The effect of age on the systemic inflammatory response in patients with community-acquired pneumonia

L. A. van Vught[1], H. Endeman[2], S. C. Meijvis[3], A. H. Zwinderman[4], B. P. Scicluna[1], D. H. Biesma[3,5] and T. van der Poll[1]

1) *Division of Infectious Diseases, Center for Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam,* 2) *Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam,* 3) *Department of Internal Medicine, Sint Antonius Hospital, Nieuwegein,* 4) *Clinical Epidemiology Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, and* 5) *Department of Internal Medicine, University Medical Center Utrecht, Utrecht, the Netherlands*

Abstract

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide. Increasing age has been associated with elevated circulating levels of pro-inflammatory mediators. We aimed to determine the impact of ageing on the systemic inflammatory response to CAP. In total 201 CAP patients were enrolled. Blood samples were obtained upon presentation, and on days 2, 3 and 5. For the current analysis patients ≤50 and ≥80 years were included. The Pneumonia Severity Index (PSI) score was calculated at presentation. The study encompassed 46 CAP patients aged ≤50 years (median 37 years) and 41 CAP patients aged ≥80 years (median 84 years). In both groups *Streptococcus pneumoniae* was the common causative microorganism. Whereas most young patients had a PSI score of I (54%), 98% of elderly patients had a PSI score ≥III ($p < 0.001$). Four elderly patients died vs. none of the young patients (p 0.045). Older patients demonstrated lower serum C-reactive protein levels on admission and during the course of their hospitalization (p 0.001) in spite of more severe disease. Serum concentrations of pro-inflammatory (interleukin (IL)-6 and IL-8) and anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonist) did not differ between age groups, although admission IL-8 levels tended to be higher in elderly patients (p 0.05). Cytokine levels were positively correlated with PSI in young but not in elderly patients. These results suggest that elderly patients show an absolute (C-reactive protein) or relative (cytokines) reduction in their systemic inflammatory response on admission for CAP.

Keywords: Ageing, community-acquired pneumonia, C-reactive protein, cytokines, systemic inflammatory response
Original Submission: 12 March 2014; **Revised Submission:** 3 June 2014; **Accepted:** 7 June 2014
Editor: M. Paul
Article published online: 14 July 2014
Clin Microbiol Infect 2014; **20**: 1183–1188
10.1111/1469-0691.12717

Corresponding author: L. A. van Vught, Center for Experimental and Molecular Medicine, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
E-mail: l.a.vanvught@amc.uva.nl

Introduction

Community acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide [1]. It is one of the most common infectious diseases requiring hospitalization and has an overall mortality of more than 3 million deaths yearly worldwide [2]. The incidence of CAP increases dramatically with high age and elderly people account for the majority of CAP-related hospital admissions [3]; more than 60% of all CAP cases occur among those aged ≥65 years of age [4]. In older adults, CAP is a potentially life threatening disease with an increased risk of severe sepsis and a more than doubled mortality rate [5]. More than one-third of all sepsis cases in elderly patients are due to pneumonia and the relative risk of sepsis is 13 times higher for those aged 65 or above [6]. Also, after hospital discharge the threat of mortality remains and almost half of all elderly patients surviving hospitalization for CAP die in the subsequent year [7]. Although older age is associated with increasing co-morbidity, institutionalization and underlying disease processes, this does not fully explain the higher disease burden and increased hospital and long-term mortality caused by infections such as CAP [7–9].

Ageing has been related to sustained low-grade inflammation, a process referred to as inflamm-ageing [10,11]. It has been suggested that inflamm-ageing can blunt acute immune responses and increase the susceptibility to infectious diseases [12].

In this study we aimed to determine differences in inflammatory responses between young and old individuals during the first days after admission to the hospital for CAP. Considering that cytokines have short half-lives in the circulation and as a consequence provide only temporary information on the systemic inflammatory response [13], we also included C-reactive protein (CRP) levels in our analysis.

Methods

Inclusion criteria

This prospective study included all patients aged 18 years and over with confirmed pneumonia admitted to the emergency department of the St Antonius Hospital (Nieuwegein, the Netherlands) from October 2004 until August 2006 [14]. Pneumonia was defined as new infiltrate on chest X-ray and at least two out of six of the following common clinical symptoms of pneumonia: cough, production of sputum, auscultatory findings concordant with pneumonia, temperature >38 or <35°C, CRP elevated three times above normal (>15 mg/L) or leukocytosis or leukopenia defined as white blood count $>10 \times 10^9$/L, $<4 \times 10^9$/L or >10% rods in leukocyte differentiation. Patients with a recent hospitalization (<30 days) or defined immunodeficiency (congenital or acquired, including prednisone or its equivalent >20 mg/day for more than three consecutive days or chemotherapy within the last 6 weeks) or haematological malignancies were excluded from participation. For each patient the Pneumonia Severity Index (PSI) [15] was calculated and clinical and laboratory parameters were recorded at inclusion. Blood was collected and processed for storage of serum samples. Medical history, causative organism, length of hospital stay, intensive care admission and mortality were assessed. The medical ethical committee approved the study and written informed consent was obtained in the emergency department from all participating patients.

Assays

Blood samples were collected from every individual at presentation (day 1). Consecutive samples were drawn at 8 am on days 2, 3 and 5. Serum was separated by centrifugation and stored at −80°C. Systemic circulating concentrations of IL-6, IL-8, IL-10 and IL-1 receptor antagonist (IL-1RA) were measured with a multiplex immunoassay kit from Biorad Laboratories (Hercules, CA, USA). CRP was measured using equipment from Roche Diagnostics (Mannheim, Germany).

Pathogen identification

At presentation to the emergency room two samples of peripheral blood cultures were taken. Blood cultures were regarded positive when a respiratory pathogen was cultured. Sputum cultures were taken at presentation or within 24 h after admission. Sputum cultures were only used for further analysis when containing less than 25 epithelial cells per view in the absence of leukocytes, or <50 epithelial cells per view when leukocytes were present. When multiple microorganisms were found, the microorganism with the most abundant growth was considered the causative pathogen. Microorganisms causing atypical pneumonia, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydophila pneumoniae* and *psittaci*, were detected using polymerase chain reactions (PCRs) for detection of microbial DNA in sputum. Antigen testing was carried out in urine samples for *Streptococcus pneumoniae* and *L. pneumophila* at admission or within the first 24 h. *Mycoplasma pneumoniae*, *Coxiella burnetti* or respiratory viruses (influenza A and B, parainfluenza viruses, adenovirus and respiratory syncytial virus) were detected using serological testing for the presence of antibodies. Only samples with a fourfold rise in antibody titres were considered positive. Viral culture for influenza viruses was carried out on pharyngeal swab samples. Pneumonia was defined as being of viral origin when a positive viral test was combined with negative cultures and negative antigen testing for bacterial pathogens.

Statistical analysis

All statistical tests were carried out using IBM SPSS version 19, taking into account a two-tailed p-value of <0.05. The difference between binary categorical data was assessed using a chi-square test or a Fisher's exact test when appropriate. All cytokine data were tested for normal distribution using Q-Q plots and histograms. Continuous, non-parametrical data were analyzed using a Mann–Whitney *U*-test. For longitudinal analyses over time, a regression analysis with mixed models, to account for correlation of the markers over time, was used. Correlations were tested using a Spearman rho test.

Results

Demographics, co-morbidities and severity of disease

A total of 201 patients were included in the study [14]. For the current analysis only a subset of patients from this previously published cohort aged ≤50 years ($N = 46$) and aged ≥80 years ($N = 41$) were analyzed. Baseline characteristics of these