Functional and immunological studies in children with chronic renal failure: the effects of uremia and dialysis treatment
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Chapter 6

Impaired antibody response to pneumococcal polysaccharide vaccine in children with renal disease.

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ABSTRACT

Pneumococcal vaccination is recommended in children with chronic renal diseases. Protection to infections with *S. pneumoniae* is related to the post-vaccination antibody titers. We investigated the anti-pneumococcal polysaccharide antibody response in children with chronic renal disease. Ten children treated with peritoneal dialysis (PD) were investigated, 7 children on hemodialysis (HD), 7 children after renal transplantation and 3 children with nephrotic syndrome without renal failure. Blood samples were collected before immunization with 23-valent pneumococcal polysaccharide vaccine and at one and six months thereafter. IgG, IgG₁ and IgG₂ antibody titers against pneumococcal capsular serotypes 3,4,6B,9V,14,19F and 23F were measured by ELISA. Transplanted children showed a lower antibody increase after vaccination for serotypes 9V and 23F compared to PD children (p<0.05). A sufficient anti-pneumococcal immune response, defined as an absolute post-immunization level of > 20 U/mL in 5 or more out of seven serotypes, was found in 11 out of 27 (41%) children. No significant differences were found among the groups. Seven children (2 HD, 2 PD, 2 Tx and 1 NS) were non-responders, defined as a post-immunization level below 20 U/mL and a less than two-fold increase of the antibody titer in five or more serotypes.

Non-responders after pneumococcal vaccination were found in a substantial number of children with renal disease. After renal transplantation the increase in antibody titer was lower than in PD children for serotypes 9V and 23F.
INTRODUCTION

Pneumococcal polysaccharide vaccination is usually recommended in children with chronic renal failure (CRF) as in several other chronic illnesses, although the incidence of vaccine-preventable diseases in these children is not really known, [1-3]. This recommendation is based mainly on data from adult patients. A higher risk of pneumococcal infections has been reported in adult patients with CRF, either on dialysis treatment or after a renal allograft [4-6]. Few studies have been performed on the antibody response after pneumococcal vaccination in children [7,8]. The results of these studies were conflicting, partly because of different assay methods used. Despite the current recommendation of pneumococcal vaccination in children with CRF, this vaccine is not uniformly given by all pediatric nephrologists [9]. This is probably, because invasive pneumococcal disease is often not considered a significant problem in children with renal disease. However, evidence of increasing resistance of Streptococcus pneumoniae to antibiotics has been reported [10,11]. This might lead to more severe infections.

Reduced serum IgG and subclasses levels have been demonstrated in children with CRF [12]. Low IgG₂ levels have been associated with a higher prevalence of reduced antibody response to polysaccharide antigens [13]. The preponderance of IgG₂ antibody response to pneumococcal capsular polysaccharide antigens is more pronounced in older individuals in comparison with children [14]. No information is available on the IgG₁ and IgG₂ antibody response to polysaccharide antigens, neither in children nor in adults with CRF.

In the present study we analyzed the IgG, IgG₁ and IgG₂ antibody response to the 23-valent pneumococcal polysaccharide vaccine in children with renal disease.

PATIENTS AND METHODS

Twenty-seven children were analyzed. Ten children were treated with peritoneal dialysis (PD), 7 with hemodialysis (HD), 7 children had undergone a renal transplantation (Tx) and 3 children were in remission from a nephrotic syndrome (NS), and had no renal failure. Patient characteristics are summarized in Table 1. No significant differences in age were found among all groups. The primary renal diseases are given in Table 2. All children were immunized with 23-valent pneumococcal polysaccharide vaccine (Pneumovax®, Merck, Sharp & Dohme, Haarlem, The Netherlands). Blood samples were collected before immunization and after 1 and 6 months. Serum samples were stored at -20°C until use.

Anti-pneumococcal antibody assay

Serum IgG, IgG₁ and IgG₂ anti-pneumococcal antibodies to seven pneumococcal serotypes, including strong immunogens (type 3, 4 and 9V), intermediate (type 14 and 19F) and weak antigens (type 6B and 23F), were quantitated by ELISA [13]. The IgG₁ and IgG₂ antibody titers were measured in the one-month post-vaccination serum samples for serotype 9V and 14 whereas total IgG levels were measured in all samples for all serotypes. Pre- and post-immunization samples from children were analyzed simultaneously and in
duplicate. All serum samples were preincubated overnight, with excess of free common cell wall polysaccharide (CPS) to remove anti-CPS antibodies [15].

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
<th>Tx</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.7 (3.6-17.6)</td>
<td>11.9 (4.4-17.3)</td>
<td>13.7 (10.9-17.8)</td>
<td>10.1 (8.9-11)</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>3.3 (0.1-9.2)</td>
<td>2.0 (0.3-9.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L)</td>
<td>-</td>
<td>110 (52-480)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Previous Tx</td>
<td>5</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Interval Tx and vaccination (years)</td>
<td>-</td>
<td>4.1 (0.6-8.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medication</td>
<td>4 pred/ciclo/azat</td>
<td>2 pred/ciclo</td>
<td>1 pred/ciclo</td>
<td>1 pred</td>
</tr>
<tr>
<td></td>
<td>1 pred/ciclo</td>
<td>2 pred/myco/ciclo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are given as medians and ranges.
PD, peritoneal dialysis; HD, hemodialysis; Tx, renal transplantation; NS, nephrotic syndrome
Pred, prednisone; ciclo, cyclosporin; azat, azathioprin; myco, mycophenolate mofetil.

A serum sample from a healthy non-vaccinated adult was included in every ELISA run as a control. Microtiter plates (Greiner Labortechnik, Langertal, Germany) were coated overnight with pneumococcal capsular polysaccharides in saline solution at 37°C. Thereafter, plates were washed (PBS/ Tween-20, 0.05% vol/vol) and incubated (2 hr at 37°C) with serial dilutions of sera in PBS, 0.05% Tween-20, and 1% bovine serum albumin (vol/vol). Subsequently, plates were washed and incubated with either alkaline phosphatase labeled goat anti-human IgG (Biosource, Camarillo, CA) or with peroxidase labeled subclass-specific murine anti-human IgG1 (MH161-1ME) or IgG2 (MH162-1ME) monoclonal antibodies (moAb) for 2 hr at 37°C (the latter two from the CLB Sanquin Blood Supply Foundation, Amsterdam, The Netherlands). After washing and incubation with enzyme substrate for 10 to 20 min at 37°C, absorbance was measured using a Titertek Multiscan (Flow Laboratories, Irvine, UK). The antibody concentrations in patient samples were calculated using a reference serum which contains 2.36 µg IgG/mL anti-type 3, 4.1 µg IgG/mL anti-type 4, 16.9 µg IgG/mL anti-type 6B, 6.9 µg IgG/mL anti-type 9V, 27.8 µg IgG/mL anti-type 14, 13 µg IgG/mL anti-type 19F and 8.1 µg IgG/mL anti-type 23F [16,17]. This preparation contains 0.83 µg IgG1/mL and 6.1 µg IgG2/mL anti-type 9V and 2.87 µg IgG1/mL and 21.23 µg IgG2/mL anti-type 14 [18]. The antibody concentrations of samples
were expressed relative to this reference pool (100 U/mL; 100% assigned for each serotype).

Table 2. Primary renal disease.

<table>
<thead>
<tr>
<th>Condition</th>
<th>PD</th>
<th>HD</th>
<th>Tx</th>
<th>NS</th>
</tr>
</thead>
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<tr>
<td>Urologic malformation</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Glomerulopathy</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Congential disease</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other diseases</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


Definitions of response and non-response to pneumococcal vaccine

Anti-pneumococcal antibody levels are given in U/mL. The relative increase was calculated as the ratio of the postvaccination titer (after 1 month) and the pre-immunization titer. An adequate response to a given serotype was defined as a ratio of 2 and a postimmunization titer of 20 U/mL. An anti-pneumococcal antibody titer higher than 20 U/mL prior to immunization, was regarded as sufficient. An adequate response to pneumococcal vaccination was defined as a sufficient response in 5 or more out of the 7 serotypes analysed. The response to an individual pneumococcal serotype was considered low or absent when the post-immunization titer remained <20 U/mL (i.e. 20% of the antibody concentration in the reference hyperimmune plasma pool of healthy adult volunteers, immunized with pneumococcal vaccine [17]). The child was considered as non-responder to pneumococcal vaccination when the post-immunization IgG antibody level was less than 20 U/mL and the antibody titer increase was less than two-fold in five or more out of the 7 serotypes analysed.

Statistical analyses

Differences between groups were tested with the Kruskall-Wallis one-way analysis of variance. The Fisher's exact test was performed to compare frequencies between groups. Two-sided P values <0.05 were considered significant. Differences between two time-points were tested with paired Wilcoxon tests.
RESULTS

Before immunization, antibody titers for IgG were sufficient (> 20 U/mL) in 12 (44%) children for pneumococcal serotype 3, in 5 (19%) for type 4, in none of the children for type 6B, in 10 (37%) for type 9V, in 4 (15%) for type 14, in 5 (19%) for type 19F and in 2 (7%) children for type 23F. Only one child had sufficient IgG antibodies in 5 or more out of seven serotypes. No differences were found in the median pre-immunization levels between the groups.

Figure 1. The median IgG antibody levels to six pneumococcal serotypes, before vaccination and after 1 and 6 months. PD, peritoneal dialysis; HD, hemodialysis; Tx, after renal transplantation; NS, nephrotic syndrome.

— PD, — HD, — Tx, — NS.
Anti-pneumococcal antibody response

The IgG antibody titers increased after immunization. The differences between pre-immunization and post-immunization titers were statistically significant for all serotypes (p<0.05). The median IgG anti-pneumococcal antibody titers, before and after vaccination, are shown in Figure 1 for each group. The increase in the postvaccination/prevaccination ratio, in all children together, was two or more for all analysed serotypes, with exception of type 6B (Table 3). Significant differences between the groups were found for type 9V and type 23F. Renal transplanted children showed a significantly lower increase of antibodies for these two serotypes compared to the children on peritoneal dialysis. For the hemodialysis children significance was not reached. The absolute post-immunization levels after one month are shown in Table 4. No significant differences were found among all groups.

### Table 3. The ratio of post/pre-vaccination anti-pneumococcal IgG antibody levels.

<table>
<thead>
<tr>
<th>Type</th>
<th>PD</th>
<th>HD</th>
<th>Tx</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>13</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>6B</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9V</td>
<td>15</td>
<td>26</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>19F</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>23F</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

Results are given as medians and ranges. *p<0.05 when compared to PD children.

### Table 4. IgG antibody response, 4 weeks after pneumococcal vaccination.

<table>
<thead>
<tr>
<th>Type</th>
<th>PD</th>
<th>HD</th>
<th>Tx</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>61</td>
<td>142</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>69</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>6B</td>
<td>0.5</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9V</td>
<td>242</td>
<td>283</td>
<td>43</td>
<td>350</td>
</tr>
<tr>
<td>14</td>
<td>43</td>
<td>51</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td>19F</td>
<td>25</td>
<td>12</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>23F</td>
<td>15</td>
<td>15</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

Results are given as medians (range) U/mL.

A sufficient response to Pneumovax was found in 11 out of 27 (41%) children: 2 HD children 6 PD children, 2 children with a renal transplant, and 1 child with a nephrotic syndrome. No significant differences were found between the groups. The number of
children with low post-vaccination antibody titers are shown in Table 5. Seven children (2 HD, 2 PD 2 Tx and 1 NS) showed a post-immunization IgG antibody level of less than 20 U/mL and a less than two-fold increase of the antibody titer in five or more out of the seven analysed serotypes. These children were therefore considered as non-responders. The prevalence of non-responders was not significantly different among the groups. The median age of the children who responded normal to Pneumovax was 14.8 (range 3.6-17.6) compared with 11.0 (4.9-17) in the group who were defined as non-responder. This difference was not significant.

<table>
<thead>
<tr>
<th>Type</th>
<th>3</th>
<th>4</th>
<th>6B</th>
<th>9V</th>
<th>14</th>
<th>19F</th>
<th>23F</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (n=10)</td>
<td>0</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>HD (n=7)</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tx (n=7)</td>
<td>3a</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>NS (n=3)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total (n=27)</td>
<td>5</td>
<td>9</td>
<td>25</td>
<td>1</td>
<td>8</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

Low antibody response is defined as post-vaccination (4 weeks after immunization) titer of < 20 U/mL.

Six months after immunization the median IgG antibody titers for all serotypes were significantly lower compared to one month after vaccination (Figure 1). The median antibody titer of serotype 3 declined with 58% (p=0.001), type 4 with 64% (p=0.002), type 9V with 71% (p=0.0005), type 14 with 19% (p=0.04), type 19F with 27% (p=0.03), and type 23F with 33% (p=0.005). Eight children (4 PD, 1 HD, 2 Tx, 1 NS) had low antibodies against 5 or more out of 7 serotypes, six months after vaccination. Seven of them were the primary non-responders and only one developed low antibody levels.

The median IgG1 antibody level, one month after vaccination, to serotype 9 was 63 (range 7-396) U/mL. The IgG2 antibody level to serotype 9V was 15 (1-948) U/mL. The IgG1 level against serotype 14 was 4 (1-1593) U/mL, the IgG2 level 29 (3-8162) U/mL. No significant differences were found between the groups. Seven children out of 27 (26%) showed a low postvaccination IgG1 level (≤ 20 U/mL) to serotype 9V and 17 (63%) a low IgG2 level. Six children (22%) had both, a low IgG1 and IgG2 level. To serotype 14, 23 children (85%) showed a low IgG1 response and 13 (48%) a low IgG2 response. Eleven children (41%) had low levels of both, IgG1 and IgG2 antibodies. No significant differences were found among the groups (Figure 2).
Anti-pneumococcal antibody response

![Diagram](Figure 2. The IgG1 and IgG2 antibody response to serotype 9V and 14, 4 weeks after pneumococcal vaccination. The lower limit of normal levels (U/mL).)

Table 6. Prevalence of reduced IgG and subclass levels.

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (n=10)</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HD (n=7)</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tx (n=7)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NS (n=3)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reduced IgG and subclass levels were defined as <2.5 percentile of normal range [19,20]

The number of children with reduced serum IgG and subclass levels are shown in Table 6. Reduced levels were defined as under the 2.5 percentile of published normal values according to age [19,20]. Fourteen children had reduced serum IgG or subclass levels. Four out of seven children, who were considered as non-responders, had reduced IgG or subclass levels (1 child with reduced serum IgG2 and/or IgG4, 1 child with reduced serum IgG1, and 1 child with reduced total serum IgG). IgG subclass deficiency was not significantly associated with low IgG1 or IgG2 antibody response against serotype 9V or 14.

**DISCUSSION**

The present study has demonstrated that more than one quarter of the children with chronic renal disease, immunized with the 23-valent unconjugated Pneumococcal vaccine did not reach sufficient IgG antibody titers. The IgG1 or IgG2 anti-pneumococcal response was low in even a higher number of children. No differences were found in the
prevalence of "non-responders" between PD, HD, and renal transplanted children. However, the IgG antibody increase in renal transplanted patients was lower for serotype 9V and 23F.

Anti-capsular polysaccharides antibodies are important for the defence against encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae type b [21-25]. Pneumococcal polysaccharide antigens behave as thymus-independent-type 2 (TI-2) antigens. Regulatory T-cells are not necessary for this immune response, but they control the magnitude of antibody titers [26-28]. Furthermore, immunological memory formation does not occur after exposure to TI-2 antigens [29-31]. It is well established that the ability to mount an antibody response to polysaccharides of encapsulated bacteria matures much later than the ability to mount antibody responses to protein antigens [32-35]. Thus, children under the age of two years have poorly developed anti-pneumococcal defence mechanism. The antibody response to pneumococcal polysaccharides is subclass restricted: young children give mainly an IgG1 response, whereas older children and adults display a more IgG2 restricted response [14,36]. IgG1 anti-polysaccharide antibodies may be less protective compared with IgG2 antibodies [36,37]. In the absence of antibodies to capsular polysaccharide, phagocytosis and killing do not occur [38]. For an adequate phagocytosis of pneumococci, binding of the IgG opsonized microorganisms with the Fc-receptor (FcγR) of effector cells is necessary. Furthermore, the individual susceptibility to pneumococcal infections is determined by a functional polymorphism of the FcγRIIa [39,40].

Pneumococcal disease is most often seen in children and elderly [41]. Antibody deficiencies, and to a lesser extent complement deficiencies, have been found to predispose for pneumococcal infections [42,43]. Children with chronic renal failure are considered to be at high-risk for pneumococcal infections although the exact incidence of pneumococcal infections in children with chronic renal failure is not documented [44]. In adult patients, data on frequency of pneumococcal infections are available in HD and post renal transplants [4-6,45]. The overall incidence of S. pneumoniae infections is probably underestimated because it is a localized infection with negative blood cultures in a high percentage of infected persons, which is in contrast to infections with Haemophilus influenzae [46].

Effective prevention of pneumococcal infections can be achieved by immunizations. Vaccination is recommended for children with chronic renal disease [1-3,9]. Fuchshuber et al. showed that the immune response to the 23-valent pneumococcal vaccine was sufficient in the majority of children with chronic renal disease, but declined rapidly within 6 months [7]. On the other hand, Furth et al. showed that pediatric patients with chronic renal disease have an adequate IgG antibody response to pneumococcal vaccine (serotype 3 and 14 were analyzed) and antibody levels remained stable during one year thereafter [8]. Pneumococcal polysaccharide vaccines are contaminated with variable levels cell-wall-polysaccharides (CPS). Anti-CPS antibodies increase after vaccination but they are not protective against pneumococcal infections [47]. In the study of Fuchshuber et al., anti-cell-wall polysaccharide antibodies (anti-CPS) were not removed. This might have given an overestimation of protective anti-pneumococcal antibody levels. Our results are not in accordance with those of Furth and Fuchshuber. We found that only 40% of the children displayed an adequate IgG
antibody response after vaccination and that 25% of the children were non-responders. The reason for this discrepancy might be the differences in methods used, in renal disease and/or age and differences in the definition of a sufficient or reduced response. The results of the present study are in agreement with those of Genner et al. who also found lower antibody responses in children after cardiac transplantation, especially when transplantation was performed in early childhood [48]. The incidence of non-responders in children with recurrent upper respiratory tract infections, analyzed by the same methods as used in here, was similar to this study [29]. However, these authors found a higher number of non-responders in children with respiratory tract infections combined with reduced Ig (IgG, IgG1, IgG2 or IgA) levels than with normal Ig levels. In a previous study we have shown that serum IgG2 deficiency is frequently seen in children with chronic renal failure [12]. In this study, about half of the children displayed low IgG or subclass levels, but the number of non-responders was not different between children with normal or low serum IgG or subclass levels. The reason for this difference might be explained by the presence of children with IgA deficiencies in the group with upper respiratory tract infections and not in our group. Furthermore, the underlying immunological disturbance in children with recurrent respiratory infections is probably different to that in children with chronic renal disease. We did not document the occurrence of recurrent respiratory tract infections in our patients but it was not a major clinical problem.

The IgG subclass response to vaccination in children with renal disease has not been reported previously. Isolated IgG1, IgG3 or IgG2 deficiency is not associated with an anti-capsular polysaccharide antibody deficiency whereas children with serum IgG2 deficiency show variable anti-pneumococcal antibodies upon vaccination [49-51]. Sanders et al. found low IgG2 antibody levels to 4 or 5 out of five serotypes in 43% of children with recurrent respiratory tract infections and normal serum Ig levels, whereas >90% (14/15) of the children with serum IgA or IgG2 deficiency failed to mount an adequate IgG2 antibody response. In the present study, we measured the IgG1 and IgG2 post-vaccination antibody titers only to serotype 9V and 14. No significant differences were found in both, the IgG1 or IgG2 response of children with normal or reduced serum IgG or subclass levels. Thus, the presence or absence of low serum Ig levels is not the only factor that is involved in the capacity to mount an adequate antibody response to pneumococcal polysaccharides. It is speculative if T-cell helper function defects might contribute to the reduced antibody response in our patients.

Vaccination with a protein conjugate vaccine converts the response from a thymus-independent to a thymus dependent response and induces B-cell memory. It has been shown that the pneumococcal conjugate vaccine is a good primer for subsequent unconjugated vaccination [52-54]. Children who were non-responder to the unconjugated vaccine mounted an antibody response after vaccination with the conjugate vaccine [52]. The conjugate vaccine might therefore be advantageous in children with chronic renal disease.
In conclusion, a considerable number of children on dialysis and after renal transplantation showed a reduced response to pneumococcal polysaccharide vaccine. Transplanted patients showed the lowest antibody response to serotype 9V and 23F. The administration of a protein-conjugate pneumococcal vaccine, followed by the unconjugated vaccine might give better protection against pneumococcal infections in patients with chronic renal diseases.

ACKNOWLEDGMENT
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