Recurrence of Pneumonia in Relation to the Antibody Response after Pneumococcal Vaccination in Middle-aged and Elderly Adults

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We have recently studied the efficacy of pneumococcal vaccine in preventing pneumonia recurrences after hospital treatment for community-acquired pneumonia in non-immunocompromised patients aged 50–85 y. Among these patients, we have now compared the antibody response to the pneumococcal vaccine between patients who developed pneumonia ($n = 50$) and patients without pneumonia recurrences ($n = 100$), during a mean follow-up period of 32 months after vaccination. The antibody levels of 5 pneumococcal serotypes were measured before, and 4 weeks, 1 y and 3 y after vaccination. A lower risk of pneumonia recurrences was seen in patients with antibody fold increases (FIs) > 4 from pre-vaccination to post-vaccination compared with patients with lower FIs ($p = 0.02$). The results suggest that in this patient category, the antibody response to pneumococcal vaccination is of importance for the risk of pneumonia recurrence.

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INTRODUCTION

Streptococcus pneumoniae is the most commonly identified cause of pneumonia leading to hospitalization (1–3). Both the incidence and case-fatality rate of pneumococcal pneumonia increase with advancing age, particularly among persons with underlying diseases (4).

The polysaccharide capsule is the principal determinant of the virulence of pneumococci (5). To date, 90 pneumococcal types have been identified by the serological properties of their capsular polysaccharides (6). Antibodies directed against these polysaccharides play a predominant role in prevention of and recovery from pneumococcal infections (5). Protection after immunization is dependent upon the production of circulating type-specific pneumococcal antibodies that act alone or together with complement protein to opsonize bacteria and promote their phagocytosis (7).

The commercially available pneumococcal vaccine in use since 1983 contains purified capsular polysaccharides from 23 pneumococcal serotypes responsible for about 90% of bacteraemic (8) and respiratory tract infections (9) with pneumococci.

Patients admitted to hospital for pneumonia have in 36–62% of cases been treated in hospital during the preceding 4–5 y (3, 10, 11), and patients treated previously in hospital for pneumonia are at an even higher risk of pneumonia subsequently (12). Therefore, immunization with pneumococcal vaccine for patients discharged after pneumonia has been proposed to prevent future admissions for pneumococcal disease (11).

We have earlier investigated the efficacy of pneumococcal vaccine in the prevention of recurrences of pneumonia in middle-aged and elderly patients after treatment in hospital for pneumonia (13). We now present data on the antibody response to the 23-valent pneumococcal polysaccharide vaccine administered 8 weeks after discharge among these patients. The aim of the present study was to determine the type-specific antibody response to 5 pneumococcal polysaccharide antigens included in the vaccine, and to compare the antibody responses between patients with and without pneumonia recurrences after the vaccination.

MATERIALS AND METHODS

Patients

All patients, 50–85 y of age, with community-acquired pneumonia, admitted to the departments of infectious diseases at 5 Swedish hospitals were reviewed for inclusion in a prospective, randomized, placebo-controlled study to evaluate the protective efficacy of 23-valent pneumococcal vaccine given after discharge from hospital (13). Immunocompromised patients were excluded from the study. The incision period lasted between March 1, 1991, and March 31, 1994, and the follow-up period ended in June, 1995.

On a follow-up visit 8 weeks after discharge from hospital the patients received either a single dose of 0.5 ml 23-valent pneumococcal vaccine or a saline solution in a double-blind, randomized fashion. For all included patients data were collected on specially-designed forms to record the presence of chronic illnesses. The patients were instructed contact the doctor locally responsible for the study if they developed fever of 38°C, or more, for more than 3 d, or it they had any other cause to suspect a recurrent pneumonia. In patients with suspected recurrence of pneumonia after the follow-up visit a clinical examination and a chest X-ray, was performed. Pneumonia was defined as clinical signs of acute lower respiratory tract disease and radiological signs of acute pneumonia, i.e. pulmonary infiltrates proved, by comparison with a previous X-ray, to be new. A questionnaire was sent to all included patients once a year to ensure that no recurrence of pneumonia had been missed.

A total of 653 patients were included in the study of the efficacy of the pneumococcal vaccine. Informed consent was obtained from all patients. During the mean follow-up period of 32 months

 ISSN 0036-5548

pneumonia was diagnosed in 115 of these patients. From this study population, sera from 50 patients, who had been given active substance, with recurrence of pneumonia during the follow-up period, were available to evaluate the type-specific serological response to the pneumococcal vaccine. For each of these patients, the following 2 vaccinated patients enrolled to the study without a pneumonia recurrence of similar age (± 5 y), and with presence/absence of chronic conditions as the case patient were selected as controls. All 150 patients had received a single intramuscular dose of 0.5 ml 23-valent pneumococcal vaccine (Pneumovax; Merck, Sharp & Dome, West Point, PA, USA) that contained 25 μg of each of the following purified capsular polysaccharide type antigens: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. Blood samples were collected from all 150 patients immediately before and 4 weeks after vaccination, from 130 patients 1 y after vaccination, and from 50 patients 3 y after vaccination. Serum was frozen at -70°C until analysed.

Microbiology

In patients with recurrence of pneumonia samples from blood, sputum, and nasopharyngeal secretions were taken on admission if possible. Two blood cultures were drawn and cultured aerobically and anaerobically. Sputum specimens, if available, were cultured quantitatively (14). Pneumococcal antigen detection, using a latex agglutination test (Slidex 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 on a follow-up visit after 8 weeks. Pneumolysin- and cell wall polysaccharide immune complexes specific for S. pneumoniae, and IgG class antibodies to pneumolysin were measured by an enzyme immunoassay (EIA) (15, 16).

Pneumococcal pneumonia-diagnostic definitions. A recurrence of pneumonia was judged to be caused by S. pneumoniae if: (i) the micro-organism was cultured from blood, or sputum ($\geq 10^5$ colony-forming units (cfu)/ml) (14) or (ii) a 2-fold or greater increase in antibodies to pneumolysin in paired serum samples (15) or (iii) presence of pneumolysin immune complexes in any serum sample (16).

Antibody response to pneumococcal vaccination. Type-specific antibodies against the pneumococcal polysaccharide types 1, 4, 14, 18C, and 19 F were measured by use of a micro-enzyme-linked immunosorbent assay described previously (17). Antibody concentrations are expressed as milligrams per litre after calibration to the assigned IgG concentrations of the international pneumococcal reference serum 89-SF (US Food and Drug Administration, Bethesda, Md) (18).

Statistical analysis

To compare the antibody responses between the patients with and without recurrences of pneumonia logistic regression was used to estimate the risk of recurrence of pneumonia overall and of recurrence of pneumococcal pneumonia in relation to pneumococcal antibody levels before vaccination 4 weeks, 1 y, and 3 y after vaccination, and also in relation to antibody fold increases (FIs) from before to 4 weeks after vaccination. In a first step we tested if the antibody level as a continuous variable influenced the risk of pneumonia recurrences. In a second step we divided the antibody levels as well as the FIs into 4 categories. We analysed the categories as dummy variables in the model to find out whether a linear assumption of an increasing risk could be rejected or not. For the antibody levels before vaccination the categories were ≤ 2, >2–3, >3–4, and >4 mg/1. For the antibody levels after vaccination the categories were ≤ 5, >5–10, >10–20, and >20 mg/l. For the antibody levels 1 y after vaccination the categories were ≤ 4, >4–8, >8–12 and >12 mg/l. For the FIs the categories were ≤ 2, >2–3, >3–4, and >4. Statistica (version 5.1) was used for statistical calculations.

The study was approved by the regional ethical committees in Sweden.

RESULTS

Patients, aetiological agents

The mean age of the 150 patients was 71 y, and 50% of patients were male. One or more pre-existing chronic diseases were documented in 67% of the patients. The most common diseases were chronic pulmonary disease, congestive heart failure, other chronic heart disease, and diabetes mellitus (Table I). Among the 50 patients with recurrence of pneumonia, evidence of infection with pneumococci was found in 15 patients (30%). One of the patients had pneumococcal bacteraemia. The remaining 14 pneumococcal pneumonia episodes were diagnosed by sputum culture (4 patients), or by a positive pneumococcal antibody test (13

Table I. *Predisposing conditions in 150 patients vaccinated with 23-valent pneumococcal vaccine 8 weeks after hospital discharge following treatment for community-acquired pneumonia*

Variable	All patients studied	Patients without recurrence of pneumonia ($n = 100$)	Patients with recurrence of pneumonia ($n = 50$)	Patients with recurrence of pneumococcal pneumonia ($n = 15$)
Mean age (y)	71	70	71	72
Median age (y)	71.5	71.5	71.5	71
Male sex	75 (50)	53 (53)	22 (44)	8 (53)
Chronic pulmonary disease	38 (25)	24 (24)	14 (28)	6 (40)
Congestive heart failure	40 (27)	27 (27)	13 (26)	3 (20)
Other chronic heart disease	20(13)	14 (14)	6 (12)	2 (13)
Diabetes mellitus	18 (12)	14 (14)	4 (8)	1 (7)
Any chronic disease	100 (67)	67 (67)	33 (66)	12 (80)

Values in parenthesis are percentages.

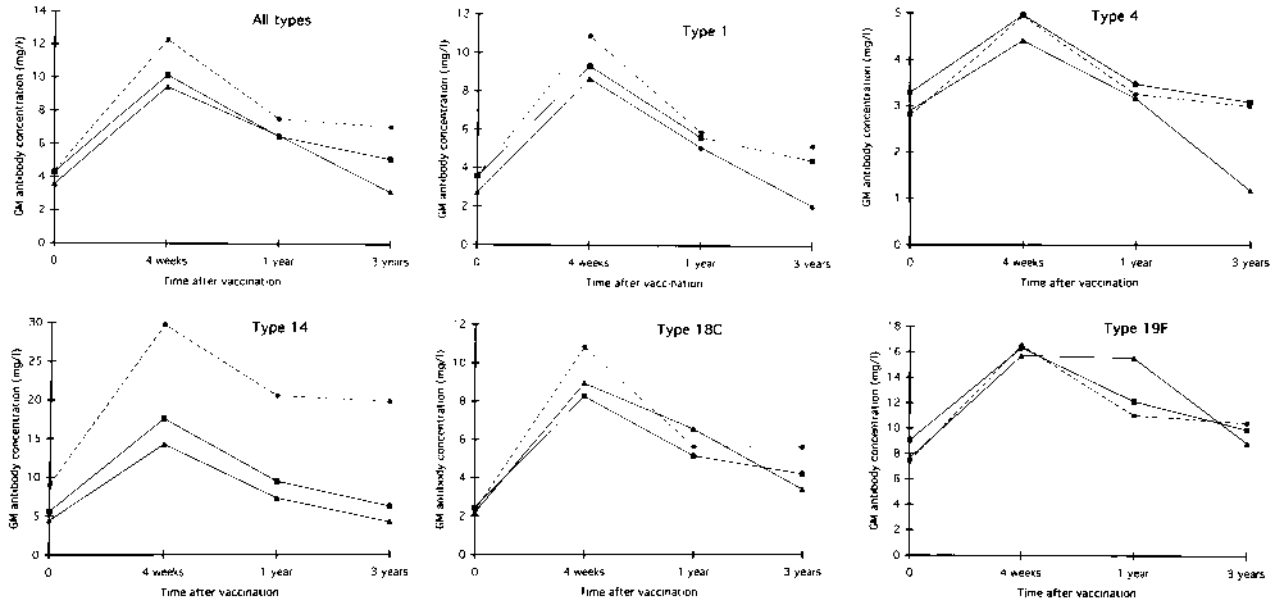

Fig. 1. Type-specific antibody responses to five pneumococcal capsular polysaccharide antigens and to the 5 antigens as a group in 150 patients vaccinated with 23-valent pneumococcal vaccine 8 weeks after hospital discharge following treatment for community-acquired pneumonia. Patients without pneumonia recurrences after vaccination ($n = 100$) are indicated with circles (*broken lines*), patients with recurrences of pneumonia ($n = 50$) are indicated with squares, and patients with recurrences of pneumococcal pneumonia ($n = 15$) are indicated with arrows.

patients). Pneumolysin immune complexes were found in 10 of these 13 patients, and 4 of them had a 2 fold or greater increase in antibodies to pneumolysin in paired serum samples.

Among other aetiological agents involved in the recurrences of pneumonia the most common were Haemophilus influenzae (8 cases) and Moraxella catarrhalis (5 cases). In 25 (50%) of the patients with recurrence of pneumonia no aetiological agent was identified.

Antibody response to pneumococcal vaccine

The type-specific antibody responses to the individual pneumococcal antigens and to the 5 antigens as a group are shown in Fig. 1. The figure shows the antibody responses to the pneumococcal vaccine in patients without recurrence of pneumonia, in patients with recurrence of pneumonia, and in patients with recurrence of pneumococcal pneumonia. As seen in the figure the antibody response in relation to patients with and without recurrence of pneumonia varied between the different types. For the 5 antigens as a group the results are expressed as combined geometric means (GM), i.e. the geometric means of the GM antibody concentrations or GM antibody FIs for the 5 pneumococcal antigens. The combined GM antibody concentrations were numerically, but not significantly, lower among patients with pneumonia recurrences than in those without recurrences 4 weeks, 1 y, and 3 y after vaccination. The patients with pneumococcal pneumonia recurrences had numerically lower antibody concentrations both before and after vaccination, compared with the patients without pneumonia recurrences, but this difference was not significant.

In the analysis of the influence on the pneumococcal antibody FI as a continuous variable and the risk of subsequent pneumonia no significant association was found. However, after separation into categories, it was found that patients with the highest GM FIs (> 4) had significantly fewer pneumonia recurrences than patients with lower FIs ($p = 0.02$) (Table II). According to the logistic regression model, these findings corresponded to a risk of recurrence of pneumonia of 0.34 (95% confidence interval 0.12, 0.97) for the patients with FIs > 4 compared with the patients with FIs ≤ 2 (Table II).

DISCUSSION

In this study we determined the antibody response to 5 pneumococcal polysaccharide antigens included in the 23-valent pneumococcal polysaccharide vaccine in 150 non-immunocompromized patients, 50–85 y of age, who were vaccinated 8 weeks after treatment in hospital for pneumonia. Our aim was to investigate whether the magnitude of the antibody responses had any impact on the risk of recurrence of pneumonia during a follow-up period of approximately 2.5 y. We selected the 50–85 y age category because the $\geq$ 50-y-old population includes most persons at high risk of serious pneumococcal infection (4), and since a protective efficacy of the vaccine is uncertain for patients > 85 y of age (19).

Although pneumococcal vaccine appears to be highly effective in preventing pneumococcal pneumonia and bacteraemia in younger adults (20), its efficacy to prevent

Table II. *Combined geometric mean antibody fold increase to five pneumococcal capsular polysaccharide antigens after vaccination with 23-valent pneumococcal vaccine in relation to recurrence of pneumonia in 150 patients*

Fold increase (FI)	Number of patients with recurrences/ number of patients (%)	Risk of pneumonia recurrence compared with patients with FI ≤ 2. Odds ratio with 95% confidence interval
≤ 2	19/51 (37%)	1
>2–3	15/39 (38%)	1.05 (0.44, 2.50)
>3–4	10/24 (42%)	1.20 (0.44, 3.27)
>4	6/36 (17%)	0.34 (0.12, 0.97)*

* $p = 0.02$ compared with the patients with pneumonia recurrences and fold increase <4 (logistic regression).

pneumonia in older subjects with or without underlying disease is much more uncertain (21, 22). In our study of the efficacy of pneumococcal vaccine in the prevention of recurrences of pneumonia in middle-aged and elderly patients after treatment in hospital for pneumonia (13) we were unable to show that the vaccine was effective in the prevention of pneumonia overall or of pneumococcal pneumonia. Some previous studies have documented a reduced serologic response to the pneumococcal vaccine in elderly persons compared with that in younger adults (23–25), while in another study no association between aging and postvaccination levels of pneumococcal antibodies was found (26). The discrepancy between these results may reflect variable numbers of poor responders included in the different studies since a subset of elderly patients may respond poorly to pneumococcal vaccine, despite adequate mean immune responses of the elderly as a group (21). An attenuated serological response in persons with chronic debilitating illnesses compared with that in healthy persons has also been demonstrated (27). Moreover, perfectly healthy individuals occasionally may also respond poorly to pneumococcal vaccination (28).

An international standard reference serum for anti-PPS antibody determinations recently became available, and antibody levels in mg/l have been assigned for various PPSs (18). Use of this reference serum (lot 89-SF), as done in the present study, make the antibody concentrations comparable with those obtained in other laboratories using a standard EIA method. In a recent population-based study of the antibody response to pneumococcal capsular polysaccharide vaccine in the elderly the standard reference serum was used (29). In the study most of the elderly subjects (≥ 65 y old) responded satisfactorily to the pneumococcal vaccine with high geometric mean fold increases. However, in that study the postvaccination levels generally were lower compared with the present study.

The concentrations of type-specific pneumococcal antibodies required for protection against pneumococcal infections are unknown. Earlier data based on radioimmunoassay (RIA) methods have suggested that a concentration of 250–300 ng of antibody per ml is needed for protection (30). However, the RIA as described by Schiffman et al. (31) does not distinguish antibodies to pneumococcal capsular polysaccharides (anti-PPS) from those to C-polysaccharides (C-Ps) (32). C-Ps antibodies are found in high concentrations in nearly all human sera (32) and are thought to have only a minor role in opsonizing pneumococci (32). No report on EIA including anti-C-Ps neutralization to determine protective antibodies to anti-PPS have been published, and it is not known whether different concentrations of antibodies are needed for protection against different types. When assessing the immunogenicity of the pneumococcal vaccine, both the post-vaccination antibody level and the antibody FI should be taken into account. It is not clear whether the absolute post-vaccination antibody level or the FI is most important the protective efficacy of pneumococcal vaccination. It has been suggested that a 50–100% increase in antibody levels indicates a meaningful response (33). In the present study we also found that the antibody response in relation to patients with and without recurrence of pneumonia varied between the different types which is in accordance with earlier findings that some serotypes are more immunogenic than others (28).

The antibody concentrations were similar in both groups before vaccination, but on all measure occasions after vaccination patients with pneumonia recurrences had lower values, although not significant, than those without recurrences. However, for patients with high FIs (>4) the risk of pneumonia recurrences was reduced to one-third compared with patients with lower FIs. Although a similar pattern was seen for patients with pneumococcal pneumonia recurrences compared with those without any pneumonia recurrences, these differences were not significant. However, a pneumococcal aetiology was established in only 15 of the 50 patients with pneumonia recurrences, and the number of events were probably too few to estimate the antibody level as a risk factor for developing a pneumococcal pneumonia (34). Our results indicate that the pneumococcal vaccine induces some protection in patients capable of producing a vigorous antibody response, but not in those with a more moderate response. However, the total number of pneumonia cases preventable with pneumococcal vaccine in elderly seems to be low (13), and the rational for using the vaccine is to prevent invasive disease rather than to prevent pneumonia.

It is currently thought that at least 30–50% of all adult CAP cases treated as in-patients are pneumococcal in origin (2, 35, 36). However, even in prospective studies of CAP the aetiology often remains unidentified. A pathogen is often demonstrated in only half of the cases or fewer (37, 38). In the present study S. pneumoniae was the most common pathogen followed by H. influenzae and M. catarrhalis. In half of the patients no aetiological agent was identified. It is probable that also some of these latter cases were due to pneumococci, since most of the tests for S. pneumoniae are rather insensitive (39). It is also possible that pneumococci were responsible for some of the pneumonias with identified aetiology other than pneumococci, since mixed infections with pneumococci and other pathogens are common (3, 36). These facts may explain the protective efficacy seen in the present study against pneumonia recurrence in general, but not against pneumococcal pneumonia.

There is evidently a need for a more immunogenic pneumococcal vaccine to protect individuals at highest risk for pneumonia. Pneumococcal polysaccharides are relatively poor immunogens compared with proteins such as tetanus toxoid (33). Conjugation to protein carriers convert polysaccharides to T-cell dependent antigens, thereby enhancing their immunogenicity (40). In infants and children protein conjugated pneumococcal vaccines are immunogenic and able to induce immunologic memory (41, 42), but only a few studies have been published on pneumococcal conjugate vaccines in adult patients (4, 43–45). In young, adult patients with Hodgkin's disease who had received 7-valent pneumococcal conjugate vaccine, a booster response was seen after revaccination with 23-valent polysaccharide vaccine (44). A pneumococcal conjugate vaccine elicited higher pneumococcal antibody titres than did polysaccharide vaccine in young adults in one study (45), but, in contrast, protein-conjugated oligosaccharides was found to offer little, if any, advantage over unconjugated polysaccharides for the immunization of healthy older adults in another study (4). Clearly, more data are needed to evaluate the possible use of conjugate vaccines in the elderly.

The results of the present study indicate that in patients, immunized with 23-valent pneumococcal polysaccharide vaccine after treatment for pneumonia, the antibody response is of importance for the risk of recurrence of pneumonia recurrences. Certain of these patients, although without known immunosuppression, seem to have an impaired antibody response to pneumococcal vaccination, and thereby an increased risk of recurrence of pneumonia. Since patients earlier treated in hospital for pneumonia are at great risk of pneumonia subsequently, further studies on more efficacious measures for protection against pneumonia recurrences are needed.

ACKNOWLEDGEMENTS

Financial support for this study was received from Merck, Sharp & Dohme and Pasteur-Mérieux, MSD, the Swedish Heart-Lung Foundation and Karolinska Institutet. We gratefully acknowledge the following physicians for their valuable assistance in data collection: Ewa Aufwerber and Gunnar Granström, Division of Infectious Diseases, Karolinska Institutet, Danderyd Hospital; Lars-Åke Burman, Department of Infectious Diseases, Umeå Hospital; Elisabet Elbel, Department of Infectious Diseases, Skövde Hospital; Margareta Höfer, Department of Infectious Diseases, Västerås Hospital; Ingrid Lindblad, Department of Infectious Diseases, Karlskrona Hospital; Bo Sundelöf, Department of Infectious Diseases, Gävle Hospital.

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Submitted June 22, 1999; accepted November 12, 1999