Functional and immunological studies in children with chronic renal failure: the effects of uremia and dialysis treatment
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Chapter 4

Immunoglobulins in chronic renal failure of childhood: effects of dialysis modalities.

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ABSTRACT

It is not clear whether low serum levels of IgG (subclasses), previously demonstrated in children on peritoneal dialysis (PD), are related to the PD procedure or to factors associated with chronic renal failure (CRF). The aim of our study was to analyze the effect of PD on serum and PD effluent (PDE) IgG and subclass levels in children with end stage renal failure.

We measured albumin, IgG, IgA, IgM and IgG subclasses in serum and PDE from children on PD (n=40) and compared serum values with those of children treated with hemodialysis (HD, n=23) or presenting with CRF but not yet dialyzed (CRF, n=63), and with a group of healthy controls (HC, n=67). Sixteen PD children could be followed sequentially from before starting PD and eight during a peritonitis episode.

Forty percent of the PD children showed reduced serum IgG₂ levels (p=0.0003), compared with 35% in HD (p=0.006), 33% in CRF (p=0.001) and 9% in HC children. IgG₁ deficiencies were observed in 25% of PD patients (p<0.0001), 4% of HD (ns), 16% of CRF (p=0.0005) and 0% of HC children. IgG₃ and IgG₄ deficiencies were observed less frequently. Peritoneal clearances were similar for total IgG, IgG₁, IgG₂ and IgG₄, but lower for IgG₃ (p<0.05). No relationships were found between clearances and age or duration of PD treatment. Total IgG (p=0.003) and IgG₁ (p=0.002) levels declined just after starting PD. Peritonitis was associated with temporarily increased peritoneal loss of Ig while the serum concentrations were unaffected. No significant relation was found between the peritonitis incidence and reduced IgG or subclasses. However, all children with two or more peritonitis episodes per year had a reduced Ig level.

Although the mean serum concentrations of immunoglobulins were normal in all studied groups, a deficiency of one or more IgG subclasses was present in all groups with renal failure, suggesting inhibition of their synthesis by the uremic state. Ig deficiencies were more frequently found in PD, likely caused by protein loss in PDE. A high peritonitis incidence was associated with reduced serum Ig levels.
INTRODUCTION

Children on peritoneal dialysis (PD) have a higher incidence of peritonitis than adults. This results in a greater morbidity and treatment failure [1-6]. A relationship with poor hygiene and technique is not probable because children on PD have a similar distribution of causative microorganisms as adults [1]. A disturbed immune function might be involved since the presence of low serum levels of IgG and/or subclasses have been described in children on PD [7-10]. It has been reported that Ig deficiency was absent before the start of PD and that the low serum levels on PD would probably result from peritoneal leakage [8]. This opinion is not shared by others who claimed that serum Ig deficiency is already present before starting PD and that this phenomenon is dependent on factors related to chronic renal failure (CRF) [11]. Our study was designed to clarify these conflicting results. Therefore, we analyzed serum and dialysate concentrations of albumin, IgG, IgA, IgM and IgG subclasses in a cross-sectional study in children varying in age and duration of PD. Serum concentrations were compared with those in children on hemodialysis (HD), children who were not yet undergoing dialysis (CRF) and healthy children (HC). In addition, a longitudinal study was done in children who were followed from before the initiation of PD for periods up to 12 months on PD. PD children were also studied in the acute phase of a peritonitis episode and during follow-up.

PATIENTS AND METHODS

Forty children treated with PD, 23 children on chronic HD, 63 children with CRF not yet dialyzed, and 67 children who underwent a minor surgical procedure (healthy controls, HC) were studied. Patients were obtained from all four pediatric dialysis centers in the Netherlands. The mean, standard deviation (SD), median and range of age, duration of PD or HD treatment are listed in Table 1. Also listed in Table 1 is the incidence of peritonitis for PD patients and the estimated glomerular filtration rate (GFR) for CRF children. Thirty-eight percent (24 out of 63) had a moderate renal insufficiency (25 to 50 ml/min/1.73 m²), 25% (16 out of 63) a severe renal insufficiency (10 to 25 ml/min/1.73 m²) and 37% (23 out of 63) preterminal renal failure (≤ 10 ml/min/1.73 m²). The renal diseases leading to CRF are summarized in Table 2. Sixteen children treated with PD were studied before starting PD and were followed longitudinally. Eight children with a peritonitis episode were studied at the time of presentation, after 14 and 28 days, and also 3 months before or after the peritonitis episode. The PD treatment consisted of nightly intermittent PD (NIPD) in all patients. From 20 PD children a standard peritoneal permeability analysis (SPA) was routinely performed. In this modification and extension of the peritoneal equilibration test (PET) the transport of low molecular weight solutes, fluid transport and protein clearances were determined [12,13].
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
<th>CRF</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>23</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.9</td>
<td>12.3</td>
<td>10.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Median</td>
<td>4.9</td>
<td>4.6</td>
<td>5.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Range</td>
<td>10.1</td>
<td>12.7</td>
<td>11.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>Mean</td>
<td>2.4</td>
<td>3.0</td>
<td>24</td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>1.9</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Range</td>
<td>1.35</td>
<td>2.2</td>
<td>4-50</td>
<td>0-7.9</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>Mean</td>
<td>0.15-8.9</td>
<td>0.4-7.2</td>
<td>24</td>
</tr>
<tr>
<td>Median</td>
<td>2.2</td>
<td>1.9</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Range</td>
<td>0.15-8.9</td>
<td>0.4-7.2</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Number with proteinuria</td>
<td>Mean</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>SD</td>
<td>1.2</td>
<td>1.6</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Peritonitis incidence (number per year)</td>
<td>Median</td>
<td>0.8</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean</td>
<td>0.8</td>
<td>0.8</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>SD</td>
<td>0.15-8.9</td>
<td>0.4-7.2</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.15-8.9</td>
<td>0.4-7.2</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.15-8.9</td>
<td>0.4-7.2</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>
| PD: peritoneal dialysis, HD: hemodialysis, CRF: chronic renal failure, HC: healthy controls. SD = standard deviation. GFR: glomerular filtration rate, approximated by the formula: 40 x Height(cm)/Plasma creatinine (µmol/l). Peritonitis incidence is defined as the number of episodes per patient year. *Number of patients with proteinuria defined as > 2 grams per day.

### Table 2. Primary renal disease

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
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<th>CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urologic malformation</td>
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<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Glomerulopathy</td>
<td>11</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Haemolytic uremic syndrome</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Congenital disease</td>
<td>6</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Other diseases</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>40</strong></td>
<td><strong>23</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

Abbreviations: see fore mentioned in Table 1.

Glomerulopathy: 15 children with focal segmental glomerulosclerosis, 6 congenital nephrotic syndrome, 2 rapidly progressive glomerulonephritis, 1 lupus nephritis, 1 Henoch-Schonlein-purpura nephritis and 1 Alport glomerulopathy. Metabolic disease: 3 children with cystinosis and 1 oxalosis. Congenital disease: 10 children with renal dysplasia, 9 nephrophthiosis, 6 polycystic kidney disease, 2 tuberous sclerosis and 1 extrophy vesicae. Other diseases: 5 children with acute tubular necrosis, 1 bilateral Wilms tumor.
Measurements

From all groups serum samples were taken for measurement of the albumin, total IgG, IgA, IgM and IgG subclass levels. Normal ranges for the serum concentrations of IgG and its subclasses increase with aging. Therefore, reduced levels were defined as under 2.5 percentile of published normal values according to age [14,15]. In the PD group albumin, Ig and subclasses were also determined in the PD effluent (PDE) obtained after a four hour dwell (40 ml/kg) with a 1.36% glucose solution (Dianel®, Baxter BV, Utrecht, The Netherlands). Albumin, total IgG and IgA in serum and dialysate effluent were measured by nephelometry on a Cobas-bio nephelometer analyzer (La Roche Diagnostics, Basel, Switzerland). IgG subclasses and IgM in serum and dialysate were measured by enzyme-linked immunosorbent assay (ELISA) [16]. Serum and dialysate samples were stored at -20 °C until use. The study was approved by the Medical Ethical Review Committee of the hospital and written informed consent was obtained from children and/or parents.

Calculations

Peritoneal clearances (Cl_{perit}) were calculated according to the following equation:

\[ Cl_{perit} (\text{ml/min/1.73 m}^2) = (D \times V/S \times t) \times (1.73/BSA) \]  

(eq. 1)

in which D and S are the concentrations of albumin or the immunoglobulins in the dialysate and serum, V is the volume of the drained bag, t the dwell time and BSA the body surface area [12, 13].

An approximation of the GFR from the children with chronic renal failure was calculated by the Schwartz formula:

\[ \text{GFR} = 40 \times H/ P_{cr} \]  

(eq. 2)

in which \( P_{cr} \) is the plasma creatinine concentration in \( \mu \text{mol/l} \) and H the height in centimeters [17].

Statistical analysis

Differences between patient groups were first tested with the Kruskal-Wallis one-way analysis of variance. In case of significant differences the Mann-Whitney test was used. The Fisher’s exact test was performed to compare frequencies between groups. Changes within groups according to time (longitudinal data) were tested with Friedman trend analysis and the paired Wilcoxon test. For relationships between measurements, the Spearman rank sum correlation test was employed. Two sided p-values <0.05 were considered significant [18].
Table 3. Serum Immunoglobulin and albumin levels (gram/liter).

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
<th>CRF</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb</td>
<td>37 (19-43)</td>
<td>41 (30-53)</td>
<td>43 (8-55)</td>
<td>46 (37-54)</td>
</tr>
<tr>
<td>IgG</td>
<td>8.0 (1.8-18.3)</td>
<td>11.9 (4.3-20.5)</td>
<td>10.6 (1.3-26.8)</td>
<td>10.9 (3.9-22.8)</td>
</tr>
<tr>
<td>IgA</td>
<td>1.0 (0.3-4.3)</td>
<td>1.5 (0.4-2.5)</td>
<td>1.4 (0.3-4.1)</td>
<td>1.3 (0.3-7.7)</td>
</tr>
<tr>
<td>IgM</td>
<td>0.8 (0.2-4.2)</td>
<td>0.8 (0.2-2.9)</td>
<td>1.1 (0-2.6)</td>
<td>1.4 (0.6-5.4)</td>
</tr>
<tr>
<td>IgG1</td>
<td>5.1 (1-13.7)</td>
<td>7.6 (3-17.1)</td>
<td>6.1 (0.9-16.7)</td>
<td>8.1 (3.4-14.9)</td>
</tr>
<tr>
<td>IgG2</td>
<td>0.8 (0.2-3.5)</td>
<td>1.3 (0.4-3.5)</td>
<td>1.5 (0-6.7)</td>
<td>1.5 (0-3.8)</td>
</tr>
<tr>
<td>IgG3</td>
<td>0.38 (0.07-1.65)</td>
<td>0.56 (0.13-1.37)</td>
<td>0.45 (0.1-1.47)</td>
<td>0.39 (0.14-1.21)</td>
</tr>
<tr>
<td>IgG4</td>
<td>0.17 (0.01-2.64)</td>
<td>0.13 (0-1.16)</td>
<td>0.25 (0.01-2.76)</td>
<td>0.32 (0.01-2.51)</td>
</tr>
</tbody>
</table>

Results are given in median values and range. Abbreviations: see for mentioned in Table 1.
Alb: albumin. Alb albumin measurement in 30 children. *p<0.001, *p=0.03, *p=0.006, *p=0.02 when compared with HC. alb: PD vs HD p=0.01, PD vs CRF p=0.001. IgG: PD vs HD p=0.005, PD vs CRF p=0.002. IgG1: PD vs HD p=0.0007, HD vs CRF p=0.02. IgG2: PD vs HD p=0.009, PD vs CRF p=0.02. IgG3: HD vs CRF p=0.03.

RESULTS

Cross sectional analysis

The healthy children were younger compared with the other groups (p<0.01), but no significant differences in age were present between the PD, HD and CRF groups (Table 1). The serum concentrations of IgG, IgA, IgM, IgG subclasses and albumin are listed in Table 3. Total IgG (p<0.001), IgA (p=0.03) and IgM (p<0.001) were lower in the PD group compared with HC. Individual IgG concentrations of both groups according to age are shown in Figure 1. Children on HD and children with CRF only had lower serum IgM and albumin levels compared with HC (both p<0.001). The serum concentrations of the subclasses of IgG were lower in the PD than in the HC group for IgG1 (p<0.001), IgG2 (p<0.001) and IgG4 (p=0.02). Individual data for IgG2 are shown in Figure 1. Children on HD had lower IgG4 levels than HC (p=0.02), but higher IgG3 concentrations (p=0.006). The CRF group had lower IgG1 values compared to HC (p<0.001).

Table 4. Prevalence of IgG and subclasses deficiency.

<table>
<thead>
<tr>
<th></th>
<th>Total n</th>
<th>IgG</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>40</td>
<td>5</td>
<td>10</td>
<td>16</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>HD</td>
<td>23</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>CRF</td>
<td>63</td>
<td>4</td>
<td>10</td>
<td>21</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>HC</td>
<td>67</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Deficiency defined as < P25 of normal range [12, 13]. Abbreviations: see Table 1.
IgG: PD vs HC (p=0.006), IgG1: PD (p=0.0001) and CRF (p=0.0005) vs HC, PD vs HD p = 0.04. IgG2: PD (p=0.0003), HD (p=0.006), CRF (p=0.001) vs HC. IgG4: PD (p=0.01) and HD (p=0.001) vs HC. HD vs CRF p = 0.01.
Figure 1. Total serum IgG and IgG₂ in healthy children (HC) and in children with peritoneal dialysis (PD). (-): 2.5th percentile of normal values [12, 13].

The prevalence of serum IgG and subclasses deficiency, defined as values under the 2.5th percentile, is listed in Table 4. The PD group displayed significantly more cases of IgG (p=0.006), IgG₁ (p<0.0001), IgG₂ (p=0.0003) and IgG₄ (p=0.01) deficiencies compared with HC. The HD group had more reduced IgG₂ (p=0.006) and IgG₄ levels (p=0.001) and the CRF group had more IgG₁ (p=0.0005) and IgG₂ (p=0.001) deficiencies. No differences were found between the PD, HD and CRF groups with the exception of IgG₁ which was more often reduced in PD patients compared with HD (p=0.04), and IgG₄ which was more often reduced in the HD group compared with CRF children (p=0.01). IgG₂ deficiency in CRF children with GFRs ≤ 10 ml/min/1.73 m² occurred in 48% (11 out of 23) compared with 13% (3 out of 24) of the children with a clearance between 25 and 50 ml/min/1.73 m² (p=0.01). No difference was found in the prevalence of IgG₂ deficiency in patients with a GFR of ≥ 10 ml/min/1.73 m² compared with a GFR between 11 and 25 ml/min/1.73 m² (44%, 7 out of 16). The percentage of children with proteinuria of more than 2 grams per day was 8% in PD (3 out of 40), 4% in HD (1 out of 23) and 13% (8 out of 63) in CRF patients (Table 1). In the CRF group 13 children had a selective IgG₂ deficiency, and only one of them had a significant proteinuria. However, two or more IgG subclass deficiencies, especially the combination of IgG₁ and IgG₂ and/or IgG₃ were present in 75% (6/8) of the children with proteinuria compared with 4% (2 out of 55) of the children without proteinuria (p<0.0001).
However, CRF children without proteinuria (n=55) had still more IgG\(_1\) (4 out of 55, p=0.038) and IgG\(_2\) (14 out of 55, p=0.025) deficiencies compared with HCs.

No difference was found between the duration of PD treatment in children with reduced serum IgG\(_1\) or IgG\(_2\) levels (median 1.3 years) or those with normal values (median 1.4 years).

![Figure 2](image2.png)

*Figure 2. Relationship between peritoneal IgG clearance and the MTAC\(_{\text{crea}}\) in PD children. MTAC\(_{\text{crea}}\): mass transfer area coefficient of creatinine calculated according to the Waniecki method. (r=0.72, p=0.0003, 95% CI: 0.4-0.9).*

The median peritoneal clearance of albumin was 76 (5 to 216) µl/min/1.73m\(^2\). For the immunoglobulins the following values were found: IgG, 52 (18 to 218) µl/min/1.73m\(^2\); IgA, 37 (2 to 250); IgM, 12 (0.3 to 90). The clearance of IgG\(_1\) was 43 (17-278) µl/min/1.73m\(^2\), IgG\(_2\): 48 (19-183), IgG\(_3\): 35 (1.9-397) and IgG\(_4\): 40 (7-329). No relationship was found between

![Figure 3](image3.png)

*Figure 3. Peritoneal IgG clearances in PD children with IgG\(_1\), IgG\(_2\) or no IgG subclass deficiency (def). (—) median. *: p=0.025*
peritoneal clearances and age or duration of PD treatment when corrected for body surface area. A positive correlation was found between the IgG clearance and the mass transfer area coefficient of creatinine (MTACcr), calculated according to the Waniowski method [19] (Figure 2). The median peritoneal IgG clearance in children with a IgG1 deficiency was 131 (24-218) µl/min/1.73m² compared with 49 (18 to 69) µl/min/1.73m² in children with a IgG2 deficiency (p=0.025) (Figure 3). No difference was found between the peritoneal IgG clearance of children with IgG2 deficiency or with no IgG subclass deficiency.

**Longitudinal analysis**

Serum values of albumin, IgG, IgA, IgM and IgG subclasses did not change with the duration of PD treatment. However, the serum concentrations of total IgG and IgG1 were significantly lower after one month PD treatment compared with just before starting dialysis treatment (p=0.003 for IgG and p=0.002 for IgG1). The time course of serum IgG is shown in Figure 4. This temporary decrease was not found for the other IgG subclasses and also not for albumin, IgA and IgM. No significant alteration of IgG and albumin concentrations was found in PDE during PD treatment (Data not shown).

![Graph](image)

*Figure 4. Serum IgG in relation to the duration of peritoneal dialysis (PD) treatment. *: p=0.003

**Peritonitis**

The mean peritonitis incidence was 1.2 episode per patient per year (median 0.8, range 0 to 8). Gram positive organisms were responsible for 43% of the peritonitis episodes. Gram negative microorganisms were cultured in 19% of the episodes, several different bacteria in 18% and yeast or fungi in 2%. In 18% of the cases the culture was negative. Serum albumin decreased during peritonitis and reached the lowest level 14 days after presentation (p=0.03, Figure 5). However, serum IgG and IgA showed no significant decline (Figure 5). This was also found for the IgG subclasses. Serum IgM was higher at the first day of presentation compared with the noninfectious state and decreased to normal
levels after one month. Peritoneal effluent concentrations of albumin (p=0.04), IgG (p=0.008), IgA (p=0.008), IgM (p=0.008) and IgG subclasses (IgG1:p=0.02, IgG2:p=0.02, IgG3: p=0.03, IgG4:p=0.02) were all higher at the time of peritonitis presentation than during stable PD. This is shown in Figure 5 for albumin and IgG. For all proteins, the increased levels returned to normal within one month.

Seventeen children had one or more episodes of peritonitis per year. A reduced serum IgG1 or IgG2 concentration was present in 11 of them (65%). In contrast, a low serum IgG1 or IgG2 level was found in 12 out of 23 children (52%) who had less than one peritonitis episode per year. The difference between these groups was not significant (p=0.35). The mean peritonitis incidence of the PD group with normal serum IgG1 or IgG2 was 0.8 episodes per year. This incidence was 1.5 episodes per year in those with low serum IgG1 or IgG2 levels (p=0.13). The individual data are shown in Figure 6. The median age in the group with the low peritonitis incidence was 11.2 years compared to 9.0 years in the higher incidence group (p=0.25). No correlation was found between the duration of PD treatment and peritonitis incidence (p=0.3). Also the IgG concentration in PDE was not related to peritonitis incidence (p=0.1).

Figure 5. Albumin (alb) and total IgG concentration in serum and peritoneal dialysis effluent (PDE) in relation to a peritonitis episode. NI: non-infectious state; > 3 months before or after a peritonitis episode. P0: at moment of peritonitis presentation. P14: 14 days after initial presentation, P28: 28 days after initial presentation. *: p = 0.003, **: p = 0.04, ***: p = 0.008.
FIGURE 6. Peritonitis incidence defined as number of episodes per patient year in children with normal serum IgG1 or IgG2 (normal Ig) or reduced IgG1 or IgG2 (reduced Ig) (<2.5th percentile of normal value). (---): median peritonitis incidence; 0.8 in normal Ig group, 1.5 in reduced Ig group. The difference between the groups was not significant (p=0.13)

DISCUSSION

Our results show that not dialyzed children with CRF had lower median serum concentrations of albumin and IgM than their HCs. Median serum IgG levels were not different, while IgG1 was reduced in children with a GFR of less than 50 ml/min/1.73 m2. Moreover, these differences are probably underestimated because of the younger age of HCs and the physiological increase of immunoglobulins with age. A deficiency of one or more IgG subclasses was present in 40% of the children with CRF. One third of the CRF children had a deficiency of IgG2, compared with only 9% in the HCs. Eighty-five percent of the CRF children with a reduced IgG2 had a GFR of less than 25 ml/min/1.73 m2. These findings are in agreement with those of Kemper et al., who reported a IgG2 deficiency in 9 out of 25 children with preterminal renal failure [11]. This secondary IgG subclass deficiency might be caused by a specific reduction of IgG2 synthesis. The latter might be secondary to a primary impairment of the B-cell function but eventually also to a defect of the B-cell control by T-cells. Indeed, renal insufficiency is associated with both B- and T-cell dysfunction [20-24]. Moreover, IgG2 deficiency is also a common finding in other diseases with a T-cell defect such as Di-George syndrome, ataxia-teleangiectasia or AIDS [25, 26]. IgG2 and IgG4 synthesis requires more T-cell help than that of IgG1 and IgG3 [25, 26]. Other observations plead for distinct control of IgG2/IgG4 and IgG1/IgG3 synthesis. In healthy children serum IgG1 and IgG3 levels increase quickly with age, whereas IgG2 and IgG4 display a slow increase. After bone marrow transplantation serum IgG2 and IgG4 levels remain low for a longer period than IgG1 and IgG3 [25, 26].

Proteinuria of more than 2 gr per day was not associated with a selective IgG2 deficiency but with an increased frequency of reduced IgG1 and IgG2 levels probably
because of urinary loss. A reduced IgG synthesis is another explanation for IgG deficiency in patients with nephrotic syndrome [27].

The median serum concentrations of albumin, immunoglobulins and IgG subclasses of hemodialysis patients were similar to those of CRF patients. The Ig loss by the HD treatment is negligible [28]. Serum IgG₃ was significantly higher and serum albumin and IgG₄ lower than the values found in HCs. The older age of the HD children compared to the HCs might be responsible for the higher serum IgG₃ values. A previous study of our group in adults also showed higher IgG₃ and lower IgG₄ concentrations, but the differences were less marked than in the pediatric population of the present study [29]. The study in adults reported a higher estimated IgG₃ synthesis in hemodialysis patients compared to HCs which might also explain the higher serum values [29]. A deficiency of one or more of the IgG subclasses was found in 48% of the hemodialysis children, concerning mainly IgG₂ and IgG₄. This has not been reported previously but is in accordance with the findings in CRF.

The PD patients had the lowest median values for albumin and the immunoglobulins. This was also the case for the IgG subclasses with the exception of the IgG₃ concentration which was similar to that in the healthy children. Also, the IgG₄ concentration was not different from the levels found in HD children. A deficiency of one or more of the IgG subclasses occurred in 60% of the PD children. Forty percent had a deficiency of IgG₂ and 25% of IgG₁. The prevalence of IgG₂ deficiency in our pediatric PD population was similar to our previous findings in adult continuous ambulatory peritoneal dialysis (CAPD) patients [29]. However a reduced serum IgG₁ level was not present in adults.

The lower serum concentrations of albumin and the immunoglobulins in pediatric PD patients are likely to be caused by loss of these proteins in the dialysis effluent. This is strengthened by the observation that serum IgG was lower at the end of the first month of PD treatment when compared with the concentrations before starting dialysis. The peritoneal transport of proteins from the circulation to the dialysate is size selective [30]. This explains the higher peritoneal clearance of albumin (MW 69,000 D), compared with that of IgG (MW 150,000 D). Peritoneal protein clearances are higher during the first hour of the dwell time compared with the hours thereafter, but this is most evident for the small proteins such as β₂-microglobulin (MW 11,800 D) [31, 32]. All children were treated with NIPD with more frequent bag exchanges and shorter dwell times compared with the standard CAPD treatment. Thus, the actual 24-hour IgG loss could have exceeded the calculated loss from a 4 hour dwell time. Furthermore, there is a marked daily variation of individual peritoneal protein clearance, especially for the higher molecular weight proteins, probably caused by alterations in effective peritoneal surface area [33]. The values found in the PD children were similar to those reported in adults when corrected for body surface area [12, 13]. Children with high low molecular weight solute clearances had also a higher protein clearance. This has also been found in adult CAPD patients [data from ref 12]. Children with an IgG₁ deficiency had a higher median peritoneal IgG clearance compared with children.
Ig in CRF children

with a selective IgG2 deficiency. The peritoneal clearances of IgG1, IgG2 and IgG4 were not different from each other and also not from values found in adult CAPD patients [29, 34]. Similarly to adults [29, 34], the clearance of IgG3 was lower than that of the other subclasses. This is most likely caused by its higher molecular weight compared with IgG1, IgG2 and IgG4. It may explain why IgG3 deficiency hardly ever occurred in the PD population.

Besides an increased loss, a decreased synthesis of immunoglobulins, for example, caused by malnutrition, could in theory be present in the PD population. We did not examine the nutritional status of our pediatric PD patients, but studies in adults have reported a similar prevalence of malnutrition in HD and PD patients [35]. No comparative study in children treated with PD or HD has been performed. Data from different reports in children have shown no evidence for a difference in nutritional status between both groups [36, 37]. A PD specific inhibition of IgG2 synthesis has been postulated in adult CAPD patients [29]. However, we are not aware of studies on the measurement of the synthesis rate of IgG subclasses in PD patients, either in children or in adults.

The serum concentrations of albumin and the immunoglobulins did not change during a follow-up of one year. This was also the case for effluent concentrations and peritoneal clearances. Also, in adult CAPD patients, the clearances of albumin and IgG did not change during a two-year follow-up period [38]. This implies that the peritoneal loss of these proteins is compensated by their synthesis creating a steady state in the absence of peritonitis.

The increased peritoneal clearances of serum proteins during peritonitis caused a decrease in the serum albumin concentration, but had no effect on serum IgG and IgA. Serum IgM was even higher in the acute phase than after recovery. This suggests that the infectious state caused an increase in the synthesis rate of the immunoglobulins. In contrast, adult patients showed reduced serum IgG levels in the acute phase of a peritonitis episode compared with the recovered state [39]. The difference between children and adults in the effects of peritonitis on the serum immunoglobulin concentrations may be explained by the presence of more inflammatory systemic symptoms in children. The presence of fever is more common in infants than adults because children are less capable of keeping the bacterial infections localized within the peritoneal cavity [5].

The role of serum IgG deficiency in the pathogenesis of peritonitis during PD is questionable. Studies in adults on serum IgG and subclasses could not establish a relationship between the two [29, 40]. However, Kuizon et al. demonstrated a correlation between IgG z-scores and the incidence of peritonitis in children [41]. We found no relationship between serum IgG and peritonitis incidence, but the latter was two times higher in the group of patients with low IgG1 or IgG2 serum levels than in those with normal values. Especially patients with a high number of peritonitis episodes were found in the group with an IgG deficiency. However, low levels of serum IgG2 in infection-prone children without a renal disease cannot exclusively explain the increased susceptibility to infections, especially with polysaccharide encapsulated bacteria [26,42]. Disturbances in immune defence
mechanisms such as specific IgG subclass antibodies against bacteria, opsonic activity and phagocytosis may contribute to infections as well.

Some studies in adults reported an inverse correlation between the opsonic activity of peritoneal dialysis effluent and the frequency of peritonitis [43-45]. IgG is a major component of the opsonic activity of dialysate. However, no relationship between dialysate IgG and peritonitis incidence was found in most of these studies [40, 43, 46-48]. No information on a possible relationship between dialysate IgG and peritonitis incidence is available in children. The present study in children confirms the absence of a relationship between dialysate IgG and peritonitis incidence.

It can be concluded that a deficiency of one or more IgG subclasses was present in a considerable number of patients from all groups, suggesting inhibition of their synthesis by the uremic state. Neither HD nor PD treatment appears to result in normalization of low Ig and subclass levels in CRF patients. The deficiencies were especially marked in children treated with PD, most likely caused by loss of these proteins in peritoneal effluent. Peritoneal clearances of the immunoglobulins were similar to those in adult PD patients when corrected for body surface area. IgG subclass deficiency did not lead to more frequent peritonitis episodes. However, a high peritonitis incidence was related to reduced IgG subclass levels.

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72


