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

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## 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

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## 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

patients are shown in Table 1. Men and women were equally distributed among young and elderly patients. As expected, elderly patients had more co-morbidities, in particular COPD (49% in the elderly vs. none in the young group, p <0.001). Use of antibiotics prior to presentation to the emergency department was equally distributed between the two groups. With regard to disease severity, the PSI was significantly higher in elderly patients (p <0.001), and elderly patients were in a higher PSI Fine class compared with young patients (p <0.001). Because the PSI Fine class differentiation contains age as a variable factor, a modified PSI Fine score was calculated leaving age out. This modified PSI Fine score was not significantly different between the two groups (p 0.132). Older patients had a longer length of stay in the hospital (median 14 days vs. 8 days for young patients, p <0.001), while the intensive care admission rate was similar in both groups. Mortality was higher in elderly patients; four elderly patients died (10%) compared with none of the young patients (p 0.045).

### Causative organisms

Table 2 shows the distribution of causative organisms in both groups. The causative microorganism could be identified for 76% of the young group and 56% of the elderly group (p <0.05). For both groups *S. pneumoniae* was the most common causative microorganism (35% in young patients and 22% in elderly patients). There was no significant difference between the two groups with regard to causative pathogens, except for atypical pathogens (in particular *M. pneumoniae*), which were not documented in elderly patients (15% vs. 0%, p 0.035).

**TABLE 1. General characteristics of patients with community-acquired pneumonia in young (≤50 years) and elderly patients (≥80 years)**

| | Age ≤50 years *N* (%) | Age ≥80 years *N* (%) | p value |
|---|---|---|---|
| Total | 46 | 41 | |
| Male, *n* (%) | 28 (61) | 20 (49) | 0.258 |
| Age, mean (±SD) | 37 (7) | 84 (4) | |
| Living arrangement | | | |
| Home | 46 (100) | 38 (93) | 0.101 |
| Nursing facility | – | 3 (8) | |
| Medical history | | | |
| COPD | – | 20 (49) | **<0.001** |
| Asthma | 5 (10) | – | 0.057 |
| Local solid tumor | – | 5 (12) | **0.015** |
| Diabetes type II oral treatment | – | 5 (12) | **0.020** |
| Diabetes type II insulin | – | 6 (15) | **0.009** |
| Hypercholesterolaemia | – | 3 (7) | 0.101 |
| CVA | – | 5 (12) | **0.020** |
| Hypertension | – | 12 (29) | **<0.001** |
| PVD | – | 5 (12) | **0.020** |
| Pre-hospital antibiotic therapy | 16 (35) | 8 (20) | 0.145 |
| PSI mean (±SD) | 51 (21) | 108 (30) | **<0.001** |
| PSI Fine class | | | |
| Low I | 25 (54) | – | **<0.001** |
| Low II | 14 (30) | 1 (2) | |
| Low III | 5 (11) | 15 (37) | |
| Moderate IV | 2 (4) | 12 (29) | |
| High V | – | 13 (32) | |
| Modified PSI Fine score (mean ± SD) | 18 (17) | 29 (29) | 0.132 |
| Length of stay, (days) median (IQR) | 8 (7–14) | 14 (10–22) | **<0.001** |
| ICU admission (%) | 4 (9) | 2 (5) | 0.680 |
| Death | – | 4 (10) | **0.045** |

Bold value indicates significance.
COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident (stroke); PVD, peripheral vascular disease; PSI, pneumonia severity index; ICU, intensive care unit.

**TABLE 2. Causative microorganism**

| | Age ≤50 years *N* (%) | Age ≥80 years *N* (%) | p value |
|---|---|---|---|
| No microorganism cultured | 11 (24) | 18 (44) | **0.048** |
| Gram positive | 19 (41) | 11 (27) | 0.156 |
| *Streptococcus pneumoniae* | 16 (35) | 9 (22) | 0.620 |
| *Staphylococcus aureus* | 2 (4) | 2 (5) | 1.000 |
| Other gram-positive bacteria[a] | 1 (2) | – | 1.000 |
| Gram negative | 3 (7) | 6 (15) | 0.215 |
| *Haemophilus influenza* | 1 (2) | 4 (10) | 1.000 |
| *Klebsiella pneumoniae* | – | 2 (5) | 0.750 |
| *Pseudomonas aeruginosa* | 1 (2) | – | 1.000 |
| Other gram-negative bacteria[b] | 1 (2) | – | 1.000 |
| Atypical | 11 (24) | 2 (5) | **0.042** |
| *Mycoplasma pneumoniae* | 7 (15) | – | **0.035** |
| *Legionella pneumophila* | 2 (4) | 2 (5) | 1.000 |
| Other atypical bacteria[c] | 2 (4) | – | **0.042** |
| Viral | 2 (4) | 4 (10) | 0.415 |

Bold value indicates significant values.
[a]Non-pneumococcal Streptococci
[b]*Acinetobacter calcoaceticus, Stenotrophomionas maltophilia.*
[c]*Chlamydophila pneumoniae/psittaci, Coxiella burnetti.*

### Levels of inflammatory markers

Admission blood was obtained for determination of CRP from all patients ($N = 87$). For the assessment of IL-6, IL-8, IL-10 and IL-1RA levels, blood was obtained from 80% of young patients ($N = 37$) and 80% of the elderly patients ($N = 33$), gradually diminishing following the duration of admission (indicated in Fig. 1). Elderly patients showed overall significantly lower serum CRP during the course of their disease compared with young patients (Fig. 1a, p 0.001). The difference was most discriminative at admission (p <0.001). In contrast, the serum concentration of IL-6, which is considered a main driver of the acute phase protein response, did not differ between elderly and young patients (Fig. 1b). Serum IL-8 levels were higher in elderly patients on admission (p 0.05 vs. young patients); although mean IL-8 concentrations remained higher in older patients on subsequent days, the difference with young patients was not significant (Fig. 1c, p 0.24). Serum levels of the anti-inflammatory cytokines IL-10 (Fig. 1d) and IL-1RA (Fig. 1e) did not differ between groups.

To determine whether serum CRP and cytokine levels correlated with severity of disease in the two age groups, we calculated Spearman's correlation coefficients of the concentrations of these inflammation markers with the PSI score, as well as with the modified PSI score (i.e. leaving the age factor

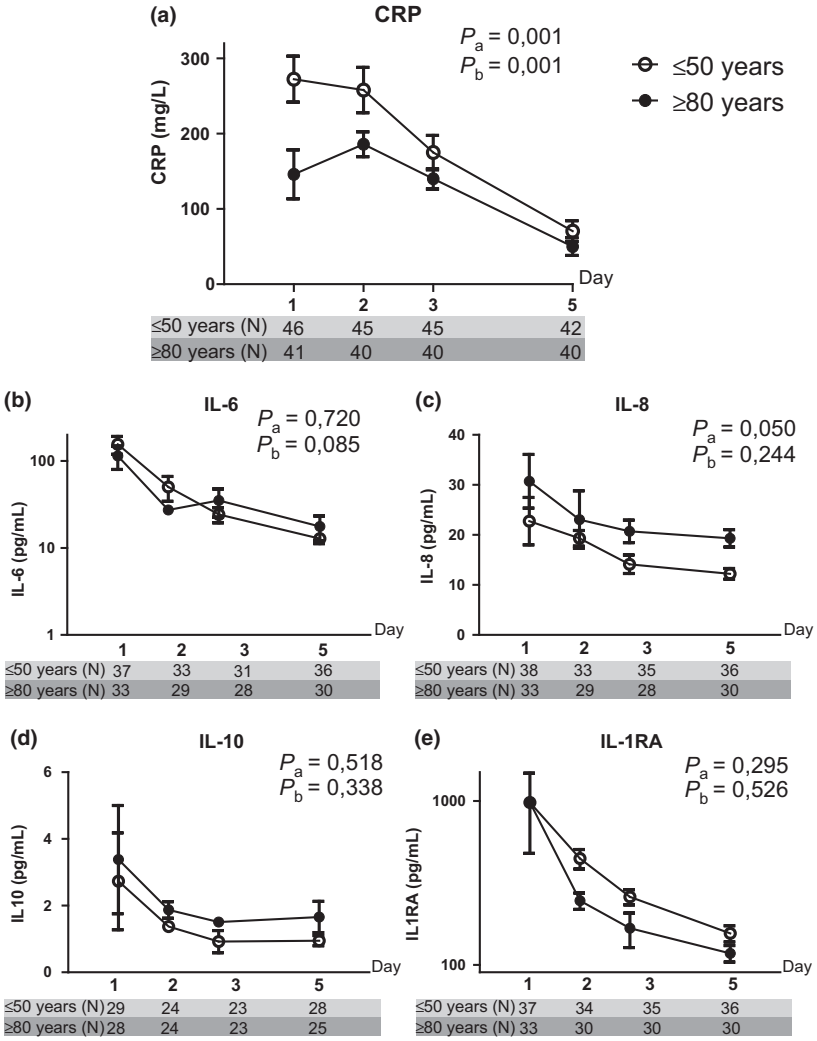


**FIG. 1.** Levels of inflammatory markers. Median values and standard error of the median. $P_a$ = Mann Whitney *U*-test day 1. $P_b$ = longitudinal analysis over time using mixed models a, CRP; b, IL-6; c, IL-8; d, IL-10; e, IL1RA.

**TABLE 3. Correlation between CRP and cytokine levels and Pneumonia Severity Index (PSI) on admission stratified according to age group**

| Age group | Cytokine | | PSI | Modified PSI |
|---|---|---|---|---|
| Age ≤50 years | CRP | *r* | 0.13 | 0.20 |
| | IL-6 | *r* | **0.40*** | **0.43**** |
| | IL-8 | *r* | 0.31 | **0.40*** |
| | IL-10 | *r* | **0.52**** | **0.57**** |
| | IL-1RA | *r* | 0.32 | **0.34*** |
| Age ≥80 years | CRP | *r* | 0.22 | 0.26 |
| | IL-6 | *r* | −0.11 | 0.00 |
| | IL-8 | *r* | −0.17 | −0.08 |
| | IL-10 | *r* | −0.04 | 0.04 |
| | IL-1RA | *r* | −0.14 | −0.05 |

Bold value indicates significance.
Modified PSI males = PSI − age; modified PSI females = PSI − (age−10).
*p value <0.05.
**p value <0.01.

out), on admission (Table 3). In young patients, admission IL-6, IL-8, IL-10 and IL-1RA positively correlated with the modified PSI score; correlations remained significant for IL-6 and IL-10 upon analysis of the unmodified PSI score. In contrast, admission cytokine concentrations did not correlate with either modified or unmodified PSI scores in elderly patients. Serum CRP did not correlate with (modified) PSI scores in either age group.

## Discussion

This study describes differences in the systemic inflammatory response between young (≤50 years) and elderly patients (≥80 years) with CAP. The major finding of this study is that older patients had lower CRP levels on admission and the days thereafter, while cytokine concentrations showed marginal differences between age groups, approaching significance only for admission IL-8.

Old age is associated with chronic elevation of pro-inflammatory cytokines and CRP, a condition that has been

referred to as inflamm-ageing [11]. It has been postulated that in ageing individuals cellular damage and reactivation of latent viral infections (such as cytomegalovirus) chronically stimulate innate immune cells, resulting in a sustained pro-inflammatory state [16]. Such a pro-inflammatory background can alter the responsiveness to pathogens, leading to failure in the consequential immune response [16]. The declined ability of elderly patients to react properly upon infection, to initiate and maintain an adequate protective immune response and to develop immunological memory has been described as immunosenescence [17]. In this context a lower immunological response is to be expected in ageing individuals. However, we did not find significant differences in the serum concentrations of the pro-inflammatory cytokines IL-6 and IL-8, or the anti-inflammatory cytokines IL-10 and IL-1RA, between young and elderly patients with CAP. In accordance, a recently conducted observational study showed a similar cytokine response between young and older CAP patients, measured by the serum levels of TNF, IL-6 and IL-10 [18]. Disease severity and 90-day mortality were higher in older patients in this study, suggesting a relatively attenuated cytokine response in this age group [18].

A recent literature review supports the hypothesis of chronic baseline inflammation in elderly people and highlights the scarce research into cytokine responses to infection in this specific patient group [19]. Another investigation also showed no differences in circulating IL-6 and IL-10 concentrations in CAP patients of different age groups, although the disease severity, measured with PSI and CURB score, was significantly higher in elderly patients [20]. In our study, elderly patients also presented with more severe disease, as reflected by a significantly longer hospital stay, higher mortality and higher severity of disease markers such as Fine class and PSI score, but indeed failed to show persistent inflammatory parameters during hospital admission matching these observations. Notably, serum cytokine concentrations were positively correlated with the PSI score only in young patients, whereas such correlations were not found in elderly patients, further suggesting that the systemic cytokine response during CAP does not reflect the severity of disease in old age. Alternatively, the PSI score may less accurately reflect CAP severity in very old patients. Our results are supported by a study conducted in the ICU, reporting no differences in a large set of cytokines and chemokines between older and younger patients with septic shock at admission [21].

The fact that old patients demonstrated cytokine levels that were similar to those measured in young patients in spite of more severe disease suggests that ageing is associated with a reduced capacity to produce cytokines upon acute infection. Several studies have provided insight into why older individuals might respond less avidly to infection than young persons. Multiple key players of the immune system have been shown to develop age-related defects. Dendritic cells, important for innate and adaptive immunity, have an impaired ability to produce pro-inflammatory cytokines such as IL-6 and IL-12 upon Toll-like receptor engagement in ageing individuals [22,23], and peripheral blood monocytes from older persons show an impaired cytokine response upon *in vitro* stimulation with lipopolysaccharide [24]. These findings are in line with reports of diminished phagocytizing capacity of dendritic cells [25], monocytes [10] and neutrophils [26] from older individuals, suggesting an age-related dysregulation in the function of innate immune cells.

The most notable finding was the overall lower serum CRP levels, both on admission and subsequent days, in old patients with CAP. CRP is a typical acute phase protein that is mainly produced by the liver upon IL-6 stimulation. In our population, this decreased CRP response, however, cannot be pinned on an overall reduction in inflammatory responses or more specifically attenuated IL-6 release. Another mechanism explaining the lower CRP concentrations in elderly patients can be a diminished synthetic function of the liver due to physiological ageing becoming apparent in acute inflammatory conditions such as CAP. In this respect it should be noted that in the absence of acute disease elderly patients tend to have elevated CRP levels in their circulation [27,28], most likely due to increased chronic diseases and other age-related processes such as cumulative oxidative damage and a decline in sex hormones [29]. To our knowledge, serum CRP concentrations as a function of age have not been reported previously in patients with CAP. In accordance with our data, one earlier investigation reported a negative correlation between admission CRP levels and age in patients with bacteraemia caused by *Escherichia coli* or *S. pneumoniae* [30].

The main limitations of this study are the small sample size and baseline differences between groups, especially with regard to co-morbidity, including COPD. In addition, the analysis is based on clinically documented CAP cases; studies focusing on microbiology-confirmed cases might yield different results. Moreover, the exact onset of the disease could not be measured and differences in clinical presentation between young and elderly patients could have resulted in differential time periods between infection and hospital admission. As such, our study can be confounded by the possibility that different stages of the immune response to CAP were studied in young and elderly patients. Finally, our investigation does not establish whether old patients have longer length of hospital stay and increased mortality as a consequence of CAP or as a consequence of exacerbation of chronic pre-existing diseases due to CAP.

In conclusion, our results indicate that elderly patients with CAP show an absolute (serum CRP) or relative (serum cytokines) reduction in their systemic inflammatory response on admission and during the course of their hospitalization.

## Transparency Declaration

We declare that we have no conflicts of interest.

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