Role of Interleukin-8 in Community-Acquired Pneumonia: Relation to Microbial Load and Pulmonary Function

Summary: In pneumonia local phagocyte activation is crucial for clearing of pathogenic microorganisms. In this context alveolar macrophage interleukin-8 secretion, phagocyte oxidative response and concentrations of lavage proteins were quantified, including interleukin-8, in 31 patients with pneumonia, 13 age matched patients with peripheral lung consolidation and six healthy volunteers; these findings were related to the impairment of gas exchange and the bacterial load in the alveolar space. Increased interleukin-8 levels were found in bronchoalveolar lavage fluid (BALF) and in alveolar macrophage supernatants from patients with pneumonia (214 ng/10⁵ AM ± 121 vs 71 ng/10⁵ AM ± 35 and 66 ng/10⁵ AM ± 30, p < 0.05). Interleukin-8 release from alveolar macrophages correlated with the upregulated spontaneous luminol enhanced oxidative response of pulmonary phagocytes but not with the neutrophil count in BALF. In pneumonia patients a significant difference was found between patients with 10⁴ or more colony forming units (CFU)/ml BALF of one pathogen and patients with less CFU or nonspecific microbiological results (261 ng/10⁵ AM ± 89 vs 179 ng/10⁵ AM ± 81 and 7.5 ng/ml BALF ± 17 vs 0.44 ng/ml BALF ± 1, p < 0.05). Further, a negative correlation between interleukin-8 release of alveolar macrophages and the arterial pO₂ at the time of BALF could be demonstrated (r = −0.47, p < 0.05). The results demonstrate local cellular activation in community-acquired pneumonia, which is related to the bacterial load in the alveolar space and to impairment of gas exchange. This is consistent with the hypothesis that pulmonary phagocytes play a central role in the pathogenesis of bacterial pneumonia, contributing not only to bacterial clearing but also to local tissue damage.

Introduction

Bacterial pneumonia is still a severe infectious disease with considerable mortality despite the advent of potent antimicrobial chemotherapeutics. In this context local phagocyte activation seems to be crucial for effective bacterial killing [1, 2], which is exemplified by chronic granulomatous disease, a congenital disorder with deficient phagocyte function and recurrent purulent infections including pneumonia [3]. However, this inflammatory process, which is primarily limited to the infected organ can, if not adequately terminated, lead to sepsis and multiorgan failure [4, 5]. Prognostic indicators, which can be quantified in an early phase of disease when infection is still compartmentalized and which are correlated to disease severity and outcome are needed.

Since alveolar macrophages are the principal resident phagocytes in the airways they are thought to play an important role in the initial phase of host response. It is evident that small amounts of inhaled bacteria are eradicated effectively by alveolar macrophages. With increasing virulence and numbers of microorganisms a rapid neutrophil influx occurs to combat invading bacteria [6, 7]. In this context a variety of chemokines have been identified, which recruit neutrophils to the lung [8]. Among them interleukin-8 appears to play a central role [9]. High interleukin-8 levels in the alveolar space have been associated with neutrophil influx into the pulmonary compartment under various conditions [10-12]. It could further be demonstrated that interleukin-8 is of some prognostic value in patients at risk of adult respiratory distress syndrome (ARDS) [13] or in AIDS-associated Pneumocystis carinii pneumonia [14].

In this study we focused on nonventilated patients with community-acquired pneumonia. The aim was to elucidate the state of cellular immunological activation in the alveolar compartment in patients who underwent bronchoscopy and bronchoalveolar lavage (BAL) for microbiological diagnosis. We quantified alveolar macrophage interleukin-8 secretions as well as interleukin-8 levels in BALF together with other parameters of phagocyte function such as oxidative response, the concentration of neutrophil secretion products and markers of alveolo-endothelial membrane integrity, relating our findings to clinical disease severity and lung functional impairment.

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Patients and Methods

**Patients:** A total of 36 patients, admitted to our hospital with community-acquired pneumonia were included in this study. The diagnosis of pneumonia was based on clinical symptoms and laboratory signs of infection (fever > 38°C, purulent sputum, elevated ESR, C-reactive protein and white blood cell count), together with the presence of new or progressing opacities on chest radiograph. The average age of the patients was 51 years with a range of 27–74 years. Seventeen were male, 19 female. Thirteen patients were immunocompromised for various reasons (hematologic malignancy: n = 3, renal transplantation: n = 4, cytotoxic therapy for systemic vasculitis: n = 6). Patients who had received antibiotic treatment before admission (n = 19), were bronchoscopically evaluated after a 24 h discontinuation of therapy, if possible. Patients without prior antibiotic therapy were evaluated within 24 h after admission.

Thirteen patients who underwent bronchoscopy for evaluation of peripheral lung consolidation (nine male, four female, mean age 54 [25–84] years), who had no clinical signs of local or systemic inflammation were accepted as age matched controls. In addition, six healthy nonsmoking volunteers were studied. None of our patients died. To quantify impairment of gas exchange all individuals had blood gas analysis on the day of BAL. Informed consent was obtained from all patients and controls and the study of healthy volunteers was approved by the ethical committee of Lübeck Medical University.

**Bronchoalveolar lavage:** Bronchoalveolar lavage was performed with a flexible fiberoptic bronchoscope under standard conditions. Briefly, a total of 100–140 ml prewarmed normal saline was injected in 20 ml aliquots into the lobe of interest with immediate vacuum aspiration after each aliquot. Mean recovery in the patients and age matched controls was 65% with a range from 35%–80% and 80% (75%–90%) in healthy volunteers. The first aliquot, which is known to represent material contaminated with bronchial secretions, was discarded. Another sample was used for quantitative microbiological cultures [15] and remaining portions were pooled. After enumeration of total cell count and cell differentials five patients with a neutrophil percentage of greater than 50% were excluded from this study. Lavage cells were washed twice and resuspended at a density of 106 viable AM/ml in PBS after amplification with the Spearman rank correlation. A p-value of less then 0.05 was considered significant.

**Chemiluminescence:** Chemiluminescence was determined in 4-ml polystyrene tubes containing 105 viable pulmonary phagocytes (alveolar macrophages + PMN) in PBS after amplification with different bystander substrates as previously described [16]: Luminol reacts with products of the MPO/H2O2/halide system which is expressed by neutrophils and absent in the mature macrophage [17], lucigenin reacts preferentially with superoxide anion [18]. In all patients the spontaneous and phorbolmyristate acetate (PMA)-stimulated chemiluminescence of pulmonary phagocytes was quantified on an automatic luminometer (Berthold LB 953). Peak concentrations of chemiluminescence, which were reached after 8–15 min were taken for calculation and results are expressed as counts per min.

**Proteins:** Concentrations of albumin, myeloperoxidase, lactoferrin and fibronectin in BALF were measured by immunoluminometric assays as previously described [19, 20].

**Data analysis:** Nonparametric statistics were used throughout this study. Differences between the different groups were compared by the Mann-Whitney U-Test. Correlations were made with the Spearman rank correlation. A p-value of less then 0.05 was considered significant.

**Results**

**Lavage Cell Counts and Microbiology**

As expected, all patients with pneumonia had a neutrophil alveolitis with a mean neutrophil count of 16%. Details of the lavage cell differentials are outlined in Table 1. Quantitative microbiological cultures were available in 29 patients. The causative microbial agent could be identified in 17 patients. Among them we found significant culture results (104 or more CFU/ml) for pneumococci (n = 3),
Haemophilus influenzae (n = 2), B streptococcus (n = 1), Pseudomonas aeruginosa (n = 4) and other gram-negative bacilli (n = 5). In addition, in two patients we found other pulmonary pathogens (Mycoplasma pneumoniae n = 1, Pneumocystis carinii n = 1). In two patients polymicrobial infection was detected. In the other 14 patients the aetiological agent could not be established as lavage microbiology was either sterile, held a yield of less than $10^4$ CFU/ml or consisted of mixed throat flora. Of those patients 12 had received prior antibiotic therapy.

Interleukin-8

Alveolar macrophages from all individuals released measurable amounts of interleukin-8 after an overnight incubation period with a range from 39 to $521 \text{ng/10}^5\text{AM}$. Interleukin-8 production from patients with pneumonia was significantly upregulated as compared to age matched and healthy controls (p < 0.05). In patients who were immunocompromised, macrophage interleukin-8 secretion was lower than in the immunocompetent group (p < 0.05). There was no statistically significant difference between the two control groups (Figure 1). In BALF interleukin-8 levels were significantly higher in patients with pneumonia as compared to age matched controls (3.66 ng/ml $\pm 0.089$ ng/ml $\pm 0.09$, p < 0.05). Interleukin-8 levels in BALF of all healthy volunteers was below the detection limit of the assay. No correlation between macrophage interleukin-8 release or interleukin-8 levels in BALF and neutrophil count could be established.

Phagocyte Chemiluminescence

In all patients high phagocyte oxidant production, as measured by basal and stimulated luminol enhanced chemiluminescence could be demonstrated (75 $\pm 79\text{cpm} \times 10^3$ (basal), 567 $\pm 711\text{cpm} \times 10^3$ (PMA) in the pneumonia group (immunocompetent + immunocompromised patients) versus 22 $\pm 5\text{cpm} \times 10^3$ (basal), 60 $\pm 21\text{cpm} \times 10^3$ (PMA) in the age matched control group, p < 0.05). This is mainly due to the lavage neutrophil fraction with the percentage of neutrophils in BAL correlating strongly with PMA-stimulated luminol enhanced chemiluminescence (r = 0.68, p < 0.05). Spontaneous luminol enhanced chemiluminescence correlated significantly with interleukin-8 concentration in the supernatants of AM (Figure 2). In contrast, there was no significant difference regarding lucigenin enhanced chemiluminescence between pneumonia patients and controls (120 $\pm 189\text{cpm} \times 10^3$ (basal), 278 $\pm 222\text{cpm} \times 10^3$ (PMA) in the pneumonia group versus 68 $\pm 34\text{cpm} \times 10^3$ (basal), 173 $\pm 101\text{cpm} \times 10^3$ (PMA) in the control group, p = NS).

Bronchoalveolar Lavage Proteins

We found elevated concentrations (median [25%–75%]) of albumin: 36 mg/l (12–69.5) vs 11 mg/l (7.2–12), p < 0.05, MPO: 686 $\mu g/l$ (158–1,239) vs 112 $\mu g/l$ (91.5–155), CAP I = immunocompetent patients, CAP II = immunocompromised patients, Co I = age matched patients with noninfectious lung disease, Co II = healthy volunteers, p < 0.05 for all differences between patients and controls, p < 0.05 regarding the difference between immunocompetent and immunocompromised patients, p = NS between the two control groups.

Figure 1: Interleukin-8 secretion of alveolar macrophages from patients with community-acquired pneumonia.

Figure 2: Correlation between interleukin-8 secretion of alveolar macrophages and luminol enhanced spontaneous chemiluminescence of pulmonary phagocytes (r = 0.53, p < 0.05).

Correlation between Interleukin-8 Concentrations and Microbiological Parameters

With regard to gas exchange we found a decrease of arterial oxygen tension in patients as compared to healthy control subjects (55 mmHg $\pm 18$ versus 85 mmHg $\pm 4$, p < 0.05, lactoferrin: 273 $\mu g/l$ (91–473) vs 184 $\mu g/l$ (56–542), p = NS and fibronectin: 430 $\mu g/l$ (330–780) vs 400 $\mu g/l$ (220–600), p = NS, in bronchoalveolar lavage fluid of patients with pneumonia compared to age matched controls with some differences between immunocompetent and immunosuppressed individuals. No correlation between interleukin-8 secretion of alveolar macrophages and lavage proteins could be demonstrated.

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Comparing these two groups we found significantly high-
interleukin-8 levels in BALF (7.5 ng/ml ± 17 vs
0.44 ng/ml ± 1, p < 0.05). Interestingly, a negative correlation could be es-
blished between macrophage interleukin-8 secretion
and the arterial pO₂ at the time of BAL (Figure 3). No cor-
relation between BALF interleukin-8 levels and arterial
pO₂ existed. To elucidate the possible effect of bacterial
load in the alveolar space
accumulation and activation with respect to spontaneous
chemiluminescence in the alveolar compartment. These
results are in accordance with recently published reports
demonstrating high interleukin-8 levels in bronchoalveo-
lar lavage fluid (BALF) in neutrophil alveolitis of other
origin [9, 10, 21], mostly in critically ill patients with ARDS
requiring mechanical ventilation and with high mortality
in those study cohorts [11, 13, 22]. In contrast, we concen-
trated on nonventilated pneumonia patients. In addition,
most current research was performed using only BALF to
to quantify cytokine levels in the pulmonary compartment
[23]. In accordance with previous studies, this phenome-
on is reflected by high albumin levels in BALF of our
pneumonia patients as compared to both control groups
[23]. Furthermore, cytokine production from many differ-
ent cell populations (e.g. alveolar macrophages, neu-
rophils, endothelial and epithelial cells) will be summarized.
Although alveolar macrophages are the primary source
for interleukin-8 in lung inflammation [9, 13, 25], all of
these cells are able to produce interleukin-8 [26, 27]. The
additional objective for using isolated alveolar macro-
phages was that alveolar macrophages provide first line
contact with the invading microorganism in vivo, resulting
in the release of recruiting signals for neutrophils, among
them interleukin-8 [9]. The possible ex vivo stimulation by
adherence on plastic and some unavoidable contamina-
tion by neutrophils had to be taken into account. The fact
that we could not demonstrate a correlation between in-
terleukin-8 and neutrophil count in BAL is in agreement
with other investigators [10, 11, 22], who discussed the im-
portance of other chemotactic mediators in the network of
phagocyte activation in the lung. Furthermore, since both
parameters were determined at one time point in the
course of inflammatory events, the sequence in which
macrophage interleukin-8 release is followed by neu-
rophil influx cannot be reflected. With regard to neu-
rophil activation we found a significant correlation be-
tween alveolar macrophage interleukin-8 release and oxi-
dative response of alveolar neutrophils. The respiratory
burst of pulmonary phagocytes is the central part of the
non-specific host response to pathogenic microorganisms
[1, 16]. From our data we cannot distinguish whether neu-
rophil chemiluminescence is due to stimulation by inter-
leukin-8, or bacteria or both. Considering current knowl-
edge, it seems likely that interleukin-8 has a priming effect
on the PMN oxidative response to triggering signals such
as bacterial cell wall products [28–30].
Accordingly, in our patients we demonstrated a clear rela-
tionship between the bacterial load in the alveolar space

**Discussion**

The main result of this study is that during community-ac-
quired pneumonia alveolar macrophages release high
amounts of interleukin-8, thereby triggering neutrophil
accumulation and activation with respect to spontaneous
chemiluminescence in the alveolar compartment. These
results are in accordance with recently published reports
demonstrating high interleukin-8 levels in bronchoalveo-
lar lavage fluid (BALF) in neutrophil alveolitis of other
origin [9, 10, 21], mostly in critically ill patients with ARDS
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**Figure 3**: Correlation between interleukin-8 secretion of alveo-
lar macrophages and arterial pO₂ at the time of bronchoalveo-
lar lavage (r = -0.47, p < 0.05) in patients with community-ac-
quired pneumonia.

**Figure 4**: Interleukin-8 secretion of alveolar macrophages in pa-
tients with positive or negative microbiological findings.
and local interleukin-8 concentration as quantified in BALF and in alveolar macrophage supernatants. Although the mechanisms of host cell activation differ between gram-positive and gram-negative bacteria, the cascade finally leads to activation of cytokine release, expression of their receptors and upregulation of adhesion molecules on the cell surface. In our study population with predominant gram-negative infections, no difference between the various pathogens could be established; however, this type of investigation would require larger patient groups.

With regard to impairment of gas exchange, we demonstrated a significant negative correlation between macrophage interleukin-8 release and the arterial pO\(_2\) at the time of bronchoscopy. This is an interesting observation, since distribution of lung infection as assessed by chest radiograph differed markedly in our patients. Considering a recently published report demonstrating unilateral upregulation of interleukin-8 in BALF of patients with lobar pneumonia [31], this phenomenon cannot simply be explained by bronchogenic transfer of cytokines into non-infected parts of the lung. However, it might be possible that in bacterial pneumonia activation of the pulmonary immune system triggers recirculation and distribution of activated immune cells into the affected organ leading to local inflammation, endothelial cell damage and interstitial edema.

Summarizing our findings, we could demonstrate that in bacterial pneumonia release of interleukin-8 by alveolar macrophages and other cells plays a central role in host response. This is followed by neutrophil influx and activation, which leads on the one hand to clearing of pathogenic microorganisms, and on the other hand to lung injury and organ malfunction. Larger patient groups and long-term follow-up studies are needed to evaluate the possible prognostic significance of these data.

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Book Review

H. L. T. Mobley, J. W. Warren (eds.)
Urinary Tract Infections
Molecular Pathogenesis and Clinical Management
439 pages
ASM Press, Washington D.C. 1995
Price: $ 79.00

Even today urinary tract infections, apart from respiratory tract diseases, are among the most frequent infections caused by microorganisms. Every year about eight million patients have been treated for urinary tract infections in the USA; in Germany, there are about two million cases per year. More than 40% of all nosocomial infections are urinary tract infections. Therefore they are the most numerous hospital-acquired infectious diseases. Moreover, it has to be emphasized that 40 to 50% of nosocomial septic cases develop as a result of urinary tract infection. These facts underline the necessity of clarifying the pathogenesis of these diseases in greater detail and to develop better strategies of diagnostics and therapy.

This book meets these demands quite well. Internationally accepted experts have compiled the latest results of research on clinical aspects and of the molecular mechanisms in the pathogenesis of urinary tract infections. According to the importance of these diseases in the sense of social medicine (J. W. Warren), a variety of different methods for the diagnosis of bacterial as well as fungal diseases is described in great detail (J. Eisenstadt, J. A. Washington). Several procedures, which are quite controversially assessed in the literature (renal culture, Fairlay’s washout technique, detection of urinary antibody-coated bacteria), are evaluated as to their clinical relevance.

Microbiological and molecular biological aspects as well as experimental models in pathogenetic research are discussed. The variety of findings concerning the properties of virulence in Escherichia coli (M. S. Donnenberg and R. A. Welch), Proteus mirabilis (H. L. T. Mobley), Klebsiella pneumoniae (C. M. Collins, S. E. F. D’Orazio), enterococci, Staphylococcus saprophyticus and Staphylococcus epidermidis (S. G. Gatermann) are compiled in excellent surveys. With data from molecular biological investigations, W. Agace, H. Connell and C. Svanborg demonstrate pathogenetic processes triggering inflammations in the urinary tract via activation of adhesion molecules and interleukins. Unfortunately, conclusive explanations are missing concerning these mechanisms which, inter alia, initiate fibrotic processes via tissue destruction and consequently result in disturbed renal function and in renal insufficiency. The principal remarks on “Treatment and Prevention of Urinary Tract Infections” by J. R. Johnson are supplemented by “Prospects for Urinary Tract Infection Vaccines” by P. O’Hanley. All chapters provide an excellent stock-taking of the different aspects of urinary tract infection. The data presented are supplemented by extensive bibliographies following every article. The book is worth reading, and by its complexity yields an extensive survey of the latest results of research, which ultimately should be confirmed in clinical work.

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