serum

Abstract

Background: Bacterial infection of the lower respiratory tract initiates an acute inflammatory response. Regulation of the inflammatory response in bacterial pneumonia depends on a complex interaction between immune cells and inflammatory cytokines. **Objectives:** We investigated the initial levels of proinflammatory cytokines and acute phase reactants (APR), e.g. C-reactive protein (CRP), upon presentation of community-acquired pneumonia (CAP) in relation to clinical and laboratory indices of infection. **Methods:** We prospectively studied 28 consecutive patients with unilateral CAP. Tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6 and IL-8 concentrations were measured by ELISA in both bronchoalveolar lavage (BAL) fluid and serum. **Results:** The concentrations of IL-1 β and IL-6 in BAL fluid were found to be significantly higher in the involved lung than those in either the noninvolved lung ($p = 0.008$ and $p = 0.012$, respectively) or serum ($p = 0.002$ and $p = 0.025$, respectively). Serum CRP concentrations were increased compared to those in the involved and noninvolved lung in BAL fluid

($p = 0.000$ and $p = 0.000$, respectively). In serum and BAL from involved lung, IL-6 concentrations were higher in the systemic inflammatory response syndrome (SIRS) group than in the non-SIRS group ($p < 0.05$), whereas CRP, TNF- α , IL-1 β and IL-8 concentrations showed no difference between SIRS and non-SIRS. There was no significant correlation between the acute physiology and chronic health evaluation II score and the cytokines. **Conclusions:** Our results indicate that the CRP level is higher in the serum than in the BAL fluid in the lung, and that IL-6 is the most important cytokine for the determination of the severity of the disease.

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Introduction

Despite the availability of new potent antibiotics, community-acquired pneumonia (CAP) is still a major clinical problem in terms of morbidity and mortality [1, 2]. It continues to be a major cause of death due to infectious disease, and is the sixth leading cause of death in both our country and the United States of America [1, 3]. The incidence and morbidity of pneumonia has not declined over the past 30 years.

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Dr. Mustafa Kolsuz
Kirmizitoprak Mahallesi, Tandogan Sokak
Soy-Gür Apt. A Blok No:40/1
TR-Eskisehir (Turkey)
Tel. +90 222 2267412, Fax +90 222 2394714, E-Mail mustafakolsuz@hotmail.com

Bacteria are normally prevented from reaching the alveoli by several defense mechanisms. Structural defenses are the initial barriers to prevent the entrance of infectious agents into the lung, and these include specific mechanical defenses, which, eventually, prevent their entrance into the alveolus. When the normal clearance of the lung is overcome, or when the bacterial burden is too large, bacteria can reach the alveoli and a complex response develops [2, 4, 5]. Alveolar macrophages are the principal resident phagocytes in the airways, and they play an important role in the initial phase of the host response. Small amounts of bacteria are effectively eradicated by alveolar macrophages. However, with an increase in virulence and the amount of microorganisms, a rapid neutrophil influx occurs. In this context, a variety of chemokines have been identified [2, 5, 6].

Bacterial infection of the lower respiratory tract initiates an acute inflammatory response. Regulation of the inflammatory response in bacterial pneumonia depends upon a complex interaction between immune cells and inflammatory cytokines. Tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6 and IL-8 are important inflammatory cytokines and early response mediators. Cytokine levels in bronchoalveolar lavage (BAL) samples reflect the degree of inflammatory activity in the lung. These cytokines are thought to mediate many host responses to bacterial infection, including the activation of immune cells leading to the production of specific antibodies [2, 4, 5, 7, 8].

Elevated levels of cytokines (TNF- α , IL-1 β , IL-6 and IL-8) in serum and BAL fluids were studied in patients with shock, sepsis, and the acute respiratory syndrome. TNF- α , IL-1 β and IL-8 were found to be related to the severity of pneumonia, and an elevated IL-8 level in BAL fluid was a poor prognostic criterion [4, 9, 10]. Cytokine levels in BAL samples reflect the degree of inflammatory activity in the lung [8]. The host inflammatory cytokine response in pneumonia is compartmentalized to the affected lung, but circulating inflammatory cytokines have also been detected in peripheral blood [2, 4]. It has been suggested that the quantitation of the inflammatory response may have prognostic implications [7, 11].

Dehoux et al. [2] reported that the clinical model of unilateral CAP enabled us to compare the inflammatory response at both the local level within the lung and at the local level versus the systemic level. In this way, each patient serves as his or her own control and environmental stimuli are minimized. The aim of our study was four-fold: (1) to determine the acute phase reactants (APR) and the levels of cytokines (TNF- α , IL-1 β , IL-6, IL-8) in both

the blood and BAL fluid in unilateral community-acquired pneumonia (CAP) patients; (2) to compare the local response in the involved lung with that of the noninvolved lung and with the systemic response; (3) to investigate any relationships between each cytokine and APR, and the disease severity, and (4) to define possible correlations of the levels of cytokines and APR with clinical and laboratory parameters.

Material and Methods

Study Design

The study was conducted between May 1999 and March 2001 at the Department of Chest Disease of the Medical Faculty Hospital of the Osmangazi University, Eskisehir. We prospectively studied 28 adult patients who had unilateral CAP. Pneumonia was diagnosed by the presence of new chest infiltrates on radiograms and at least one of the major, or two of the minor criteria were as follows [12]: *major criteria*: cough, sputum production or fever, and *minor criteria*: dyspnea, pleuritic chest pain, pulmonary consolidation on physical examination or white blood cell count (WBC) >12,000/ml.

Patients with hospital-acquired pneumonia, immunosuppression, bilateral infiltrates on radiograms, coagulation disorders, malignancy and respiratory failure were excluded.

Two groups of patients with pneumonia were studied; one group consisted of patients treated in an outpatient setting, whilst patients of the other group were hospitalized with mild-moderate infection [1]. The severity of the disease was also defined by the systemic inflammatory response syndrome (SIRS) and the acute physiology and chronic health evaluation (APACHE II) system within 24 h of admission. SIRS was defined using the guidelines developed by the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference [13]. Criteria for inclusion into the SIRS group were two or more of the following conditions: temperature >38°C or <36°C; heart rate >90 b.p.m.; respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg, and WBC >12,000/mm³, <4,000/mm³, or >10% immature (band) forms.

The study protocol was approved by the University of Osmangazi Ethical Committee, and written informed consent was obtained from each patient before entrance into the study.

Methods

Clinical data were collected for each patient. Blood samples were withdrawn from each patient for APR, WBC and biochemical analyses. Serum C-reactive protein (CRP) concentration was measured using the immunonephelometric method with a commercially available kit (Behring; Marburg, Germany). WBC, fibrinogen and erythrocyte sedimentation rate (ESR) were assessed using a 'Coulter STKS', 'STA compact' and manually, respectively.

Patients underwent posteroanterior and lateral chest radiographs on the day of admission and every 3 days thereafter. As has been previously established, resolution was accompanied by a diminution in the density of opacity as air returns to the lobe, and it is usually complete, with the lung architecture being restored to normal. Complication is defined as the presence of pleural effusion, empyema and cavitory image [14].

Table 1. Demographic and clinical parameters of the patients

	Outpatients n = 10	Inpatients n = 18	Non-SIRS n = 10	SIRS n = 18
Age, years	51.6 ± 20.8	45.1 ± 15.9	43.7 ± 16.3	54.0 ± 19.0
Males/females	5/5	14/4	6/4	13/5
APACHE II score	5.9 ± 4.4	10.1 ± 3.7*	6.3 ± 4.7	9.9 ± 3.7*
Smoking	4	12	5	11
Antibiotic use	2	3	3	2
Comorbidity	4	6	5	5
Complication	0	6	0	6
Died	0	1	0	1

* $p < 0.05$.

Fiberoptic bronchoscopy was performed in all patients within 24 h of admission, in accordance with the guidelines laid down by the American Thoracic Society [15]. Thirty minutes before bronchoscopy was performed, a premedication was administered, using 0.5 mg atropine and 5 mg diazepam i.m. Larynx and upper airways were adequately anesthetized with a 4% lidocaine spray and pentacaine. Supplemental nasal oxygen was administered throughout the procedure. The bronchoscope was passed through the mouth, and BAL was performed successively on the noninvolved contralateral lung, and then on the site of pneumonia. The bronchoscope was wedged into the involved lung bronchus, and lavage was then performed. Five 20-ml sterile saline solutions were injected and withdrawn by gentle aspiration with a 20-ml syringe. BAL fluids were centrifuged at 1,000 r.p.m. for 10 min, and the supernatant was frozen at -30°C until a cytokine assay was performed. There was no significant difference in the amount of fluid recovered from the involved and noninvolved lung (mean \pm SD = 35 ± 3.2 vs. 33 ± 3.4 ml, respectively). Plasma samples were taken just prior to fiberoptic bronchoscopy.

Cytokine and CRP

The levels of immunoreactive TNF- α , IL-1 β , IL-6 and IL-8 in serum and BAL fluid were determined with an immunoenzymatic assay (Bender Med Systems, Medsystems Diagnostics, Vienna, Austria) in accordance with the manufacturer's recommendations. The detection limit of TNF- α , IL-1 β , IL-6 and IL-8 in serum and BAL fluid samples were 5.0, 1.0, 1.4 and 11.0 pg/ml, respectively. In serum and BAL fluid, CRP levels were measured using the immunonephelometric method with a commercially available kit (Behring).

Statistical Analysis

All analyses were performed with SPSS statistical computer programs. Results were expressed as means \pm SEM. Nonparametric statistical tests were used for comparison of cytokine concentrations, in particular, the Mann-Whitney U test and the χ^2 test. Correlations were analyzed with Spearman's correlation coefficient. Differences between the data obtained from involved and noninvolved lungs were analyzed with Wilcoxon's paired nonparametric test. A p value of ≤ 0.05 was considered significant.

Results

Of the 28 patients included in the study, 19 (67.9%) were male and 9 (32.1%) were female. Their mean age was 47.4 ± 17.7 years. Eighteen (64.3%) patients had two or more criteria of SIRS on admission, with the remaining 10 (35.7%) not having the minimum two criteria. Ten (35.7%) patients were treated in an outpatient setting, and 18 (64.3%) patients with CAP required hospitalization because of mild-moderate infectious disease. The demographic and clinical parameters of the patients are given in table 1.

The mean APACHE II score was 8.6 (range 1–17). The APACHE II score for the hospitalized and SIRS groups were significantly higher than those found in the outpatient and non-SIRS groups (10.1 ± 3.7 and 5.9 ± 4.4 , respectively, $p < 0.05$, and 9.9 ± 3.7 and 6.3 ± 4.7 , respectively, $p < 0.05$).

Respiratory complications included parapneumonic effusion ($n = 4$) and empyema ($n = 2$) in all the SIRS and hospitalized patients. Comorbidity was present in 10 (35.7%) patients. The most frequent comorbidities were diabetes mellitus ($n = 3$, 10.7%) and cardiac failure ($n = 3$, 10.7%). Five patients received antibiotic treatment prior to the study. Sixteen patients were smokers. No statistically significant differences were found between the groups for analyzed clinical variables, including age, gender, smoking habits, prior use of antibiotics, comorbidity and complications.

Patients with SIRS had significantly higher temperatures, pulse rates and WBC ($p < 0.05$) than patients without SIRS, but respiratory rate and APR were not significantly higher (table 2).

Table 2. Mean (\pm SE) clinical and laboratory data in patients with CAP

	Outpatients n = 10	Inpatients n = 18	Non-SIRS n = 10	SIRS n = 18
Temperature	37.4 \pm 6.0	38.3 \pm 12.1*	37.2 \pm 9.5	38.3 \pm 10.7*
Pulse rate	92.5 \pm 12.4	102.5 \pm 14.4	89.8 \pm 9.8	103.5 \pm 14.2*
Respiratory rate	26.2 \pm 1.7	26.3 \pm 3.3	24.8 \pm 2.7	26.8 \pm 2.9
WBC, n/mm ³ \times 10 ³	11.1 \pm 4.9	16.7 \pm 7.4	11.2 \pm 5.1	16.7 \pm 7.3*
ESR, mm/s	76.3 \pm 30.6	71.9 \pm 33.1	78.2 \pm 30.5	70.8 \pm 32.9
CRP, mg/dl	12.85 \pm 8.88	17.08 \pm 8.78	13.0 \pm 9.2	16.9 \pm 8.6
Fibrinogen, mg/dl	619 \pm 216	747 \pm 270	623 \pm 259	753 \pm 268

* p < 0.05.

Table 3. Cytokine concentrations in the patients

	Serum	BAL		p ^a	p ^b
		involved	noninvolved		
<i>All patients</i>					
CRP, mg/dl	15.78 \pm 8.8	2.18 \pm 0.3	0.27 \pm 0.12	0.0001	0.0003
TNF- α , pg/ml	26.4 \pm 57.3	21.0 \pm 33.0	11.1 \pm 10.0	0.468	0.072
IL-1 β , pg/ml	3.73 \pm 4.5	30.1 \pm 78.2	6.2 \pm 4.5	0.002	0.008
IL-6, pg/ml	39.1 \pm 72.4	203.3 \pm 361.4	21.4 \pm 42.5	0.025	0.012
IL-8, pg/ml	52.8 \pm 37.6	453.0 \pm 629.9	98.2 \pm 92.1	0.085	0.122
<i>SIRS (n = 18)</i>					
CRP, mg/dl	16.9 \pm 8.6	2.69 \pm 0.8	1.0 \pm 0.3	0.001	0.0005
TNF- α , pg/ml	29.0 \pm 16.4	22.8 \pm 8.7	12.1 \pm 2.9	0.522	0.152
IL-1 β , pg/ml	4.08 \pm 1.3	58.1 \pm 40.6	7.0 \pm 1.7	0.015	0.007
IL-6, pg/ml	49.6 \pm 20.3	283.5 \pm 101.0	29.76 \pm 12.37	0.038	0.022
IL-8, pg/ml	59.4 \pm 10.1	746.6 \pm 298.2	139.5 \pm 39.3	0.002	0.003
<i>Non-SIRS (n = 10)</i>					
CRP, mg/dl	13.0 \pm 9.2	2.36 \pm 1.2	1.1 \pm 0.6	0.031	0.008
TNF- α , pg/ml	21.8 \pm 7.5	17.7 \pm 7.9	9.2 \pm 1.7	0.748	0.319
IL-1 β , pg/ml	3.1 \pm 0.4	14.5 \pm 3.6	5.7 \pm 1.0	0.207	0.257
IL-6, pg/ml	20.3 \pm 10.3	58.9 \pm 29.9	5.6 \pm 1.1	0.286	0.137
IL-8, pg/ml	58.9 \pm 8.3	289.9 \pm 66.8	76.3 \pm 16.8	0.044	0.120

^a Serum and BAL fluid from the involved lung.

^b BAL fluid from the involved and noninvolved lung.

Cytokine and CRP Concentrations in Serum and BAL Fluid

No correlation was found between WBC and cytokine levels of serum. CRP levels in serum and BAL fluid of patients with SIRS were found to be higher than in the patients without SIRS, which in itself was not significant ($p > 0.05$).

The cytokine concentrations of patients are given in table 3. IL-8, IL-6 and IL-1 β levels in BAL fluid from the involved lung were found to be significantly higher in

SIRS patients than the same levels in the serum (289.9 \pm 66.8 vs. 59.4 \pm 10.1 pg/ml, respectively, $p = 0.002$; 283.5 \pm 101.0 vs. 49.6 \pm 20.3 pg/ml, respectively, $p = 0.038$, and 14.5 \pm 3.6 vs. 4.0 \pm 1.3 pg/ml, respectively, $p = 0.015$). There were no differences in TNF- α levels in serum and BAL fluids from the involved and noninvolved lung. The serum CRP concentrations of patients were higher than those in the BAL fluid from the involved lung (16.9 \pm 8.6 vs. 2.6 \pm 0.8 respectively, $p = 0.001$).

Table 4. Cytokine levels of patients according to the severity of pneumonia

	SIRS n = 18	Non-SIRS n = 10	Outpatients n = 10	Inpatients n = 18
<i>Serum</i>				
CRP, mg/dl	16.9 ± 8.6	13.0 ± 9.2	128.5 ± 31.4	170.8 ± 20.7
TNF- α , pg/dl	29.0 ± 16.4	21.8 ± 7.5	14.5 ± 5.4	33.0 ± 16.5
IL-1 β , pg/dl	4.08 ± 1.3	3.1 ± 0.4	3.0 ± 0.4	4.0 ± 1.3
IL-6, pg/dl	49.6 ± 20.3	20.3 ± 10.3*	10.1 ± 2.2	55.2 ± 20.4**
IL-8, pg/dl	59.4 ± 10.1	58.9 ± 8.3	47.0 ± 6.7	56.0 ± 10.4
<i>BAL from the involved lung</i>				
CRP, mg/dl	2.69 ± 0.8	2.36 ± 1.2	26.5 ± 4.7	39.7 ± 18.0
TNF- α , pg/dl	22.8 ± 8.7	17.7 ± 7.9	22.0 ± 8.1	20.4 ± 8.7
IL-1 β , pg/dl	58.1 ± 40.6	14.5 ± 3.6	13.7 ± 3.5	59.5 ± 40.5
IL-6, pg/dl	283.5 ± 101.0	58.9 ± 29.9*	85.8 ± 39.7	268.6 ± 101.7
IL-8, pg/dl	746.6 ± 298.2	289.9 ± 66.8	312.2 ± 81.2	706.4 ± 292.3
<i>BAL from the noninvolved lung</i>				
CRP, mg/dl	1.0 ± 0.3	1.1 ± 0.6	13.5 ± 3.8	11.3 ± 1.7
TNF- α , pg/dl	12.1 ± 2.9	9.2 ± 1.7	9.6 ± 1.9	11.7 ± 2.7
IL-1 β , pg/dl	7.0 ± 1.7	5.7 ± 1.0	5.3 ± 0.9	8.1 ± 1.7
IL-6, pg/dl	29.76 ± 12.37	5.6 ± 1.1	5.6 ± 1.3	28.4 ± 11.7
IL-8, pg/dl	139.5 ± 39.3	76.3 ± 16.8	74.0 ± 16.0	152.6 ± 42.0**

* $p < 0.05$, compared with SIRS and non-SIRS. ** $p < 0.05$, compared with out- and inpatients.

The mean concentrations of CRP, IL-6 and IL-1 β in BAL fluid from the involved lung were significantly higher than those from the noninvolved lung. Serum CRP levels were also higher compared to those in BAL fluid from the involved lung in non-SIRS patients (13.0 ± 9.2 vs. 2.3 ± 1.2 , respectively, $p = 0.031$). The mean concentrations of IL-8 in BAL fluid from the involved lungs were higher than in the serum in non-SIRS patients (746.6 ± 298.2 vs. 58.9 ± 8.3 , respectively, $p = 0.044$).

Cytokine concentrations of patients with SIRS and non-SIRS are given in table 4. IL-6 levels in serum and BAL fluids from the involved lung were higher in SIRS patients than in non-SIRS patients (49.6 ± 20.3 vs. 20.3 ± 10.3 pg/ml, respectively, $p < 0.05$, and 283.5 ± 101.0 vs. 58.9 ± 29.9 pg/ml, respectively, $p < 0.05$). However, only serum IL-6 levels were significantly higher in hospitalized patients than in outpatients (55.2 ± 20.4 vs. 10.1 ± 2.2 , respectively, $p < 0.05$). These differences were not found when serum and BAL TNF- α , IL-1 β and IL-8 levels were compared ($p > 0.05$).

Correlations between Serum and BAL Cytokines

In patients, TNF- α levels in serum were correlated with both serum IL-1 β and IL-8 ($r = 0.756$, $p = 0.0002$,

and $r = 0.608$, $p = 0.0005$, respectively). IL-1 β levels in serum correlated with serum IL-8 ($r = 0.656$ and $p = 0.001$). In BAL fluids from the involved lung, CRP levels were correlated with IL-6 levels ($r = 0.528$ and $p = 0.029$), and IL-1 β levels were correlated with both IL-8 and TNF- α levels ($r = 0.865$, $p = 0.0001$ and $r = 0.391$, $p = 0.040$, respectively). TNF- α levels in BAL fluid from the involved lung were correlated with serum levels of TNF- α , IL-1 β and IL-8 ($r = 0.709$, $p = 0.0002$ and $r = 0.756$, $p = 0.0002$ and $r = 0.556$, $p = 0.003$, respectively).

When comparing the BAL fluids from the involved lung to the noninvolved lung, TNF- α was correlated with TNF- α ($r = 0.635$ and $p = 0.0004$), IL-8 was correlated with IL-8 ($r = 0.440$ and $p = 0.025$) and IL-6 was correlated with IL-6 ($r = 0.681$ and $p = 0.0003$), but no correlation was found between involved-lung BAL fluid IL-1 β and noninvolved-lung BAL fluid IL-1 β ($r = 0.383$ and $p = 0.053$).

Correlations between Cytokine Levels and Clinical Parameters

No correlation was found between the APACHE II score and cytokine levels of serum and BAL fluid. However, serum CRP levels were correlated with the

APACHE II score ($r = 0.545$ and $p = 0.004$). Serum WBC was correlated with serum CRP and BAL fluid IL-6 levels from the involved lung ($r = 0.434$, $p = 0.027$ and $r = 0.372$, $p = 0.050$, respectively).

Smokers and nonsmokers had similar cytokine levels. The cytokine levels were not different between the patients who had used antibiotics and those who had not used antibiotics before admission to our clinic.

APACHE II score and serum CRP levels were significantly higher in patients with comorbidity than in patients without comorbidity (11.0 ± 1.5 vs. 7.3 ± 0.8 , $p = 0.033$, and 22.2 ± 2.3 vs. 12.3 ± 1.9 , $p = 0.004$, respectively).

IL-6 levels in BAL fluid from the involved lung were significantly higher in the patients who had complications than in those without (248.2 ± 84.6 vs. 38.9 ± 19.9 , $p = 0.024$).

Discussion

This study documents systemic and local levels of CRP, TNF- α , IL-1 β , IL-6 and IL-8 in unilateral CAP. The main results of our study can be summarized as follows: (a) the inflammatory cytokines, except for TNF- α , are higher in the involved lung than in the serum and noninvolved lung; (b) the involved-lung IL-6 level in serum and BAL fluid is a major predictor of disease severity; (c) the inflammatory cytokines do not correlate with the APACHE II score and CRP levels, and (d) CRP levels of BAL fluid from the involved lung is higher than from the noninvolved lung, but lower than serum levels.

The presence of circulating proinflammatory cytokines in patients with pneumonia has been described. Several studies have shown an increased inflammatory lung response in pneumonia. The production of cytokines in response to local bacterial infection has been shown to be largely confined and compartmentalized. In previous studies, patients with unilateral pneumonia had higher levels of cytokines in the involved lung compared with the noninvolved lung and serum [2, 4, 10, 16, 17].

TNF- α , IL-1 β and IL-8 concentrations in BAL fluid were higher than in the serum. TNF- α and IL-1 β were normal or slightly increased in the serum because IL-1 β and TNF- α are locally produced within the lung and act as a local mediator of inflammatory response. However, increased IL-6 levels were noted in the serum, suggesting that IL-6 acts both as a local and systemic mediator of inflammatory responses [2, 4, 10, 18].

In contrast to Dehoux et al. [2], in our patients, IL-1 β and IL-6 levels in BAL fluid from the involved lung were higher than in the serum. Serum and BAL fluid TNF- α levels of the patients were similar. Consequently, TNF- α may act as a local and a systemic mediator of inflammatory responses, like IL-6.

Although cytokine levels in BAL fluid from the involved lung were higher than in the serum and noninvolved lung [2, 10, 19], Chollet-Martin et al. [17] showed that there were no statistically significant differences in TNF- α and IL-8 plasma and BAL fluid levels in pneumonia. In our study, IL-1 β and IL-6 BAL fluid from the involved lung were significantly higher than in the serum, but there were no significant differences in TNF- α and IL-8 serum and BAL fluid levels.

Our study provides confirmatory evidence of lung compartmentalization with regard to cytokine production. We confirmed that CRP and cytokine levels in the BAL fluid from the involved lung were higher than in the noninvolved lung, but TNF- α and IL-8 levels were not statistically significant. This suggests that TNF- α and IL-8 act as both local and systemic mediators of inflammatory responses.

TNF- α level in serum and in BAL fluid from the involved lung were correlated with the IL-1 β level. These results are in accordance with a recently published report demonstrating that IL-1 β might be induced by TNF- α and serves to potentiate the effect of TNF- α [20].

Correlations between serum and BAL fluid cytokine levels of patients were studied. No correlation was found between the serum and BAL fluid concentrations of TNF- α , IL-1 β and IL-8 from the involved and noninvolved lung [2, 17, 21]. However, serum concentrations of IL-6 were correlated with IL-6 concentrations in BAL fluid from the involved side, suggesting that IL-6 produced in the lung contributes at least in part to serum levels of the cytokine [2]. Our study demonstrated that the serum concentration of TNF- α correlated with the TNF- α concentration in BAL fluid from the involved lung in both SIRS and non-SIRS groups. Therefore, TNF- α may act as a local and systemic mediator of inflammatory responses, similar to IL-6, but we were unable to find an explanation for this situation.

Correlations between disease severity and cytokine concentrations have been described previously. However, the results of our study differed from those of others in several points. Puren et al. [7] studied pneumonic patients who were treated in the intensive care unit and in the non-intensive care unit. They found that the plasma concentrations for IL-1 β and IL-6 were not significantly differ-

ent, although the values for TNF- α were significantly higher in the intensive care unit patients in comparison to the non-intensive care unit patients, and TNF- α correlated with the severity of pneumonia but not with outcome [7]. In the study of Monton et al. [4], serum TNF- α and IL-6 levels were designed to assess the severity of pneumonia. Elevated levels of serum IL-6 were used as a marker of infection severity [22, 23]. Serum concentrations of TNF- α and IL-1 β were most strongly associated with the degree of lung injury [24]. Higher serum levels of TNF- α and BAL fluid levels of IL-8 were correlated with the severity of disease and simplified acute physiological and lung injury scores [17, 18, 25].

Glynn et al. [26] found that serum IL-6 levels were significantly higher in the SIRS group compared with the non-SIRS group. In our study, the serum cytokine levels were higher in hospitalized patients with pneumonia and in SIRS patients. IL-6 levels of SIRS patients in serum and BAL fluid from the involved lung were significantly higher than in the non-SIRS group. However, only serum IL-6 levels of the hospitalized patients were significantly higher than in the outpatients, indicating that IL-6 correlated with the severity of pneumonia in our patients.

Contradictory results exist regarding correlations between serum cytokine levels and APACHE II score results. Some studies reported a significant correlation between the APACHE II score and serum TNF- α , IL-1 β and IL-6 levels [7, 26], whereas in others serum TNF- α and IL-1 β levels did not correlate with the APACHE II score [16]. In our study, the APACHE II score was significantly higher for the SIRS group than the non-SIRS group, but there was no significant association between the APACHE II score and the individual cytokines.

CRP is an APR synthesized by the liver in response to tissue injury and inflammation. It is a good indicator of bacterial infections [27, 28]. To our knowledge, CRP levels have not been reported in the lung and alveoli during inflammatory states. Galve-de Rochemonteix et al. [29] hypothesized that the CRP concentrations in alveoli were lower than in the blood. We found that serum CRP levels were higher than in the BAL fluid, and levels in the involved lung were also higher than those in the noninvolved lung. CRP production in the lung may have been induced by systemic stimuli and then reached the inflammatory site of the body.

IL-1 β , IL-6 and TNF- α induce synthesis of CRP by the liver both in vitro and in vivo [29–31]. There was no significant correlation between CRP and IL-1 β , IL-6 or TNF- α by radioimmunoassay, but plasma CRP concentration was correlated with the IL-6 concentration, which

was measured by bioassay [30]. A significant correlation was found between CRP and IL-6 levels using a chemiluminescent enzyme immunoassay [32]. In our study, CRP and IL-6 levels in BAL fluid from the involved lung were significantly correlated, confirming previous studies.

Kosmos et al. [19] found that patients with parapneumonic effusion presented significantly higher levels of TNF- α . IL-6 levels in BAL fluid from the involved lung were also higher than in the patients who had complications.

In summary, we have demonstrated, in accord with previous studies, that cytokine production was localized and compartmentalized within the lung in unilateral pneumonia. IL-6 is the most important cytokine in serum and BAL fluid to determine disease severity and complications. Because of the limited sample size, we were unable to assess the relationship between serum and BAL fluid cytokine levels and outcome.

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