Duration of antibiotic treatment and symptom recovery in community-acquired pneumonia
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CHAPTER

Long-term Symptom Recovery and Health-Related Quality of Life in Patients with mild to moderate-severe Community-acquired Pneumonia

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Chest, in press
Chapter 7

Abstract

Study Objectives - The long-term outcome of patients with community acquired pneumonia (CAP) in terms of symptom resolution and Health Related Quality of Life (HRQL) is unknown. Our objective was to determine the rate of symptom resolution using validated patient-based outcome measures, and to assess HRQL 18 months after the episode.

Participants - Patients were recruited from a group enrolled in a randomized trial comparing two durations of treatment of CAP. Between 2000 and 2003 we included 102 adults with a mild to moderate-severe CAP (pneumonia severity index ≤ 110).

Interventions - CAP-related symptoms were assessed until month 18 using the CAP-score. The CAP score was divided in a Respiratory and a Well-being section to assess the recovery of respiratory and well-being symptoms separately. The HRQL was assessed at 18 months using the SF-36 questionnaire and compared to a Dutch reference group.

Results - Respiratory symptoms resolved within 14 days, while the well-being symptoms resolved more slowly. Taking the pre-pneumonia status into account, patients recovered fully from pneumonia after 6 months. Patients with comorbid conditions had significantly more symptoms pre-pneumonia and during follow-up than patients without comorbidity, but at all time points the proportion of patients that reached 80% or more of the pre-pneumonia health level did not depend on comorbidity, age or etiology. SF-36 scores at 18 months were significantly impaired in 4 of the 8 dimensions for patients with comorbid illness, but did not differ from the reference population for patients without comorbid illness.

Conclusion - Patients with mild to moderate severe CAP recover fully from pneumonia after 6 months. The presence of symptoms beyond 28 days and any impairment in HRQL was found to reflect age and comorbidity rather than the persistent effects of the pneumonia itself.
Introduction

Community-acquired pneumonia (CAP) is a common acute medical disorder worldwide and one of the most frequent reasons for antibiotic treatment, in general practice as well as in hospitals. To assess the efficacy of antibiotic treatment in CAP clinicians and researchers rely on clinical outcome measures, such as mortality, recurrence rates or adverse events, and the use of health care resources, measured through length of hospital stay. Unfortunately, these measures do not fully capture all features of outcome that are important to patients. The latter also include the rate of resolution of disease-related symptoms and the negative impact the disease episode has on subjective well-being.

Studies that have used the patients' perspective to assess recovery have demonstrated that a substantial number of patients with CAP still experience pneumonia-related symptoms 4-6 weeks after cessation of antibiotic treatment. Even at 90 days the prevalence of pneumonia-related symptoms was still substantial. None of these studies did assess symptom resolution by properly validated measures. The pre-pneumonia status was often not taken into account, and the long-term outcome of CAP patients, in terms of symptom resolution and Health Related Quality of Life (HRQL), has not been studied.

A follow-up study of survivors of an outbreak of Legionnaires' disease (LD) in the Netherlands showed that symptoms and an impaired HRQL can persist for more than 1.5 years. That study was unable to answer the question whether L. pneumophila itself, (severe) pneumonia in general, or the outbreak situation was responsible for this very prolonged impact of the disease episode on the subjects' well-being.

In this paper we report on a long-term follow-up of a cohort of patients who participated in a randomized trial investigating the optimal duration of antibiotic treatment in mild to moderate-severe CAP. Our objectives were to determine the rate of symptom resolution using validated patient-based outcome measures and to assess HRQL 18 months after the episode.

Patients and Methods

Study population

The study group was sampled from a cohort of patients enrolled in the DATES-p trial, a randomized, double-blind, placebo-controlled multicenter trial comparing two durations of treatment of CAP. That trial is reported in detail elsewhere. The study protocol was reviewed and approved by the ethics committees of all participating hospitals. Inclusion criteria for the trial were: temperature > 38°C, clinical signs of pneumonia, radiological evidence of a new infiltrate consistent with pneumonia, and a pneumonia severity index (PSI) of ≤ 110. The main exclusion criteria were: pregnancy, a history of allergy to amoxicillin, severe underlying disease, treatment with an effective antimicrobial agent for longer than 24 hours prior to admission, any other infection necessitating the administration of concomitant systemic antibiotics, a concurrent disease considered likely to interfere with the clinical course of pneumonia, and serious respiratory insufficiency (arterial pO2 < 6.67 kPa), or admittance to the ICU. Patients who met the eligibility criteria and had given written informed consent were treated with intravenous amoxicillin. After three days patients with significant clinical improvement were randomized to 5 days placebo or 5 days oral
amoxicillin. All randomized patients were followed until 28 days after the beginning of antibiotic treatment. The clinical outcome of the two groups, including the symptom recovery during the first 28 days, turned out to be comparable. All included trial patients, as well as patients who did not sufficiently improve after three days to be randomized, were invited to the long-term follow-up study. Only those patients who had completed 18 months of follow-up in January 2003 (the moment of analysis) are reported here.

Baseline Data Collection
Baseline data were collected of all patients at the day of enrolment in the main study. These included demographic characteristics, co-morbidity, a complete physical examination, and blood and sputum cultures. At baseline and at day 28 serum was collected for determination of antibodies against respiratory viruses and atypical respiratory pathogens. At baseline a chest radiograph was performed.

Outcome assessments
Pneumonia-related symptoms were assessed using the CAP-score. The CAP-score has been developed to evaluate the course of pneumonia-related symptoms in hospitalized patients with mild to moderate-severe CAP. It has been fully validated and its psychometric properties have been evaluated. The CAP-score is an 8-item questionnaire, based on respiratory symptoms (the presence and severity of dyspnoea, coughing, coughing up sputum, coughing up sputum with ease, the colour of sputum) and on wellbeing symptoms (fitness and the general state of health). The response of the patients to these eight items is used to calculate a CAP-score. Low values of the CAP-score indicate more severe symptoms. The CAP-score was obtained at study entry (day 0) and at seven follow-up visits (day 3, 7, 10, 14, 28, six months and 18 months) for the randomized group and at four follow-up visits (day 3, 28, six months and 18 months) for the non-randomized group. At day 0, patients were also asked to retrospectively evaluate their symptoms and general health status 1 month before the onset of pneumonia (pre-pneumonia). All questionnaires were obtained either by interview (in person or by telephone) by trained interviewers, or by written completion of a mailed version of the questionnaire. At 18 months HRQL was assessed by an additional questionnaire: the SF-36, which was obtained either by telephone or by mail. The SF-36 comprises 36 items that address the following 8 dimensions reflecting different aspects (dimensions) of the quality of life: physical function (PFZ), physical role function (RPZ), pain dimensions (BPZ), general health perception (GHZ), vitality (VTZ), social function (SFZ), emotional role function (REZ), and mental health dimension (MHZ). Each dimension is scored from 0 to 100, with higher scores indicating quality of life.

Analysis
The generalizability of the CAP study sample was assessed by comparing baseline characteristics of respondents and non-respondents, using Fisher’s exact test (for categorical variables), the t-test (for continuous variables with normal distribution) or the Mann-Whitney test (for continuous variables with non-normal distribution). The same test statistics were used where appropriate for subgroup comparisons.
Symptom resolution over time was described with the median and interquartile ranges of the CAP-score. The Wilcoxon test was used to analyze the change in CAP-score during follow-up, by comparing the CAP score at any time period during follow-up with the pre-pneumonia score.

The 8 dimensions of the SF-36 score were converted to standard scores on the basis of the scores of an age- and sex-matched representative reference sample of the Dutch population. Standardized scores indicate the distance in standard deviations between the observed score and the score of the reference population. A mean standard score of 0.20 is considered to indicate a small deviation from the reference population, and mean standard scores of 0.50 and 0.80 are considered to indicate moderate and large deviations from the reference population, respectively. A one-sample t-test was used to test for differences between the CAP group and the Dutch reference population.

Results

CAP patients were enrolled between November 2000 and July 2003. All 153 patients who had completed follow-up in January 2003 were approached to participate in the follow-up study. In total, 102 patients (66%) returned the CAP-questionnaire and/or the SF-36 questionnaire (figure 1). Of these 102 patients, 91 patients returned at least one CAP-questionnaire beyond 28 days and 71 patients returned the SF-questionnaire at 18 months.

Figure 1  Overview of patient population with community-acquired pneumonia (CAP) that were approached to participate in the study
Demographic characteristics and features of the initial pneumonia episode of these 102 patients were comparable with those of non-respondents, except for median age (65 versus 48 yrs, p < 0.05) and the baseline pneumonia severity score (PSI) (mean, 71 versus 62, p < 0.05), which were considerably higher in the respondents’ group (table 1). Of the participating patients, 11 % were classified as PSI risk class 1, and 36 %, 36 % and 17 % as PSI risk class 2, 3 or 4, respectively.

Table 1 Baseline characteristics of respondents and non-respondents

<table>
<thead>
<tr>
<th></th>
<th>Respondents n (%)</th>
<th>Non-respondents n (%)</th>
<th>p *</th>
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</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>60 (59)</td>
<td>27 (53)</td>
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</tr>
<tr>
<td>Female</td>
<td>42 (41)</td>
<td>24 (47)</td>
<td></td>
</tr>
<tr>
<td>Age, years (Median IQR)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Underlying disease, n (%)</td>
<td></td>
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<tr>
<td>COPD</td>
<td>64 (63)</td>
<td>30 (59)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (27)</td>
<td>10 (20)</td>
<td>0.42</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>16 (17)</td>
<td>5 (10)</td>
<td>0.45</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>39 (42)</td>
<td>24 (50)</td>
<td>0.48</td>
</tr>
<tr>
<td>PSI score Mean (SD)</td>
<td>71 (23)</td>
<td>62 (22)</td>
<td>0.03</td>
</tr>
<tr>
<td>CAP-score pre-pneumonia Mean (SD)</td>
<td>72 (23)</td>
<td>91</td>
<td>0.08</td>
</tr>
<tr>
<td>CAP-score at presentation Mean (SD)</td>
<td>34 (19)</td>
<td>91</td>
<td>0.06</td>
</tr>
<tr>
<td>Length of hospital stay, days Median (IQR)</td>
<td>8 (5-11)</td>
<td>6 (4-11)</td>
<td>0.10</td>
</tr>
<tr>
<td>X-ray findings, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Unilateral infiltrate</td>
<td>90 (96)</td>
<td>41 (96)</td>
<td>0.82</td>
</tr>
<tr>
<td>Single lobe</td>
<td>87 (96)</td>
<td>33 (94)</td>
<td>0.86</td>
</tr>
<tr>
<td>Detected pathogen at study entry, n (%)</td>
<td>39 (38)</td>
<td>20 (39)</td>
<td>0.80</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>24 (23)</td>
<td>16 (31)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease. PSI, Pneumonia severity index. CAP-score, community-acquired pneumonia score. * Fisher’s exact test, t-test or the Mann-Whitney test where appropriate. † some patients had more than one underlying disease.

Symptom recovery in CAP patients

After a significant decline at the moment of pneumonia, the CAP-score showed a stepwise recovery during follow-up (figure 2A). Recovery was most pronounced during the first 14 days. At day 28 day the CAP-score had not yet reached the pre-pneumonia level (p < 0.05, Wilcoxon test).

We divided the CAP-score into a Respiratory section, consisting of the dyspnoea symptoms, cough and sputum, and a Well-being section, which contains the items on fitness and the general state of health. The Respiratory score returned within 14 days to the pre-pneumonia level (figure 2B), while the Well-being score showed less improvement. At 28 days patients still had significantly lower scores than at the pre-pneumonia level (p < 0.05). At six months the Well-being score had returned to the pre-pneumonia level (p = 0.15) (figure 2C).
Next, we explored whether patient or disease characteristics influenced symptom recovery. Gender and smoking were not found to be associated with recovery. There was no significant difference in pre-pneumonia CAP score between smokers and non-smokers (median CAP-score 69 versus 77 points, \( p = 0.45 \), Mann-Whitney test). Also during follow-up the CAP score did not differ for smokers and non-smokers (\( p > 0.5 \) at all moments). Younger patients (< 25th percentile) had less symptoms before the pneumonia episode than older patients (> 75th percentile), with a median CAP-score of 93 versus 62 points (\( p < 0.01 \), Mann-Whitney test). The percentage of patients that reached 80% or more of the pre-pneumonia level was comparable in both age groups at all evaluation moments. At six months this percentage was 73% in younger patients versus 80% in older patients. Patients with comorbid illness had a lower median pre-pneumonia CAP score than patients without comorbid illness (Figure 3, 65 versus 89 points, \( p < 0.01 \)). This difference persisted during follow-up (\( p < 0.01 \) at six months). However, the percentage of patients that reached 80% or more of the pre-pneumonia level was at all evaluation moments comparable in both patient groups. At six months this percentage was 74%.

Figure 2 Symptom recovery of patients with community-acquired pneumonia

Scores expressed as medians, interquartile ranges, and 10th/90th percentiles. The Respiratory score (B) contains the CAP items dyspnoea, coughing and sputum. The Well-being score (C) contains the CAP items fitness and general state of health. Day -30 represents the pre-pneumonia level, at day 0 antibiotic therapy is started; day 540 is end of follow-up.
Patients with pneumococcal pneumonia had more symptoms pre-pneumonia than patients with non-pneumococcal pneumonia (other bacterial aetiology or undetermined aetiology) (median CAP-score of 68 versus 78 points), although this difference was not statistically significant. The percentage of patients that reached 80% or more of the pre-pneumonia level was at all evaluation moment comparable in both groups. At six months this percentage was 83% in the pneumococcal patients compared to 71% in the non-pneumococcal patients.

Quality of life of CAP patients
The calculated standard scores of the eight dimensions of the SF-36 of pneumonia patients are presented in figure 4A. Eighteen months after the pneumonia-episode pneumonia patients had significantly lower scores in two of the eight dimensions of the SF-36 compared to a Dutch age- and sex-matched reference population: physical functioning (standard score -0.58; p < 0.01) and general health (standard score -0.55; p < 0.01).

As premorbid conditions have been associated with impaired HRQL, we investigated whether patient or disease characteristics influenced the long-term quality of life of patients with CAP. Patients with comorbid illness had significantly more impairment in physical function, physical role function, general health, vitality, emotional function and mental health than patients without comorbid illness. Compared to the Dutch reference population this group had significantly lower scores in four dimensions: physical function, physical role function, general health, and vitality, while the group without comorbid illnesses did not differ from the Dutch reference population (figure 4B). Gender, smoking, age or the presence of S. pneumoniae were not associated with the HRQL.

The HRQL was significantly better for patients who at 18 months had high CAP-scores (CAP-score above the 75th percentile) compared to those with low CAP-scores (CAP-score below the 25th percentile), in all dimensions except emotional function and mental health.
Long-term Symptom Recovery and Health-Related Quality of Life in CAP

A  CAP patients compared to the Dutch reference population

![Graph A]

B  CAP patients with or without comorbid illness compared to the Dutch reference population

![Graph B]

Figure 4  Health related quality of life (HRQL) in patients with community-acquired pneumonia at 18 months after the episode

Health related quality of life (HRQL) scores for patients with community-acquired pneumonia (CAP) (A) and CAP patients with or without comorbid illness (B) versus the Dutch reference population. The questionnaire was completed in 71 patients. * p < 0.01, patients with CAP versus a Dutch reference population. Standard scores of < 0 indicate an HRQL worse than that of the reference population, and scores > 0 indicate better HRQL. Standard scores of 0.2 and -0.2, 0.5 and -0.5, and 0.8 and -0.8 indicate a small, moderate, or large deviation from the reference population, respectively.

Discussion

We assessed the long-term symptom recovery and HRQL in patients with mild to moderate severe CAP. We demonstrated that respiratory symptoms of patients with CAP recover within 14 days, while well-being symptoms resolved more slowly. After 6 months most patients recovered fully from pneumonia. Older patients, patients with comorbid illness and
patients with pneumococcal pneumonia had more symptoms pre-pneumonia than patients without those conditions, but at all time points the percentage of patients that reached 80% or more of the pre-pneumonia level was not found to be associated with comorbidity, age or etiology. HRQL was significantly impaired at 18 months after the pneumonia diagnosis for the SF-36 dimensions physical function and general health. This can be attributed to patients with comorbid illness, who had significantly more impairment in 4 of the 8 SF-36 dimensions, while patients without comorbid illness did not differ from the reference population. HRQL and CAP-score were related, as patients with high CAP-scores also had a better quality of life.

Several limitations of this study should be noted. Patients enrolled in this study represent a group of patients with mild to moderate-severe CAP (PSI score ≤ 110). This implies that the results of this study may underestimate the symptom severity and time to recovery in patients with severe CAP. Patients with severe CAP are at higher risk for complications and death. Yet, of the CAP patients evaluated in the hospital, 60-80% has a PSI score equal to or below 110, and so does the majority of non-hospitalised patients, including those seen by general practitioners. We related the resolution of symptoms during follow-up to the pre-pneumonia symptom level, retrospectively established at the time of admission. Although this method may be prone to recall bias, the return to the pre-pneumonia level of the Respiratory and Well-being CAP scores suggests that patients can score their symptoms in retrospect. Next, the evaluations around day 10 represent only the patients that were randomized. These patients had to be substantially improved at day 3 to be randomized and their score may overestimate symptom resolution at day 10. Except for the pre-pneumonia CAP-score, which was higher in the randomized group (p = 0.52) and a shorter length of hospital stay (median 7 versus 11 days, p < 0.01), all other baseline characteristics of both groups were comparable. Finally, as a pre-pneumonia HRQL was not assessed, we cannot establish whether the impairment in HRQL at 18 months was pre-existent. The fact that impairment in HRQL was mainly found in patients with preexistent comorbid disease suggests that the lower HRQL is not the result of the pneumonia episode. The study had insufficient power to detect small deviations (0.20) in standard scores from the reference population, both among patients with and without co-morbid illness.

Published data on the rate of symptom resolution in patients with pneumonia are limited. Although on the short term symptom resolution continued during the follow-up period (maximal follow-up period 90 days), a significant proportion of patients still experienced at least one pneumonia-related symptom at the end of follow-up. Our results now show that, when taking the pre-pneumonia status into account, patients recover fully from pneumonia on the long term (at 6 and 18 months). Cough and fatigue have been shown to be the slowest to resolve, with a median time to resolution of 14 days reported in one study. This corresponds well with our findings that resolution of respiratory symptoms occurred within 14 days, while the resolution of well-being symptoms took much longer.

An important question is whether at day 0 patients with persistent symptoms can be distinguished from those who will recover completely. The use of the CAP-score made it possible to assess symptom resolution in several sub-groups in a validated manner. An earlier study identified younger age and absence of asthma or COPD as predictors of complete symptom resolution. Those studies that also assessed the presence of symptoms prior to the onset of pneumonia demonstrated that a substantial amount of patients already had symptoms before the pneumonia episode. We have shown the presence of symptoms beyond 28 days to be related to age and/or comorbidity rather than to the persistent effect of pneumonia itself.
Quality of life in patients with CAP has been assessed in two studies 7, 17, in one study after a follow-up period of 90 days 7. At that evaluation moment the scores on all dimensions were still somewhat lower as compared to the pre-pneumonia level; the differences varying between 0.8 (mental health) and 7.3 points (general health). HRQL was significantly impaired in our patients 18 months after the pneumonia diagnosis for the dimensions physical function and general health, but this was most probably due the presence of underlying diseases. This is in line with the finding that comorbid conditions increase the risk of an impaired functional status or quality of life 16, 18, 19. Our results are in contrast with the follow-up study of patients with Legionnaires' disease, in whom HRQL seventeen months after the diagnosis of LD was impaired in 7 of the 8 dimensions 10, which was not associated with comorbid conditions. Baseline characteristics of LD and our patient groups were not comparable in all respects (data not shown): age and length of hospital stay were considerable higher in the LD group, and the percentage of COPD was significantly lower in the LD group (11% versus 24%, p = 0.02). The percentage of bilateral and multilobular infiltrates was considerably higher in the LD group, suggesting that this group had a more severe disease than our patients with CAP, although no increased risk was found for an impaired HRQL in post-LD patients who were admitted to ICU or were ventilated mechanically compared to patients who were not 10. Taken together, this suggests that LD differs from community-acquired pneumonia in general, with more long-term sequelae affecting HRQL.

In conclusion, our results confirm that pneumonia-related symptoms may persist for more than four weeks in patients with mild to moderate severe CAP but that most patients recover fully from pneumonia after 6 to 18 months. Any symptoms beyond 28 days are more likely to reflect the effects of age and/or comorbidity rather than the persistent effect of the pneumonia itself.

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Reference List


