Pneumococcal vaccine in children and young adults with chronic renal disease

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Abstract

Background. Pneumococcal vaccination has been recommended for immunocompromised children over 2 years including patients with chronic renal disease. However, the effect of vaccination and revaccination is variable and the indication for immunization is a subject of controversy.

Methods. Forty children and young adults with chronic renal diseases (including the idiopathic nephrotic syndrome, chronic renal failure, patients undergoing dialysis and after transplantation) were vaccinated with a 23-valent pneumococcal vaccine. The efficacy of the vaccine was evaluated by measuring antibody titres before and 4 weeks, 6 months, and 12 months after vaccination. Twenty-two patients were submitted to a revaccination 1 year after the first vaccination.

Results. A sufficient immune response, defined as an at least fourfold increase of postvaccinal antibody titres and an antibody titre >200, was observed in 83% of the patients 4 weeks after vaccination, but only in 68% after 6 months, and in 48% after 1 year. Revaccination produced a significant immune response in 11/22 patients (50%) followed by a rapid decline of antibody levels within 6 months. Both vaccinations were well tolerated.

Conclusions. The currently available vaccine is without major side-effects and effective in producing a significant immune response. Antibody levels should be monitored in vaccinated patients with chronic renal diseases considering the rapid decline as early as 6 months after vaccination. Evaluation of the efficacy of revaccination in these patients requires further investigations.

Key words: vaccination; Streptococcus pneumoniae; renal failure; Strep. pneumoniae

Introduction

Streptococcus pneumoniae (SP) is a common pathogen and a source of substantial morbidity and mortality accounting for an estimated 40,000 deaths annually in the United States, with most of the recorded deaths occurring in risk groups [1]. In a recent recommendation by the Advisory Committee on Immunization Practices [2], pneumococcal vaccination has been recommended for immunocompetent adults at increased risk of pneumococcal disease (e.g. pulmonary disease, diabetes), and for immunocompromized adults and children over 2 years including patients with chronic renal failure and nephrotic syndrome, and organ transplant recipients receiving immunosuppressive medication. Previous studies in children with chronic renal diseases receiving a 14-valent vaccine have documented a diminished immune response and a loss of protective antibodies in a considerable portion of patients [3,4]. About 90% of SP infections leading to hospitalization are caused by 20 different serotypes; the capsular polysaccharide antigens of these serotypes are included in the presently available 23-valent vaccine licensed in Germany, replacing the 14-valent vaccine. Thus far no studies have evaluated the efficacy of the 23-valent vaccine in children with renal disease, and recommendations for immunization against SP are the subject of some controversy [5,6]. Recent reports of infections caused by antibiotic-resistant SP underscore the need for a protective vaccine for high-risk patients [7].

We therefore analysed serum antibody levels prior to vaccination, the efficacy of the 23-valent pneumococcal vaccine and the duration of the immune response in children and young adults with nephrotic syndrome, with chronic renal failure, and in dialysed and transplanted children. In addition the effect of a revaccination was evaluated.

Subjects and methods

A total of 58 patients, treated at the paediatric nephrology unit of the University Children's Hospital of Cologne, aged 2.9–27 years (mean 12.9 years) were studied. These included 47 children aged 2.9–18 years (mean 10.5 years) and 11 adults aged 18–27 years (mean 23.2 years). Eight patients were lost for follow-up, and 10 had already protective antibody titres ≥200. Forty individuals with a mean age of
14.5 years (2.9–27 years) and an antibody titre <200 were vaccinated (Table 1). Among these were nine patients with idiopathic steroid-sensitive nephrotic syndrome and normal renal function. At the time of investigation, all were in remission without proteinuria; four were treated with prednisone or cyclosporin. In addition we investigated 11 patients with chronic renal failure. The calculated GFR [8] ranged from 5 to 34 ml/min per 1.73 m². Two patients had proteinuria in the nephrotic range. On dialysis, we analysed 13 patients, seven undergoing haemodialysis and six with continuous ambulatory peritoneal dialysis (CAPD). Seven patients received renal transplants for a mean time of 21.5 months prior to the investigation. The calculated GFR in this group ranged from 51 to 92 ml/min per 1.73 m².

Informed consent as well as parental consent for each child was obtained before entering the study. The 23-valent vaccine Pneumovax® 23 (Behringwerke, Marburg, Germany), was administered subcutaneously in the upper extremities in a dose of 0.5 ml. The vaccine contains 25 μg of each polysaccharide antigen of the following serotypes (Danish nomenclature): 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. The efficacy of vaccination was evaluated by measuring the antibody response to the whole vaccine, i.e. to the mixture of the 23 capsular polysaccharides. Sera were obtained prior to and 4 weeks, 6 months and 1 year respectively, after the vaccination.

The determination of IgG-antibody levels to Pneumovax® 23 was performed by enzyme-linked immunosorbent assay (ELISA). Pneumovax® 23 was used as the antigen. Because of the poor binding of carbohydrates to plastic surfaces, the carbohydrate mixture was derivatized according to Barrett et al. [9]: the content of five vials Pneumovax® 23 (0.5 ml each), was added to 1.5 ml 0.01 M NaOH and mixed immediately. The solution was transferred into a tube containing 6.5 mg cyanuric chloride (Sigma Chemical Co.) and gently mixed, keeping the pH at 8.3. After a few minutes the mixture was transferred into a tube containing 0.3 mg poly-L-lysine in 0.3 ml 0.05M Tris buffer, pH 8.1. The solution was dialysed against phosphate-buffered saline (PBS), pH 7.4. It was then diluted to 100 ml with PBS, pH 7.4, dispensed in 100-ml samples to Maxisorb microtitre plates (Nunc, Denmark) and incubated for 24 h at room temperature. The plates were washed three times with distilled water, incubated for 10 min. with washing buffer (PBS, pH 7.4, containing 0.05% Tween 20 and 0.5 M NaCl) to block surface hydrophobic absorption capacity. The washing buffer was removed and the plates were then dried at room temperature and stored at 4°C.

Serum samples were stored at −70°C until used. Serial fivefold dilutions were prepared from 1:25 to 1:3125 (reference serum included). Samples of 0.1 ml of the serial dilutions were added to the wells and incubated for 2 h at 37°C. After washing 3 times with washing buffer, 0.1 ml of an appropriate dilution of alkaline phosphatase-conjugated goat anti-human immunoglobulin (Sigma Chemical Company) was added to the wells and incubated at 4°C overnight. The plate was again washed as above, and 0.1 ml substrate solution (p-nitrophenylphosphate, 1 mg/ml in 0.05 M sodium carbonate buffer pH 9.6, containing 0.001 M magnesium chloride) was added to each well. After incubation for 1 h at 37°C the reaction was stopped by addition of 50 μl 1 M NaOH and the absorbance was measured at 414 nm on a multichannel photometer (Titertek Multiscan; Flow Laboratories). Each sample was tested twice on one plate. The antibody titre (calculated according to Caulfield and Shaffer [10]) was arbitrarily defined as the reciprocal of that serum dilution showing a positive signal as compared to a standard (reference serum), which was used for the calculation of the cut-off and applied to each plate.

Antibody levels >200 were considered as protective against pneumococcal infections. A significant immune response ('responders') was defined as an increase of antibody levels of at least two twofold dilution steps, as well as postvaccinal antibody titres above 200.

Twenty-two patients whose antibody titres decreased to original levels were submitted to a revaccination 1 year after the primary vaccination. These included three patients with idiopathic nephrotic syndrome, seven with chronic renal failure, eight chronic dialysis patients, and four renal allograft recipients. The efficacy of the revaccination was evaluated 4 weeks and 6 months later as described above.

The immunization antibody level of pneumococcal serotypes in healthy children and adults is variable but generally low, since it depends on specific antigenic stimulation by homologous or cross-reacting antigens [11,12]. For ethical reasons the study was designed without a control group. The antibody response to the 23-valent vaccine Pneumovax® 23 in healthy controls is well known: most healthy children and young adults show a twofold or greater rise of antibody levels after vaccination [1,11,12]. The response to some capsular types may be weaker in children <5 years [13]. The response to vaccine in children <2 years is generally poor. The study was approved by the Ethical Committee of the University of Cologne.

**Results**

**First vaccination**

The distribution of basic antibody levels is summarized in Table 2. Prior to vaccination, 48 of 58 patients

<table>
<thead>
<tr>
<th>Table 1. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to vaccination</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>CRF</td>
</tr>
<tr>
<td>HD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>TX</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

NS, idiopathic nephrotic syndrome; CRF, chronic renal failure; HD, haemodialysis; PD, peritoneal dialysis (CAPD, CCPD); TX, after transplantation.

*aAge in years; bGFR in ml/min per 1.73 m².*
Table 2. Distribution of prevaccination antibody titres

<table>
<thead>
<tr>
<th>Category</th>
<th>NS (100%)</th>
<th>CRF (100%)</th>
<th>HD (100%)</th>
<th>PD (100%)</th>
<th>TX (100%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200</td>
<td>15 (71%)</td>
<td>14 (93%)</td>
<td>6 (86%)</td>
<td>5 (71%)</td>
<td>8 (100%)</td>
<td>48 (83%)</td>
</tr>
<tr>
<td>&gt;200</td>
<td>10 (29%)</td>
<td>1 (7%)</td>
<td>1 (14%)</td>
<td>2 (29%)</td>
<td>0</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Median</td>
<td>134</td>
<td>46</td>
<td>26</td>
<td>56</td>
<td>62.5</td>
<td>54</td>
</tr>
</tbody>
</table>

NS, idiopathic nephrotic syndrome; CRF, chronic renal failure; HD, haemodialysis; PD, peritoneal dialysis; TX, after transplantation.

(83%) with chronic renal disease had antibody levels <200. Titres were lowest in the haemodialysed (median 26) and highest in the nephrotic patients (median 134). Most of the patients with antibody levels >200 were in the nephrotic group, whereas in the transplanted patients all antibody levels were <200.

Four weeks after vaccination, 36 of 40 patients (90%) showed an increase of antibody levels of more than fourfold ($P<0.001$), compared to 75% after a postvaccination period of 6 months and 60% after 1 year (Figure 1). The percentage of patients with antibody levels after vaccination >200 was similar:

![Graph showing immune response after vaccination](https://academic.oup.com/ndt/article-abstract/11/3/468/1839937)

AB = antibody, NS = idiopathic nephrotic syndrome, CRF = chronic renal failure, HD = haemodialysis, PD = peritoneal dialysis, TX = after transplantation.

* responders - increase in antibody levels of at least two twofold dilution steps and postvaccinal antibody levels above 200
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88% after 4 weeks, 73% after 6 months, and 65% after 1 year.

Whereas the immune response after 4 weeks was sufficient in most of the patients (88%), the percentage of responders decreased with every period of observation: 68% after 6 months, and 48% after 1 year. No significant differences were observed between the four groups, nor between patients with or without proteinuria.

Revaccination

Twenty-two of the vaccinated patients (55%), whose antibody titres decreased to prevaccination level, received a booster vaccination (Table 3). The revaccination was less effective than the first immunization: 19 patients showed antibody levels >200 and 10 patients (45%) had a significant response to the vaccine 4 weeks after revaccination. However, the decrease of antibody levels measured after 6 months was much more pronounced, leaving 15 of 22 patients (68%) probably without sufficient protection.

Side-effects

Generally, both vaccinations were well tolerated: minor side-effects, like itching and burning at the injection site were noted in only four patients after the first vaccination.

Discussion

Patients with renal diseases such as the idiopathic nephrotic syndrome, chronic renal failure, patients after renal transplantation and those undergoing dialysis have a high risk of SP infections [14,15], and therefore vaccination seems advisable. However, recommendations for immunization against SP of these risk groups are discussed controversially [5,6].

Previous reports evaluating the efficacy of the 14-valent vaccination in patients with renal diseases have reported a weak and delayed immune response in adult patients with chronic renal failure and on dialysis [16,17]. In children with nephrotic syndrome, the immune response was equal to controls at up to 6 weeks after vaccination and independent of relapse or remission [18]. Later reports have shown a decline of antibody levels at 1 and 5 years after vaccination respectively [3,4]. However, no previous studies have evaluated the efficacy of the currently available 23-valent pneumococcal vaccine in patients with renal diseases.

According to Schiffmann [19], antibody concentrations of about 200–300 ngN/ml should be regarded as normal preimmunization level, and after immunization, antibody concentrations of about 1500–2000 ngN/ml as a positive response to the pneumococcal vaccine with protective effect. This corresponds to a four- to eightfold increase of the antibody amount. These results were obtained as geometric mean titres of antibodies to 12 different pneumococcal capsular polysaccharide antigens contained in a 14-valent vaccine [19]. Although we used the 23-valent vaccine, we assume that a 4–8-fold increase of the antibody titre is also indicative of a positive response connected with protection. Since prevaccination antibody titres in our test system most frequently ranged around 50, post-vaccination titres of at least 200 were accepted as a positive response, i.e. a probable protective effect. Although the immune response to individual capsular antigens is known to differ widely [20,21], antibodies to single antigens were not measured, since the decision for revaccination was based on overall antibody response. Antibodies to pneumococcal cell wall polysaccharide were found in low concentration and therefore neglected (data not shown).

In our patients, antibody levels against SP infections were low prior to immunization, which corresponds to prevaccination antibody levels found by Spika et al. in 11 of 12 paediatric control subjects [11]. After the first vaccination the immune response was prompt in most patients resulting in a significant increase of

<table>
<thead>
<tr>
<th>AB increase</th>
<th>NS (100%)</th>
<th>CRF (100%)</th>
<th>HD (100%)</th>
<th>PD (100%)</th>
<th>TX (100%)</th>
<th>Total (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks after vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 twofold dilution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps</td>
<td>3 (100%)</td>
<td>7 (100%)</td>
<td>4 (100%)</td>
<td>4 (100%)</td>
<td>4 (100%)</td>
<td>22 (100%)</td>
</tr>
<tr>
<td>Responders*</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>19 (86%)</td>
</tr>
<tr>
<td>6 months after second vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 twofold dilution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Responders</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7 (32%)</td>
</tr>
</tbody>
</table>

AB, antibody; NS, idiopathic nephrotic syndrome; CRF, chronic renal failure; HD, haemodialysis; PD, peritoneal dialysis; TX, after transplantation.

*Responders, increase in antibody levels of at least 2 twofold dilution steps and postvaccinal antibody titres > 200.
antibody titres in 83% of patients within 4 weeks. However, protection from pneumococcal disease also implicates maintenance of antibody levels >200. Similar to previous studies in immunocompromized children and adults [3,22], we observed a rapid decrease in antibody levels in many patients as early as 6 months after vaccination, leaving roughly 50% of them without immune protection after 1 year. In contrast, after vaccination antibody levels for most pneumococcal vaccine types remain elevated at least 5–10 years in healthy adults, a more rapid decline may occur in children [1].

The possible causes for a rapid antibody decline after immunization of patients with chronic renal diseases are multiple. First, polysaccharides in general are weak antigens. Second, it has been stated that the nephrotic syndrome is an immunologically mediated disease with generally diminished humoral and cellular immune function [14]. However, our patients with nephrotic syndrome were vaccinated during remission. Although it has been difficult to demonstrate consistent abnormalities in immune function with the tests currently available [15], we must assume that an abnormal immune response is present during remission, explaining the rapid antibody decline. Proteinuria in nephrotic range is considered as a risk factor leading to excessive urinary losses of serum immunoglobulins. Like other investigators [11], we found no differences in antibody response between two proteinuric CRF patients and non-proteinuric patients. Third, disruption of mucocutaneous barriers, lymphocytopenia with decreased T- and B-cell populations and immuno-suppressive medications like corticosteroids or cyclosporin are known to inhibit immune responsiveness in patients with chronic renal failure [14]. Finally, continuous immunoglobulin losses via the peritoneal membrane may contribute to the immune deficiency in patients undergoing peritoneal dialysis [23].

Although re-vaccination after 3–5 years should be considered for children with nephrotic syndrome ... who would be ≤ 10 years old at revaccination’ [2], the indication for booster vaccination in children with renal diseases is not clearly defined. No significant further increases in antibody titres but more severe local reactions after revaccination with a 12-valent pneumococcal vaccine were reported in healthy children [24]. In a study using the 14-valent pneumococcal vaccine (Pneumovax) in 33 adult renal transplant recipients and 17 haemodialysis patients, revaccination provoked no serious side-reactions, but the immune response observed after revaccination was weaker compared to the primary vaccination [25]. We did not note any side-effects after the second vaccination. However, we observed a dramatic decrease in protective antibody titres within 6 months in almost all of our patients comparable to other studies [17,25,26]. Longer revaccination periods of at least 2 years might be more effective in producing a more sustained protection against SP infections [26].

In summary, patients with chronic renal disease have a low prevalence of protective antibody levels against pneumococcal infections. The currently available 23-valent vaccine with capsular polysaccharides was without major side-effects and was highly effective in producing a significant immune response at 4 weeks after vaccination, but failed to produce protective antibody titres over more than 1 year in about one-half of all patients. Therefore, antibody levels in patients with renal diseases should be monitored after vaccination, and revaccination should be considered on an individual basis. To evaluate the efficacy of a booster vaccination and the optimal time for revaccination, additional studies are desirable. The high efficacy of polysaccharide vaccines conjugated to appropriate protein antigens has been demonstrated in normal subjects [27,28]. Hopefully, a future protein-conjugated vaccine can produce a more sustained response in patients requiring protection from pneumococcal infection.

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References

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