Recurrence of Pneumonia in Middle-aged and Elderly Adults after Hospital-treated Pneumonia: Aetiology and Predisposing Conditions

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In order to investigate the predisposing conditions and aetiological agents in patients with recurrent pneumonia, we prospectively studied 653 immuno-compromised patients, 50–85 years of age, who had been treated in hospital for community-acquired pneumonia. After an average patient follow-up period of 32 months, 11 variables were examined for association with the following end points: death, recurrence of pneumonia and recurrence of pneumococcal pneumonia. During the follow-up period there were 171 episodes of pneumonia in 115 of the 653 patients, and 52 deaths (all causes). Multivariate analysis showed that age, male sex, congestive heart failure and presence of other chronic diseases were significantly associated with higher mortality. Age and chronic pulmonary disease were associated with recurrence of pneumonia. The major aetiological agents were Streptococcus pneumoniae (26%), Haemophilus influenzae (11%) and Moraxella catarrhalis (6%). We conclude that pneumonia recurrences are common in middle-aged and elderly patients after treatment in hospital for community-acquired pneumonia. The recurrence risk is higher in elderly patients, and in those with chronic pulmonary diseases. Given the prominence of H. influenzae and M. catarrhalis found in the present study, these organisms should always be considered when choosing the initial antibiotic in patients with recurrent pneumonia.

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INTRODUCTION
Although recurrent pneumonia has long been a recognized clinical problem, it has received scant attention in journals and textbooks. There are few multiple-case reviews, and the majority of data are from paediatric series (1). Disorders that have been associated with recurrent pneumonia in middle-aged and elderly adults include chronic pulmonary diseases, congestive heart failure, diabetes mellitus, chronic lymphocytic leukaemia, multiple myeloma, acquired hypogammaglobulinaemia, alcoholism, neurologic and oesophageal diseases (2, 3).

Patients admitted for pneumonia have, in 36–62% of cases, been treated in hospital during the preceding 4–5 years (4–6), and patients earlier treated in hospital for pneumonia are at even higher risk of subsequent pneumonia (7). Since Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP) among patients requiring hospitalization (4, 8) it has been proposed that immunization with pneumococcal vaccine for patients discharged after pneumonia could be a cost-effective measure (6). We have investigated the efficacy of pneumococcal vaccine to prevent recurrences of pneumonia in patients treated in hospital for pneumonia (9). As a part of that investigation we studied predisposing conditions and aetiological agents in patients with pneumonia recurrences, which we report in this paper.

PATIENTS AND METHODS
Patients
All patients aged 50–85 years with community-acquired pneumonia admitted to the departments of infectious diseases at the hospitals in Danderyd, Umeå, Gävle, Västerås, Karlskrona, and Skövde, Sweden, were reviewed for inclusion in the study. No immunocompromised patients, i.e. patients with HIV infection, myeloma, other active malignant disease, immunoglobulin deficiency, asplenia or those receiving cytostatic or dialysis treatment were included; neither were patients incapable of following study instructions, patients previously vaccinated with pneumococcal vaccine or patients with known hypersensitivity to vaccine components. Approval from the respective ethical committees were obtained before the study started, and informed consent was obtained from all patients. The inclusion period lasted from 1 March 1991 to 31 March 1994, and the follow-up period ended in June 1995.

On a follow-up visit 8 weeks after discharge from hospital, the 653 patients were randomized to receive either a single dose of 0.5 ml 23-valent pneumococcal vaccine (Pneumovax; Merck, Sharp & Dohme, West Point, PA, USA) intramuscularly, or a saline solution. Data were collected on specially-designed forms to record the presence of chronic illnesses and the history of smoking and alcohol consumption. Patients who smoked >5 cigarettes daily were defined as regular cigarette smokers and patients with documented medical or psychosocial problems caused by alcohol abuse were defined as alcoholics. The patients were instructed to contact the doctor locally responsible for the study if they developed a temperature of 38°C, or more, for more than 3 days, or if they had any other cause to suspect recurrent pneumonia. In patients with suspected recurrence a clinical examination and a chest X-ray were performed. Once a year a questionnaire was sent to all patients included as supplement to the follow-up. This questionnaire served us to ensure that no recurrence of pneumonia had been missed.

Microbiology
In patients with recurrence of pneumonia, samples from blood, sputum, and nasopharyngeal secretion were taken on admission. Two blood cultures were drawn and cultured aerobically and anaerobically. Sputum specimens, if available, were cultured quantitatively (10). Pneumococcal antigen detection, using a latex ag-
Table 1. Predisposing conditions and outcome variables in 653 patients discharged after hospital treatment for community-acquired pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients studied (n = 653)</th>
<th>Death (n = 52)</th>
<th>Recurrence of pneumonia (n = 115)</th>
<th>Recurrence of pneumococcal pneumonia (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>69</td>
<td>74</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Male sex</td>
<td>313 (48)</td>
<td>37 (71)</td>
<td>51 (44)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>112 (17)</td>
<td>9 (17)</td>
<td>19 (17)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>8 (1)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>143 (22)</td>
<td>16 (31)</td>
<td>40 (35)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>134 (21)</td>
<td>26 (46)</td>
<td>30 (26)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Other chronic heart disease</td>
<td>86 (13)</td>
<td>8 (15)</td>
<td>12 (10)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (9)</td>
<td>9 (17)</td>
<td>9 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Other chronic diseases&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98 (15)</td>
<td>17 (33)</td>
<td>14 (12)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>320 (49)</td>
<td>27 (52)</td>
<td>60 (52)</td>
<td>17 (50)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

<sup>a</sup> Rheumatic diseases and collagenosis (n = 29), central nervous system disorders (n = 17), cerebrovascular or general arterosclerotic disease (without cardiac symptoms) (n = 10), renal or gastro-intestinal disease (n = 7), neuromuscular diseases (n = 5), inactive malignancies (n = 5), others (n = 25).

... glutination test (Stidex pneumo-kit, BioMérieux, Marcy-l’Étoile, France) was performed on sputum specimens as well as on urine samples. Serum specimens for serological studies were obtained on admission and at a follow-up visit after 8 weeks. Pneumolysin- and cell wall polysaccharide immune complexes specific for S. pneumoniae, and IgG class antibodies to pneumolysin, Haemophilus influenzae and Moraxella catarrhalis, were measured with an enzyme immunosassay (EIA) (11–14). Chlamydial group-specific antibodies were measured with a complement fixation test and with EIA using re-lipopolysaccharide (rough type e LPS) from an enterobacterial mutant that cross-reacts with chlamydial LPS as antigen, as described previously (15). IgG, IgA, and IgM antibodies specific for chlamydial species were measured with a microimmunofluorescence test (16). If there was evidence of cross-reactivity the case was defined as due to Chlamydia species (17).

Specimen collection in pneumonia recurrences
In the 171 pneumonia recurrences diagnosed during the follow-up period, blood cultures were drawn in 136 cases and nasopharyngeal secretion was obtained in 141 cases. Sputum was cultured in 87 cases, 50 of which were examined for pneumococcal antigen. The presence of pneumococcal antigen in urine samples was examined in 62 cases. Paired sera for antibody examination were obtained in 96 cases.

Diagnosis definitions
Recurrent pneumonia was defined as ≥2 episodes of non-tuberculous pulmonary infection, with radiographically demonstrable parenchymal infiltrates, and, in most instances, fever, purulent sputum, leukocytosis, and a response to antibiotic therapy (2,19). These episodes were separated by an asymptomatic interval of at least 2 months or complete clearing of the acute infiltrate.

The following diagnostic criteria were used for the respective pathogens: S. pneumoniae: (1) positive cultures from blood or sputum (≥10⁵ colony-forming units (cfu)/ml), (2) detection of pneumococcal antigen in sputum or urine, (3) a ≥2-fold increase in antibodies to pneumolysin (16); or (4) the presence of pneumolysin- or cell wall polysaccharide immune complexes in any serum sample (12); H. influenzae and M. catarrhalis: positive cultures from blood or sputum (≥10⁵ cfu/ml) or a ≥3-fold titre rise to the respective antigen between paired sera (16); Chlamydia pneumoniae, C. trachomatis, C. psittaci and C. spp.; a ≥4-fold increase in titre between paired sera in any immunoglobulin class or an IgG or IgA titre of ≥512 (16); M. pneumoniae, and respiratory tract viruses: a ≥4-fold rise in antibody titre between paired sera or an elevated steady antibody titre of ≥512 in ≥2 samples (16).

Statistical analysis
The outcome for the included patients was assessed for 3 end points: death, recurrence of pneumonia, and recurrence of pneumococcal pneumonia. 11 variables from the recorded data (Table 1) were examined for association with the 3 outcome variables. To describe the influence of the potential risk factors over time, the relative risks for the 3 end points were analysed using a proportional hazard regression model (20)—i.e. the intensities related to the risk factors (covariates) for the end points under study were assumed to be proportional. The association between the 11 variables and the 3 end points was examined both with univariate analysis and in a multiple regression model (20) initially testing all 11 variables and then providing a best-fitted model with a reduced number of variables. Associations were considered statistically significant if the p value was <0.05.

The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

RESULTS

Patients
A total of 653 patients were studied. The mean age was 69 years (range 50–85 years) and 48% were male. Of the patients, 376 (58%) had ≥1 pre-existing disease (Table 1). 320 patients were vaccinated with pneumococcal vaccine and 333 received placebo.

Recurrence of pneumonia
During the mean follow-up period of 32 months, 171 cases of pneumonia were diagnosed in 115 patients. Hospital...
Recurrence of pneumonia

Table II. Risk factors for death, recurrence of pneumonia, and recurrence of pneumococcal pneumonia according to univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>Hazard ratio with 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>confidence interval</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>Hazard ratio with 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>confidence interval</td>
</tr>
<tr>
<td>Death</td>
<td>&lt;0.01</td>
<td>1.07/year (1.03-1.10)</td>
</tr>
<tr>
<td>Male sex</td>
<td>&lt;0.001</td>
<td>2.84 (1.54-5.11)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>&lt;0.0001</td>
<td>3.65 (2.12-6.30)</td>
</tr>
<tr>
<td>Other chronic disease</td>
<td>&lt;0.001</td>
<td>2.82 (1.58-5.04)</td>
</tr>
<tr>
<td>Recurrence of pneumonia</td>
<td>&lt;0.01</td>
<td>1.03/year (1.01-1.06)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>&lt;0.001</td>
<td>2.02 (1.38-2.97)</td>
</tr>
<tr>
<td>Recurrence of pneumococcal pneumonia</td>
<td>&lt;0.05</td>
<td>2.02 (1.00-4.09)</td>
</tr>
</tbody>
</table>

*The tables includes only those factors that were present in ≥10 patients with a p value of <0.05 in the univariate analysis.

Mortality

52 patients died during follow-up. Of the 115 patients with recurrence of pneumonia 15 patients (13%) died compared with 37/566 (7%) of patients without recurrence of pneumonia (Fisher's exact test p = 0.02). Pneumonia was the cause of death in 4 patients.

Individual risk factors

In the univariate analysis age, male sex, congestive heart failure and presence of other chronic diseases were significantly associated with death (Table II). Age also correlated with pneumococcal pneumonia. Chronic pulmonary disease was associated with recurrence of pneumonia as well as with recurrence of pneumococcal pneumonia. In the multivariate analysis (Table II) the same variables correlated with death and recurrence of pneumonia as in the univariate analysis. No predisposing condition was significantly associated with recurrence of pneumococcal pneumonia in the multivariate analysis. However, there was a weak but nonsignificant correlation with chronic pulmonary disease (p = 0.07).

Aetiology

In 73 of the 171 pneumonia recurrences (43%) evidence of infection with one or more micro-organisms was found. In 44 recurrences (26%). In 33 of these cases there were no signs of infection with other micro-organisms while 11 patients had evidence of mixed infections. Streptococcus pneumoniae was isolated from blood in 6 cases and from sputum in 8 cases. In 6 of these latter cases pneumococcal antigen was detected in sputum as well. In 1 patient pneumococcal antigen was detected in urine. Serological evidence of pneumococcal infection was found in 36 recurrences. In 11 of these, S. pneumoniae was also detected by culture.

Haemophilus influenzae was the aetiological agent in 18 recurrences (11%). The micro-organism was isolated from sputum in 9 cases, and in 13 recurrences a significant titre rise between paired sera was found. 11 recurrences (6%) were caused by M. catarrhalis. The micro-organism was isolated from sputum in 8 cases, and in 7 cases serological evidence of infection was found. 10 of the 18 patients (45%) with pneumonia caused by H. influenzae and 5/11 patients (56%) with pneumonia caused by M. catarrhalis had a
chronic pulmonary disease compared with 12/34 (35%) of the patients with pneumoniae caused by S. pneumoniae. Infection with respiratory viruses was detected in 8 recurrences (Table III). In 2 of these cases evidence of dual infection with S. pneumoniae was found.

**DISCUSSION**

Recurrent pneumonia in adults had not been examined in a truly comprehensive way since the often-quoted study by Winterbauer et al. (19) published in 1969. That study however, was retrospective, included only patients treated in hospital, and the bacteriological data were, in the authors’ own words, “sketchy at best”. The present study of 653 patients discharged from hospital after treatment for CAP is, to our knowledge, the first attempt to prospectively assess the aetiological agents and the predisposing conditions in patients with recurrence of pneumonia.

In the pre-antibiotic era, recurrences of pneumonia was regarded as more common than in any other acute infectious disease (21). At that time, multiple studies subsequently established a 13.6–31% incidence of recurrence among cases of pneumonia (22, 23). The incidence of recurrent pneumonia today is unknown. In a study of 359 patients who were hospitalized with pneumonia during 12 months, 12 were admitted more than 1 occasion because of recurrence (24). In another study performed in a Navajo Indian reservation, multiple episodes of pneumonia were observed in 14.5% of patients under the age of 15 and 7.6% of those over 15 during 2 years (25). In accordance with an earlier retrospective study (7), we found a high incidence of recurrent pneumonia in patients earlier treated in hospital for CAP in the present investigation. The observed incidence of pneumonia of 9.8 per 100 person-years is 5 times higher than the overall incidence of pneumonia in persons over 60 years of age in the Scandinavian population (26). The results indicate that recurrent pneumonia remains a highly prevalent clinical problem.

In the present study hospital admission was required in two-thirds of the pneumonia episodes. This figure is higher than in an earlier population-based British study (27) but is of the same magnitude as in another Scandinavian study (26). The difference may reflect a different definition of pneumonia; in the British study less than half of the patients had acute radiographic changes.

The relative benignity of recurrent pneumonia, with a lower case fatality rate in patients with recurrent infection compared with the initial attack of pneumonia, has been alluded to in pre-antibiotic studies (22, 23), as well as in Winterbauer’s study (19). This was supported by the present study; only 4/171 episodes of pneumonia were fatal, although patients <50 years old were not included.

Among patients requiring hospitalization of CAP, S. pneumoniae is the most common cause (4, 8, 24, 28, 29) and often accounts for 50% or more of the agents identified in these patients. Also in patients with recurrent pneumonia the pneumococcus seems to be the most common organism (19). This was confirmed by the present study in which more than half of the pneumonia cases with an identified aetiology were caused by pneumococci.

Haemophilus influenzae and M. catarrhalis were the second and third most common pathogens identified. Evidence of pulmonary infection caused by 1 of these pathogens was found in 37% of the pneumonia cases with an identified aetiology. The high figures might in part be explained by the relatively high prevalence of chronic pulmonary disease in the patients with pneumonia recurrences. In patients with chronic pulmonary disease, H. influenzae is a well-known cause of CAP, and also has been reported with increasing frequency as the aetiological agent of serious human infections (30). Moraxella catarrhalis is rarely a primary pulmonary pathogen in the normal host, but has emerged as an important pathogen in elderly individuals with chronic pulmonary diseases (30). However, in the present study, H. influenzae and M. catarrhalis were also fairly common as aetiological agents in patients without chronic pulmonary diseases. These agents caused 13% of the recurrences of pneumonia in patients without chronic pulmonary diseases compared with 20% in patients with chronic pulmonary diseases.

Infections with atypical agents were uncommon in the present study. In contrast to other studies from Scandinavia (16), and North America (31), few cases of pneumonia were caused by C. pneumoniae, which could be explained by the epidemic nature of this infection (16). That only 1 recurrence was caused by M. pneumoniae was probably due to the high age of the population studied (32). The aetiological diagnostic procedures did not include legionella spp. since these are uncommon causes of CAP in Sweden and other Scandinavian countries (4, 33–35).

Most patients with recurrent pneumonia have underlying illnesses (1, 19). In the present study a majority (58%) had a pre-existing disease. In Winterbauer’s study (19) underlying diseases with extra-thoracic manifestations (such as diabetes mellitus, alcoholism, and chronic sinusitis) were as common as intra-thoracic diseases. In the present study, the most common diseases were intra-thoracic; chronic pulmonary disease, congestive heart failure, and other chronic heart diseases. Diabetes mellitus is often listed as a predisposing cause of recurrent pneumonia, but there is no convincing evidence of any causal relationship (3). We found the same proportion of patients with diabetes mellitus among patients with recurrence of pneumonia as among all patients studied.

In the present study, chronic pulmonary disease was, apart from age, the only investigated risk factor that correlated with recurrence of pneumonia. Precise data are lacking concerning the role of recurrent pneumonia in patients with chronic pulmonary diseases (2). It is known that some of the defence mechanisms against bacterial pneumonia are...
impaired in patients with chronic obstructive disease. As the vital capacity decreases, the patient's cough may become less effective, and in some patients, there is loss of normal mucociliary function as a result of widespread squamous metaplasia of the airway epithelium (2, 3). Decreased synthesis of surfactant with loss of opsonization activity has also been demonstrated in these patients (3).

Chronic pulmonary disease, however, was not associated with death. The strongest mortality predictors found in the multivariate analysis were congestive heart failure and the heterogeneous group of “other” chronic diseases. In contrast to earlier studies on mortality in patients hospitalized for pneumonia (8, 36), we found a higher mortality in men.

As we have reported earlier (9), we could not demonstrate any efficacy of pneumococcal vaccine in preventing pneumococcal pneumonia or preventing pneumonia overall in the patient population studied. The patients who received the vaccine had many recurrences of pneumonia and pneumococcal pneumonia as those on placebo. Neither did pneumococcal vaccination affect the mortality rate.

We conclude that pneumonia recurrences are common in middle-aged and elderly immunocompetent patients earlier treated in hospital for CAP. Chronic pulmonary disease, together with age, were the most important predisposing conditions in patients with recurrent pneumonia. The aetiological agents most commonly involved were S. pneumoniae, H. influenzae and M. catarrhalis. In view of the prominence of H. influenzae and M. catarrhalis found in the present study these organisms should always be considered when choosing the initial antibiotic in patients with recurrent pneumonia.

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REFERENCES

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