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# 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/$10^5$ AM ± 121 vs 71 ng/$10^5$ AM ± 35 and 66 ng/$10^5$ 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 $10^4$ or more colony forming units (CFU)/ml BALF of one pathogen and patients with less CFU or nonspecific microbiological results (261 ng/$10^5$ AM ± 89 vs 179 ng/$10^5$ 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 $pO_2$ 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 fibreoptic 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 $10^6$ viable AM/ml in M199 supplemented with 5% fetal calf serum (FCS) and penicillin/streptomycin. Endotoxin contamination was less than 25 pg/ml (M199) or 100 pg/ml (FCS), as determined by the limulus amebocyte lysate assay.

*Interleukin-8:* Interleukin-8 was quantified in BALF and in the supernatants of alveolar macrophages. For collection of supernatants alveolar macrophages were seeded at a density of $10^6$/ml into 96-well flat bottom microtiter plates for 3 h at 37°C, allowing the cells to adhere. Nonadherent cells were removed by gentle washing with warm cell culture medium. After another incubation period of 16 h supernatants from triplicate wells were removed, pooled and immediately frozen at −80°C until use. Interleukin-8 was determined by a sandwich ELISA using commercially available antibodies. Briefly, 96-well flat bottom microtiter plates were covered with a polyclonal goat anti-IL-8 antibody over night (R&D Systems, USA). After washing and blocking of nonspecific binding sites supernatants from AM were diluted 1:50 and incubated for 4 h. BALF was used undiluted in this assay. A commercially available monoclonal anti-IL-8 antibody (clone 6217.11, R&D Systems) was used as capture antibody and the reaction was quantified photometrically at 405 nm using ABTS as substrate. Recombinant human interleukin-8 (R&D Systems) was used to produce a standard curve. Lower detection limit of this assay was 0.05 ng/ml. Inter- and intraassay variations were 8% and 7%, respectively.

Table 1: Lavage cell differentials (mean ± SD) from patients with community-acquired pneumonia.

| | CAP I | CAP II | Co I | Co II |
|---|---|---|---|---|
| Alveolar macrophages % | 76±16 | 78±18 | 94±4 | 93±4 |
| Alveolar macrophages × $10^5$/ml | 89±12 | 81±10 | 134±143 | 151±41 |
| PMN % | 17±13 | 14±15 | 1±1 | 1±1 |
| PMN × $10^5$/ml | 20±15 | 15±16 | 1±1 | 2±2 |
| Lymphocytes % | 6±6 | 6±5 | 5±4 | 6±4 |
| Lymphocytes × $10^5$/ml | 7±7 | 6±5 | 7±6 | 10±6 |
| Eosinophils % | 2±2 | 2±2 | 0±1 | 0±0 |
| Eosinophils × $10^5$/ml | 2±2 | 2±2 | 0±1 | 0±0 |

CAP I = pneumonia in immunocompetent patients, n = 18; CAP II = pneumonia in the immunocompromised host, n = 13 and controls, Co I = age matched patients with noninfectious lung disease, n = 13; Co II = healthy volunteers, n = 6, PMN = polymorphonuclear leukocytes.

*Chemiluminescence:* Chemiluminescence was determined in 4-ml polystyrene tubes containing $10^5$ 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/$H_2O_2$/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 ($10^4$ or more CFU/ml) for pneumococci (n = 3),



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*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 aetiologic 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*

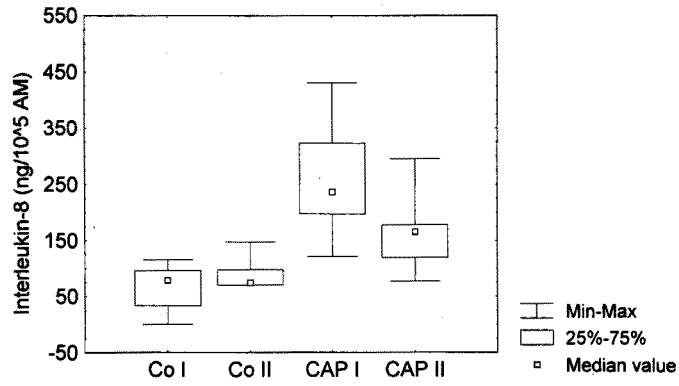
Alveolar macrophages from all individuals released measurable amounts of interleukin-8 after an overnight incubation period with a range from 39 to 521 ng/$10^5$ AM. Interleukin-8 production from patients with pneumonia was significantly upregulated as compared to age matched and healthy controls ($p < 0.05$). 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 ± 11 vs 0.089 ng/ml ± 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 ± 79 cpm * $10^3$ (basal), 567 ± 711 cpm * $10^3$ (PMA) in the pneumonia group (immunocompetent + immunocompromised patients) versus 22 ± 5 cpm * $10^3$ (basal), 60 ± 21 cpm * $10^3$ (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 ± 189 cpm * $10^3$ (basal), 278 ± 222 cpm * $10^3$ (PMA) in the pneumonia group versus 68 ± 34 cpm * $10^3$ (basal), 173 ± 101 cpm * $10^3$ (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 µg/l (158–1,239) vs 112 µg/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.

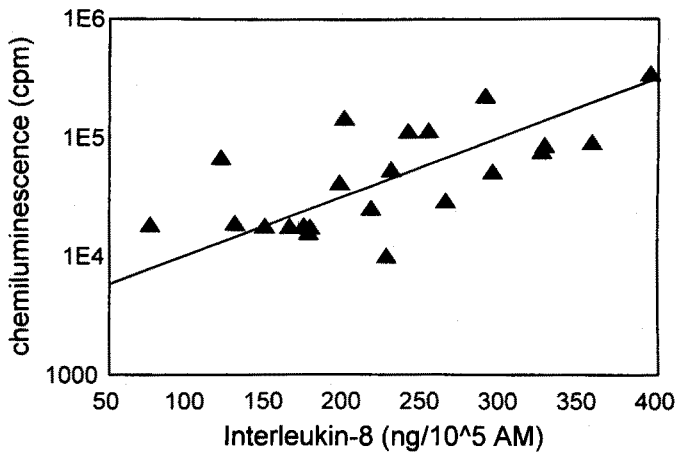



Figure 2: Correlation between interleukin-8 secretion of alveolar macrophages and luminol enhanced spontaneous chemiluminescence of pulmonary phagocytes ($r = 0.53$, $p < 0.05$).

$p < 0.05$, lactoferrin: 273 µg/l (91–473) vs 184 µg/l (56–542), p = NS and fibronectin: 430 µg/l (330–780) vs 400 µg/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.

*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 ± 18 versus 85 mmHg ± 4,

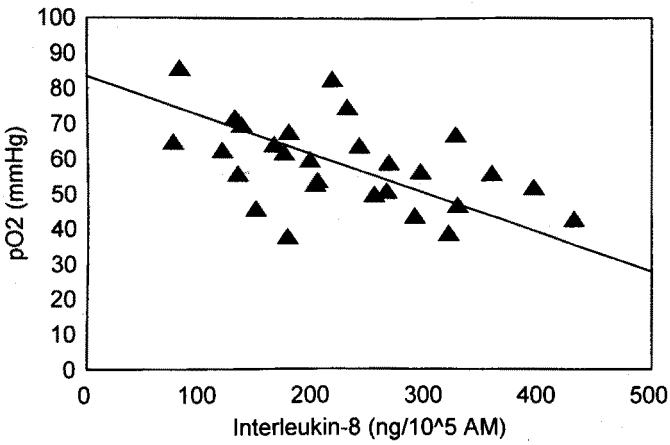
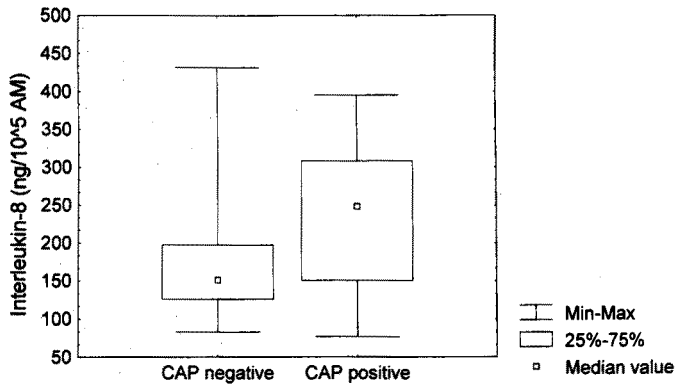



Figure 3: Correlation between interleukin-8 secretion of alveolar macrophages and arterial $pO_2$ at the time of bronchoalveolar lavage ($r = -0.47$, $p < 0.05$) in patients with community-acquired pneumonia.




CAP positive = patients with community-acquired pneumonia with $10^4$ cfu of at least one pathogen per ml lavage fluid, CAP neg = patients with community-acquired pneumonia with less than $10^4$ cfu/ml lavage fluid, sterile cultures or nonspecific microbiological findings ($p < 0.05$).

Figure 4: Interleukin-8 secretion of alveolar macrophages in patients with positive or negative microbiological findings.

$p < 0.05$). Interestingly, a negative correlation could be established between macrophage interleukin-8 secretion and the arterial $pO_2$ at the time of BAL (Figure 3). No correlation between BALF interleukin-8 levels and arterial $pO_2$ existed. To elucidate the possible effect of bacterial antigen quantity on the interleukin-8 release of alveolar macrophages, we subdivided our patients according to the results of quantitative microbiological cultures. Patients with $10^4$ or more CFU of one pathogen per ml of lavage fluid were compared to those with either less CFU/ml or nonspecific microbiological findings (mixed throat flora). Comparing these two groups we found significantly higher interleukin-8 levels in BALF (7.5 ng/ml ± 17 vs 0.44 ng/ml ± 1, $p < 0.05$) and in alveolar macrophage supernatants in patients with positive microbiological results (Figure 4).

## Discussion

The main result of this study is that during community-acquired 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 bronchoalveolar 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 concentrated on nonventilated pneumonia patients. In addition, most current research was performed using only BALF to quantify cytokine levels in the pulmonary compartment [11, 13]. With the use of BALF a variable dilution error has to be considered, which is due to the increased capillary leakage in lung inflammation of bacterial pneumonia [23]. In accordance with previous studies, this phenomenon is reflected by high albumin levels in BALF of our pneumonia patients as compared to both control groups [23]. Furthermore, cytokine production from many different cell populations (e.g. alveolar macrophages, neutrophils, 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 macrophages 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 contamination by neutrophils had to be taken into account. The fact that we could not demonstrate a correlation between interleukin-8 and neutrophil count in BAL is in agreement with other investigators [10, 11, 22], who discussed the importance 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 neutrophil influx cannot be reflected. With regard to neutrophil activation we found a significant correlation between alveolar macrophage interleukin-8 release and oxidative response of alveolar neutrophils. The respiratory burst of pulmonary phagocytes is the central part of the nonspecific host response to pathogenic microorganisms [1, 16]. From our data we cannot distinguish whether neutrophil chemiluminescence is due to stimulation by interleukin-8, or bacteria or both. Considering current knowledge, 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 relationship between the bacterial load in the alveolar space

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 noninfected 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 be 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. Connel* 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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