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Cytokine Responses in Patients with Pneumonia

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1. INTRODUCTION

The importance of proinflammatory cytokines was first appreciated in studies of patients with sepsis or septic shock, but during the 1990s, the research expanded to include a wide range of infectious and other inflammatory conditions. The first investigations of the role of cytokines in lower-respiratory-tract infections were published in 1992. Since then, clinical studies have been performed on different aspects of inflammation in pneumonia. One group of studies focuses on the pathogenesis of bacterial pneumonia. A second group studies the relation between the microbial etiology of pneumonia and the ensuing inflammatory response. A third group relates the cytokine response in bacterial pneumonia to severity [i.e., SIRS *(1)*, APACHE II *(2)*, or other clinical scoring systems]. A fourth group of studies investigates the role of age in relation to the inflammatory response caused by an acute bacterial pneumonia. Finally, in a few studies, the impact of immunomodulating therapy has been investigated.

The methods for the detection and quantification of cytokine levels vary considerably between different studies, which makes the comparison of results difficult. As sample preparation and storage also influence cytokine measurements, uniform handling of samples is of major importance. In the present chapter, we review the findings presented thus far describing the cytokine responses in adult human subjects with pneumonia. The results are discussed from a clinical point of view.

2. CYTOKINE RESPONSES AND PATHOGENESIS OF BACTERIAL PNEUMONIA

The role of cytokines in the pathogenesis of bacterial infection was primarily studied in patients with septic conditions. As cytokines were found to be central mediators of inflammation, research was soon broadened to include focal infections as well as other inflammatory conditions.

Interleukin (IL)-8 was first demonstrated in bronchial secretions from 105 of 151 patients undergoing mechanical ventilation in the intensive care unit (ICU) *(3)*. When patients with severe pneumonia were compared to patients with acute respiratory distress syndrome (ARDS), elevated broncho-alveolar lavage (BAL) fluid levels of IL-8 were correlated to severity *(4)*. Patients with pneumonia had lower levels of BAL IL-8 than patients with ARDS, but plasma IL-8 concentrations were similar in the two groups. In 42 patients with community-acquired pneumonia (CAP), blood levels of tumor necrosis factor (TNF)-α, IL-6, and soluble IL-2R were compared to polymorphonuclear leukocyte and monocyte chemiluminescence response showing elevated levels of cytokines and activated phagocytes in most patients compared to controls *(5)*. The inflammatory response to pneumonia is compartmentalized to the affected lung, as shown by Dehoux et al. *(6)*. In 15 patients

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with unilateral pneumonia, the BAL fluid levels of TNF-α, IL-1β, and IL-6 were determined in the affected lung and compared with the levels in the nonaffected lung. BAL fluid levels of all three cytokines were higher in the involved lung compared to the noninvolved lung (*see* Fig. 1). In a later study, a similar result was obtained for IL-8 *(7)* (*see* Fig. 2). The concentrations of IL-8 and another CXC chemokine, growth-related oncogene (GRO)-α were measured in BAL fluid from patients with bacterial pneumonia (n = 12), ARDS (n = 13), or *Pneumocystis carinii* pneumonia (n = 48) *(8)*. Patients with bacterial pneumonia and patients with ARDS had comparable levels of IL-8 and GRO-α suggesting a role also for GRO-α as a chemoattractant in inflammatory conditions in the lung. BAL fluid concentrations and blood concentrations of TNF-α IL-6 and IL-8 were compared in a study of 74 mechanically ventilated patients *(9)*. Patients with bacterial pneumonia and/or ARDS had comparable high levels of IL-6 and IL-8 but no consistently detectable TNF-α in BAL fluid. In blood, the levels of IL-6 and TNF-α were elevated in the group of patients with bacterial pneumonia and/or ARDS. Elevated concentrations of IL-8 in BAL fluid from 31 patients with CAP were also found by Bohnet et al. *(10)* and the levels of IL-8 in BAL fluid were higher in patients with positive microbiological results. Comparison of TNF-α, IL-6, and IL-8 mRNA levels in alveolar macrophages from patients with CAP and BAL fluid levels of the same three cytokines showed elevated mRNA content only for IL-8, but increased concentrations of IL-6 and IL-8 *(11)*. Another potent neutrophil chemoattractant, transforming growth factor (TGF)-β, was studied in 35 patients with pneumonia *(12)*. The BAL fluid concentrations of TGF-β and IL-8 were measured within 12 h from admission to hospital. The levels of TGF-β1, TGF-β2, and IL-8 were found to be elevated in patients with a defined microbiological etiology to the pneumonia. In patients with CAP (n = 8) or nosocomial pneumonia (n = 12) treated with mechanical ventilation in the ICU, serum levels of TNF-α and IL-6 were higher than the concentrations in the ventilated noninfectious controls *(13)*. BAL fluid levels of IL-6 were also higher in the pneumonia group, but there was no correlation between lung bacterial burden and BAL fluid cytokine levels. All patients with pneumonia in this study had received antibiotic treatment prior to inclusion into the study.

In summary, the studies presented so far have demonstrated the presence of several proinflammatory cytokines in secretions from the respiratory tract of patients with bacterial pneumonia. In most cases, this compartmentalized response is accompanied by a systemic response, primarily of IL-6.

3. CYTOKINE RESPONSES RELATED TO ETIOLOGY

3.1. Streptococcus pneumoniae

The patients included in studies of the cytokine responses in pneumonia vary considerably. In the studies with a well-documented etiology of the pneumonia *Streptococcus pneumoniae* is the most frequent isolated bacteria. In the studies of unilateral bacterial pneumonia, it was demonstrated that the cytokine response to *S. pneumoniae* is local *(6,7)*. BAL fluid concentrations of TNF-α, IL-1β, IL-6, and IL-8 were significantly higher in the involved lung compared to the noninvolved lung. None of the patients were bacteremic and serum TNF-α, IL-1β, and IL-8 levels were not different from those of the control groups. The absence of measurable levels of TNF-α, IL-1β, and IL-8 in the circulation in patients with pneumonia on admission to the hospital is in accordance with the results of other studies and most probably reflects an early brief appearance after onset of disease. However, serum concentrations of IL-6 were elevated in the patients with nonbacteremic pneumonia. The demonstration of elevated IL-6 in serum is in accordance with our studies of patients with pneumonia caused by specific microbial pathogens. In those studies, infections with *S. pneumoniae* were found to cause the highest levels of circulating IL-6 and the patients with bacteremic pneumococcal infection had the highest levels *(14)* (*see* Fig. 3). Most patients with bacterial pneumonia treated in the hospital have elevated serum IL-6, as shown by Örtqvist et al *(15)*. In that study, high levels of IL-6 were associated with longer duration of fever, longer stay in the hospital, and slower recovery, both clinically and radiographically. The finding of the highest levels of IL-6 among patients with pneumococcal

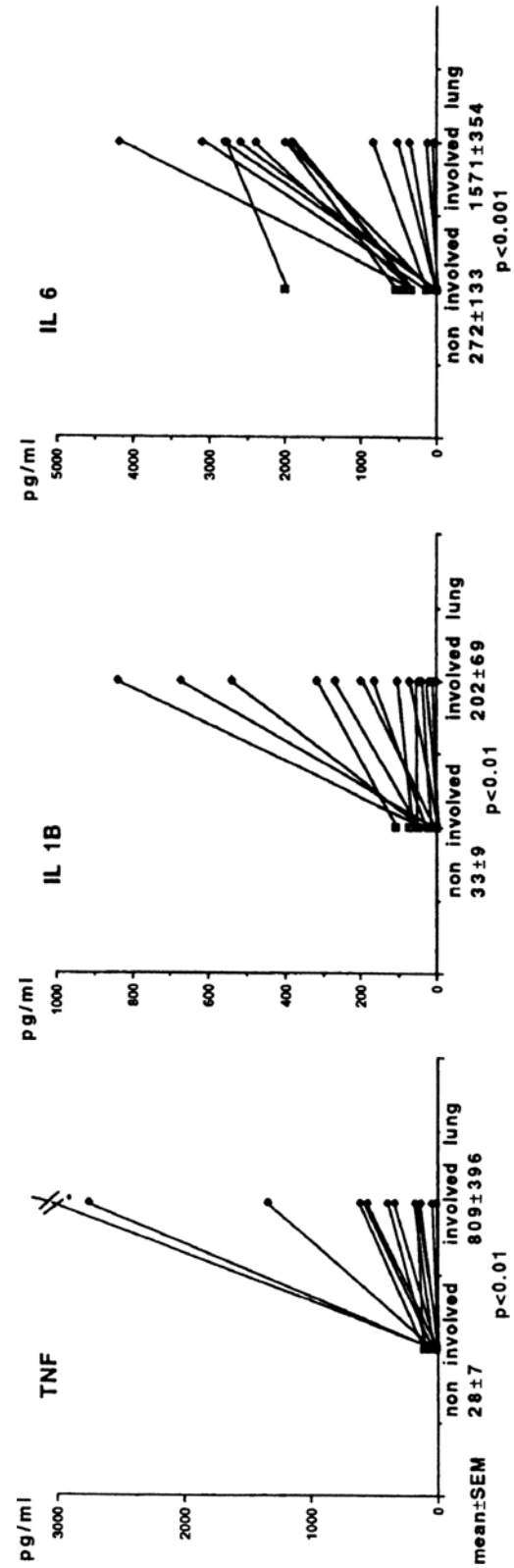

Fig. 1. IL-1β, TNF-α, and IL-6 concentrations in BAL fluids. Cytokines were measured by enzyme-linked immunosorbent assay in BAL fluids recovered from the involved lung and contralateral, noninvolved lung of patients with unilateral pneumonia (n = 15) prior to antibiotic therapy. (Reproduced from ref. *6* with permission.)

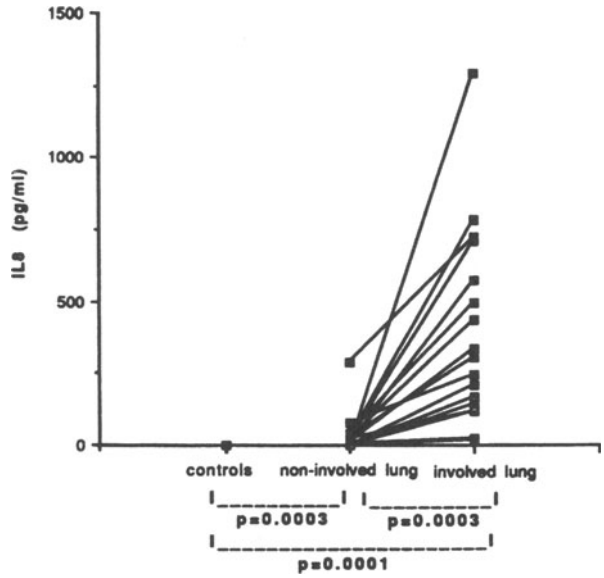

Fig. 2. IL-8 concentrations in BAL fluid recovered from the involved lungs and the contralateral, noninvolved lungs of patients with unilateral pneumonia (n = 17) prior to antibiotic therapy and from healthy controls (n = 8). (Reproduced from ref. *7* with permission.)

infection was confirmed in this study *(15)* and in a study of 20 patients with bacteremic pneumococcal pneumonia and 20 patients with pneumonia caused by *Mycoplasma (16)*. Bacteremic pneumococcal pneumonia was also found to be associated with high levels of IL-8 and granulocyte colony-stimulating factor (G-CSF) in serum in comparison to patients with pneumonia caused by atypical agents or influenza A infection *(17)* (*see* Fig 4). Patients with bacteremic pneumococcal pneumonia had high levels of IL-6 and G-CSF on admission to the hospital and the serum concentrations decreased within 24 h when appropriate antibiotic treatment was started promptly *(18)* (*see* Fig. 5). The levels of IL-6 were not significantly different from the serum concentrations in patients with bacteremic infections caused by β-hemolytic streptococci, *S. aureus*, or *Escherichia coli*. In bacteremic pneumococcal pneumonia the serum concentrations of G-CSF were higher than those in patients with bacteremic infections caused by other Gram-positive bacteria such as β-hemolytic streptococci and *S. aureus (18)*. Although the concentrations of TNF-α in serum were elevated also in patients with Gram-positive bacteremia including *S. pneumoniae*, the levels were significantly lower than those in patients with Gram-negative bacteremic infection *(18)*. The serum levels of TNF-α, IL-1β, IL-6, macrophage inflammatory protein (MIP)-1β, sTNF-R, IL-1RA, and IL-10 were measured on admission to the hospital and d 3 and 7 in 22 patients with pneumococcal pneumonia *(19)*. IL-6 decreased from high levels on admission to low levels on day 3 thus supporting previous findings. The levels of TNF-α, sTNF-R, IL-1RA, IL-6, and IL-10 showed sustained elevation on d 7 compared to the control group, indicating prolonged inflammatory activity. Thus, in patients with pneumonia, pneumococcal infections elicit the highest levels of IL-6 and G-CSF, which may have a potential for clinical use as markers of a pneumococcal etiology of the pneumonia.

3.2. Chlamydia pneumoniae, Mycoplasma pneumoniae, *and* Legionella

Few studies are performed on the cytokine responses in adult patients with atypical pneumonia. The first study comparing bacterial and atypical or viral agents was performed in 1993 *(14)*. In that study, it was shown that patients with pneumonia caused by *Chlamydia*, *Mycoplasma*, influenza A virus and respiratory syncytial (RS) virus, had lower serum concentrations of IL-6 compared to

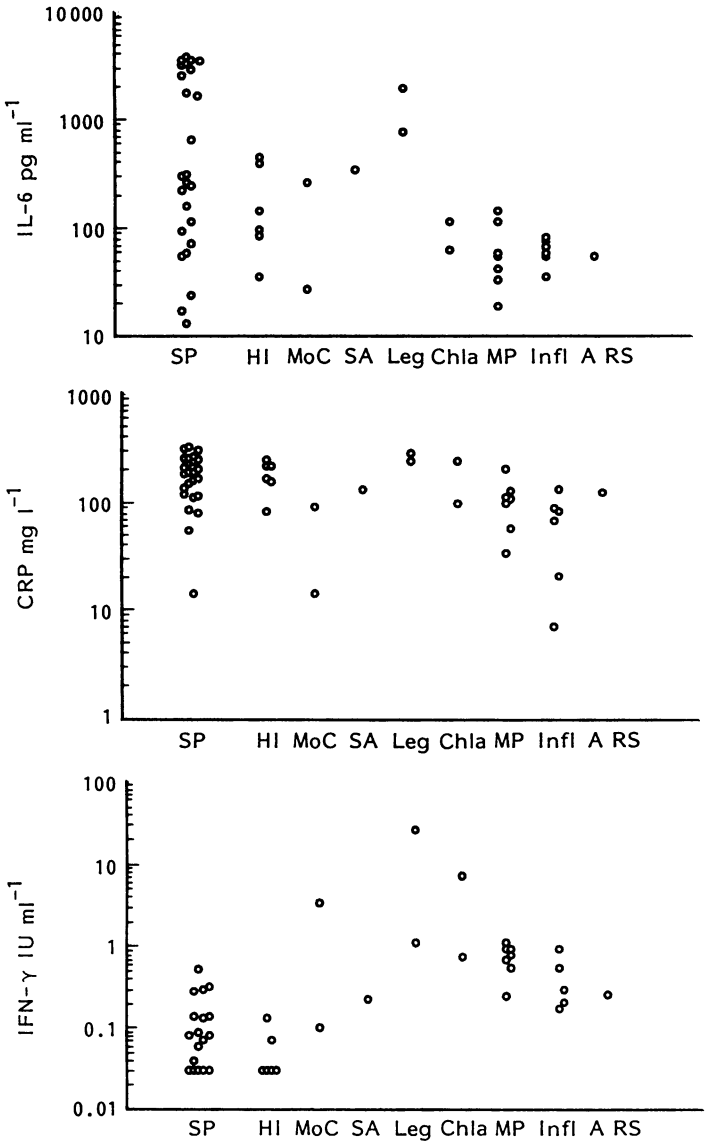

Fig. 3. Serum IL-6, C-reactive protein and interferon-γ_concentrations on admission in patients with pneumonia of different etiologies. SP: *S. pneumoniae* (n = 27), HI: *H. influenzae* (n = 6), MoC: *M. catarrhalis* (n = 2), SA: *S.aureus* (n = 1), Leg: *Legionella spp.* (n = 2), Chla: *Chlamydia spp.* (n = 2), MP: M. *pneumoniae* (n = 7), Infl A: influenza A (n = 6), RS: respiratory syncytial virus (n = 1). (Reproduced from ref. *14* with permission from Elsevier Science.)

patients with pneumonia caused by common bacterial pathogens such as *S. pneumoniae* and *H. influenzae*. In contrast, IFN-γ was shown to be elevated in the group with viral or atypical microorganisms. The finding of lower IL-6 levels in patients with atypical pneumonia such as *Mycoplasma* was supported by the three following studies. In a study of 203 patients with CAP, 16 patients with *Mycoplasma* and 13 patients with viral pneumonia were found to have lower levels compared to patients with pneumococcal pneumonia or other bacteremic pneumonia on admission to hospital *(15)*. Lieberman et al. compared 20 patients with bacteremic pneumococcal pneumonia with 20 patients with pneumonia caused by *Mycoplasma (16)*. Inversely, IL-1β was found to be higher in

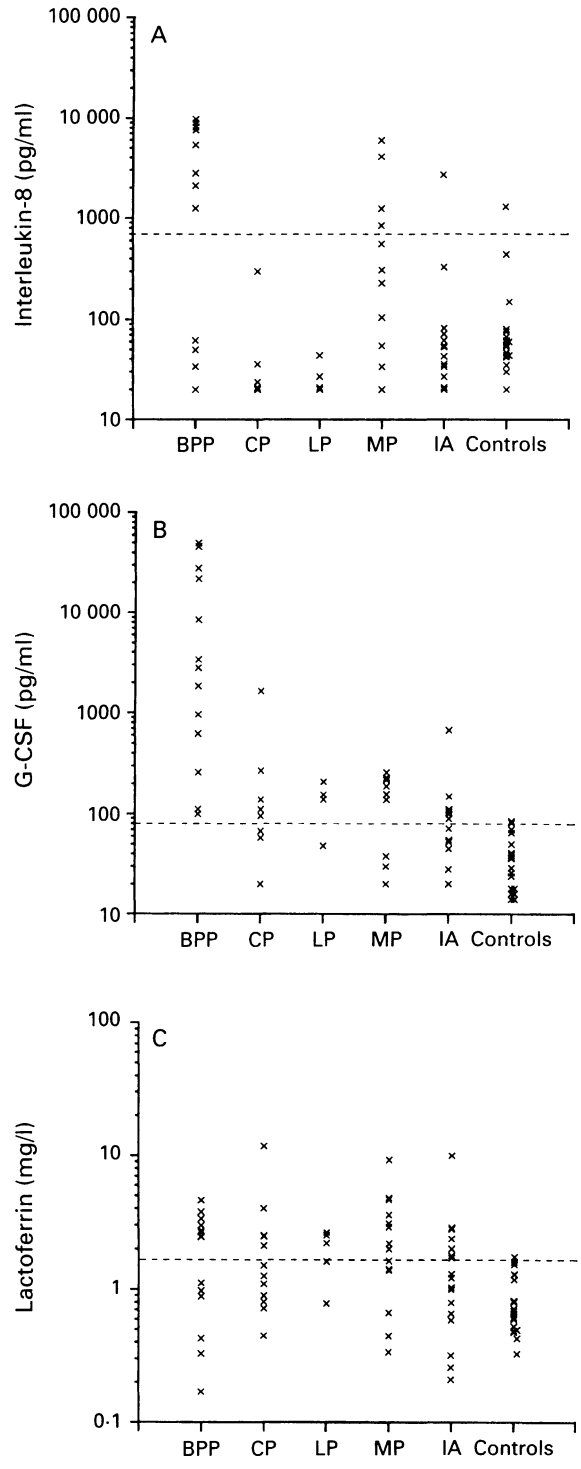

Fig. 4. Distribution of serum concentrations of IL-8 **(A)**, G-CSF **(B)**, and lactoferrin **(C)** in 63 patients with bacteremic pneumococcal pneumonia (BPP), *Chlamydia* pneumonia (CP), *Legionella* pneumonia(LP), *Mycoplasma* pneumonia (MP), influenza A infection (IA), and in 20 blood donors (controls). (Reproduced from ref. *(17)* with permission from the BMJ Publishing Group.)

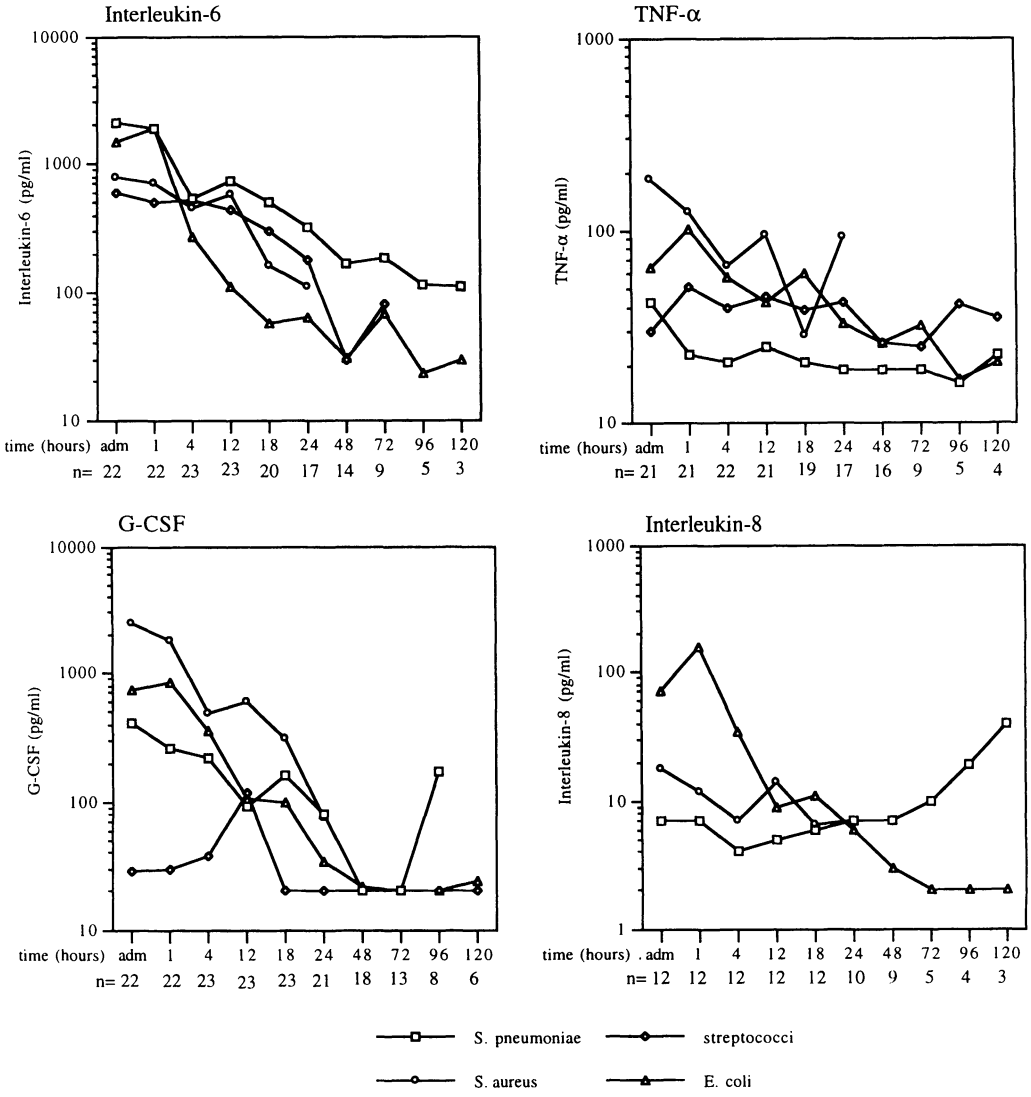

Fig. 5. Median serum levels of IL-6, TNF-α, G-CSF and IL-8 in bacteremic nonfatal cases. Time-points on the *x*-axis are admission (adm), 1 h later ($t = 1$), and 4, 12, 18, 24, 48, 72, 96, and 129 h from admission. *n* is the number of patients sampled at each time-point. (Reproduced from ref. *18* with permission from Taylor & Francis, Stockholm, Sweden.)

patients with *Mycoplasma pneumonia* on admission to the hospital compared to the patients with bacteremic pneumococcal pneumonia. In a study of patients with *Chlamydia* pneumonia ($n = 13$) and *Mycoplasma* pneumonia ($n = 14$), serum concentrations of TNF-α, IL-6, and IFN-γ were found to be elevated on admission *(20)* (*see* Fig. 6). No significant differences between the etiological groups were found, but the levels of IL-6 were in the low range in accordance with our previous study *(14)* and most patients had elevated IFN-γ. The serum concentrations of G-CSF was investigated in eight patients with *Mycoplasma* pneumonia and compared with levels in patients with diverse bacterial infections *(21)*. Serum concentrations were found to be low in the group of patients with *Mycoplasma* pneumonia, a result which is in agreement with the findings in our study *(17)*. Patients with pneumonia caused by *Mycoplasma* ($n = 14$), *Chlamydia* ($n = 12$), and *Legionella* ($n = 6$) had lower levels of

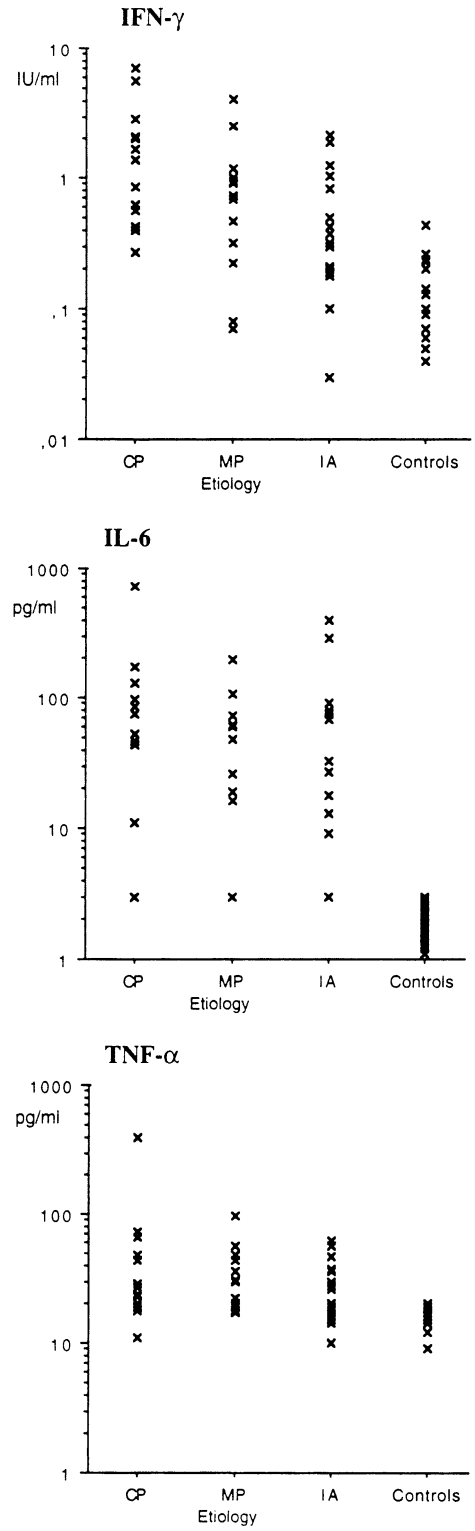

Fig. 6. Scatter of the concentrations of IFN-γ, IL-6 and TNF-α in serum of patients with CP (*Chlamydia pneumoniae*) or MP (*Mycoplasma pneumonia*) or IA (influenza A infection) and in 20 controls. (Reproduced from ref. *20* with permission from S. Karger AG, Basel.

G-CSF in comparison with patients with bacteremic pneumococcal pneumonia. Only three studies include patients with *Legionella* pneumonia *(14,17,22)*. In our previous studies we found elevated levels of IL-6 and IFN-γ but low concentrations of IL-8 and G-CSF on admission to the hospital *(14,17)*. In a study, of 14 patients with *Legionella* pneumonia using bloodsamples taken at variable time-points during the hospital stay, Tateda et al. found elevated levels of the cytokines IFN-γ and IL-12, low levels of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and no IL-4 or IL-10 *(22)*. The results from these three studies show that in infections caused by intracellular micro-organisms such as *Legionella*, the cytokine response is associated with elevated circulating levels of Th1 cytokines such as IFN-γ and IL-12.

Thus, studies of clinically less severely ill patients with pneumonia have shown that differences do exist in the blood concentrations between different etiologies of the pneumonia. Based on the results presented here determination of blood IL-6 and IFN-γ/IL-12 might have a differential diagnostic potential.

4. CYTOKINE RESPONSES AND SEVERITY

Studies of the systemic inflammatory host response in the critically ill have demonstrated the pathophysiological role of cytokines. It has been shown that the levels of most cytokines reflect that the severity of the condition may be the cause of inflammation becoming infectious, traumatic, or other. In the case of bacterial pneumonia, few studies examine clinical severity grading in relation to systemic cytokine levels. Plasma levels of IL-1β, TNF-α, and IL-6 were measured in critically ill patients with pneumonia, less severely ill patients with pneumonia, severely ill postoperative patients without infection, and a group of patients with nonpneumonic infection *(23)*. In this study, TNF-α was found to be a marker of severity of pneumonia, IL-1β to mark severity of infection, and IL-6 to reflect infectious or noninfectious severity. Using SIRS as the severity classification, bacteremic pneumococcal pneumonia was found to be comparable to other bacteremic infections *(18)* and the serum levels of IL-6, TNF-α, and G-CSF reflected clinical severity. De Werra et al. compared patients with septic shock, cardiogenic shock, and bacterial pneumonia and found plasma levels of TNF-α to reflect severity in patients with infection, whereas plasma IL-6 was highest in septic shock patients, normal in seven patients with pneumonia, and elevated in cardiogenic shock *(24)*. The finding of normal IL-6 levels in patients with bacterial pneumonia is unusual, as most other studies demonstrate high levels of IL-6 even in nonbacteremic patients cared for in a common infectious disease department. Serum IL-10 was studied in 38 patients with CAP divided into a SIRS group and a non-SIRS group and correlated with APACHE II scores *(25)*. IL-6 and IL-10 were found to correlate with severity of illness. Comparing patients with severe pneumonia and ARDS, Bauer et al. found serum TNF-α and IL-1/β to reflect the severity of the lung injury *(26)*. In the studies presented so far, IL-6 consistently emerges as a marker of severity. In individual studies, other cytokines such as IL-10, G-CSF, and TNF-α were also found to mark the severity of the illness.

5. CYTOKINE RESPONSES AND AGE

Previous investigations have shown that increasing age confers increasing impairment of the immune system. In the case of bacterial pneumonia, studies have focused on the ability of elderly patients to mount an inflammatory response to infection. Gon et al. demonstrated lower serum values of G-CSF, GM-CSF, TNF-α, IL-1β, IL-8, and MIP-1α in elderly patients in the acute stage, and the levels in both young and older patients declined on recovery *(27)*. The definition of recovery was set to a span of 5–14 d, which makes comparison with the following study difficult. The inflammatory response during pneumococcal infection was studied in 22 patients divided into groups of young and elderly patients. The circulating concentrations of IL-1β, TNF-α, IL-6, MIP-1β, IL-1RA, IL-10, and sTNFR-I were measured on admission and after 3 and 7 d in the hospital *(19)*. In this study, aging was shown to be associated with prolonged inflammatory activity, but levels of cytokines in young and

old patients were similar on admission. Glynn et al. found no difference in serum IL-10 levels in patients divided into groups younger than 60 or older than 70 yr of age, but serum IL-6 concentrations were higher in the patients older than 70 yr of age *(25)*. In that same study, IL-6 and IL-10 were correlated to severity, which raises the question of whether the elderly patients were more severely ill than the younger. Although older age is associated with impaired immune functions, elderly patients may respond with high cytokine levels, but the response may be dysregulated and prolonged.

6. CYTOKINE RESPONSES AND IMMUNEMODULATION

Immunomodulating therapies have been tried in several studies of patients with sepsis or septic shock with disappointing results. Few investigations have been performed on the effect of modulating the cytokine response during acute bacterial pneumonia. Thirty patients with severe CAP were randomized to receive either a single dose of hydrocortisone (10 mg/kg body wt) or placebo before the administration of antibiotics in addition to standard treatment for pneumonia *(28)*. TNF-α was measured on admission and after 2, 6, and 12 h after antibiotic therapy was started. In this study, hydrocortisone had no effect on the serum levels of TNF-α or on the clinical course. A recent study investigated the effect of daily methylprednisolone given after the administration of antibiotics on the inflammatory response in pneumonia in patients treated with mechanical ventilation in the intensive care unit *(29)*. Patients receiving methylprednisolone had lower serum levels of IL-6 and C-reactive protein (CRP) and a lower neutrophil count in BAL fluid. However, the dosage and treatment period varied considerably. Recombinant human (rh) G-CSF for the treatment of CAP was studied in a prospective, double-blind, randomized, placebo-controlled study *(30)*. In all, 756 patients were studied, 376 received placebo and 380 rh G-CSF. The study showed that treatment with rh G-CSF was not harmful but gave no important benefit compared to placebo. In view of the disappointing results of immunomodulation in septic conditions and the complexity of the cytokine response to infection, a better characterization, of an appropriate and a dysregulated cytokine response is needed. Specific markers have to be established and related to the timing of treatment at specific stages during disease.

7. CONCLUSION

The role of cytokines as mediators of inflammation in pneumonia is being defined. The results from studies investigating bacterial pneumonia point to the following:

- In nonbacteremic pneumonia, the inflammatory response is mainly local and the cytokines demonstrated in BAL fluid so far are IL-8, IL-6, TNF-α GRO-α and TGF-β.
- The systemic response in nonbacteremic pneumonia is characterized mainly by elevated levels of IL-6.
- In pneumonia, blood levels of IL-6, IL-8, and G-CSF correlate with severity and prognosis and high levels may suggest *S. pneumoniae* as a probable causative agent.
- In bacteremic pneumonia, the cytokine response is comparable to that of other bacteremic infections.
- Patients with pneumonia caused by intracellular micro-organisms such as *Legionella* have circulating levels of Th1 cytokines such as IFN-γ and IL-12.
- In elderly patients, the cytokine response may be dysregulated and prolonged.
- Immunomodulation in pneumonia by way of suppressing the inflammatory host response using corticosteroids or by stimulating production of phagocytes and phagocytic activity has demonstrated no positive effects so far.

In summary, the cytokine response in human pneumonia is being characterized. Use of single cytokines or groups of cytokines as prognostic or etiological markers in individual cases is made difficult by the large variation in the immune response of individual patients at specific time-points.

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