PART SIX

Pediatrics
Peritoneal dialysis prescription in children should be individualized—based not only on numerical targets ($K_t/V_{urea}$, $K_{crea}$), but also on consideration of the peritoneal membrane, a dynamic dialysis membrane. In fact, the effective peritoneal surface area is at least a triple entity: an anatomic area, a contact area, and an exchange area.

The anatomic area appears to be twice as large in infants as in adults if expressed per kilogram of body weight (BW), although the area is independent of age if expressed per square meter of body surface area (BSA). Therefore, scaling of the intraperitoneal fill volume (IPV) by BSA in square meters is necessary to avoid a low IPV/area ratio, which results in a functionally “hyperpermeable” peritoneal exchange.

The contact area (the wetted membrane) is only a fraction of the anatomic area—that is, 30%–60% in humans (by computed tomography). Contact area depends on a variety of factors, such as posture and fill volume, that affect the degree of recruitment of membrane contact area.

The exchange area is influenced by both the anatomic area and the contact area. However, it is mainly governed by the specific vascular area as determined by the peritoneal vascular perfusion and the capillaries available for exchange. Vascular area is dynamically affected by a variety of factors, such as the composition of the peritoneal dialysis fluid, the fill volume, and possible inflammatory agents.

Key words
Children, peritoneal membrane, anatomic, contact, exchange

Introduction
To be optimal, peritoneal dialysis (PD) should be individualized and adapted to the requirements of the patient. In that respect, various parameters are important: for example, intraperitoneal fill volume (IPV), renal residual function, and the properties of the peritoneal membrane. But, in contrast to a standard hemodialysis prescription, a PD prescription cannot choose the dialyzer. Thus, the PD prescription is not primarily selected based on the peritoneal membrane area recruited for the dialysis exchange (a dynamic process).

During the last decade, we have learned that, in children, the peritoneal membrane is a dynamic dialysis membrane. In fact, the effective surface area of the peritoneal membrane involved in dialysis exchange should be considered in bedside practice to be at least a triple entity: an anatomic area (SA), a contact area (SC), and an exchange area (SE).

Anatomic surface area
The peritoneum is a large, intricately arranged serous membrane that lines the abdominal wall [parietal peritoneum (PP)] and the visceral organs of the abdominal cavity [visceral peritoneum (PV)]. The PV accounts for approximately 90% of the total anatomic surface of the peritoneal membrane; the PP accounts for only 10%. Nevertheless, the relative contributions of the PV and the PP in peritoneal dialysis may not necessarily correlate to anatomic surface. In fact, studies using eviscerated rats suggest that the contribution of the PP to peritoneal exchange is much less than would be predicted from the relative surface areas of PP and PV.

Only a few measurements of anatomic surface area have been performed. Putiloff (1), who assessed, post mortem, the PP and PV surface areas of an infant (weight: 2.9 kg) and an adult (weight: 70 kg), found that the anatomic surface per unit body weight was about twice as large in the infant (522 cm²/kg) as in the adult (284 cm²/kg). On the other hand, a constant, age-independent relationship is noted between anatomic surface area and body surface area (BSA) in square meters. In fact, the anatomic surface area approximates the surface area of the skin (1,2).
From the aforementioned data, it appears that young people with a low body weight will receive less dialysate in proportion to the anatomic surface area of their peritoneal membrane if weight is used as the determinant of IPV. They may therefore appear to be high transporters during a peritoneal equilibration test (2). To avoid this functional state of “hyperpermeability” in infants and children as compared with adults, scaling of the fill volume by BSA in square meters was proposed (3,4). Indeed, the prescribed fill volume directly modifies the ratio IPV/SA (2,3). Therefore, scaling the IPV by BSA (mL/m²), particularly in infants and small children, is good clinical practice (3,4). It avoids certain potential clinical consequences—for example, loss of ultrafiltration capacity (5) owing to the functional hyperpermeability induced by a too-low IPV that has been scaled simply to weight (4).

**Contact surface area**

In a PD exchange, it is the contact surface area that is important, not the anatomic surface area. The mass transfer area coefficient [MTAC (4)] or the permeability surface area product (PS) provides information about the effective SC, the “wetted membrane” in contact with the dialysis solution. The mass transfer coefficient (MTC) of the effective membrane surface area is a solute characteristic factor. The area factor (A) depends on the SC, a dynamic area influenced in humans by the fill volume (6,7) and patient position (7), and in animals by mechanical factors [for example, agitation (8)] and by pharmacologic factors [for example, surfactant (8)].

Studies in rodents by Flessner and colleagues (8) demonstrated that, during a dialysis exchange, SC is significantly less than SA. Only approximately 25% – 40% of SA is in contact with dialysate after instillation of a quantity of dialysis solution scaled to approximate a 2-L to 3-L exchange in a 70-kg human subject. Those authors also demonstrated that the contact area could be increased with agitation or administration of surfactant, leading to increased peritoneal transport (9). In fact, the mean SC/SA ratio of mouse peritoneum increased by a factor of 4 when surfactant was added to the PD fluid (8).

In humans, Chagnac (10) developed a method that applies stereologic techniques to a computed tomography scan, imaging the peritoneal membrane to estimate SC. The contact area during a 2-L dialysis exchange was only approximately 0.55 m², a value lower than previous estimates suggested.

Thus, in animals and in humans, only a fraction of SA is used for dialysis exchange. The data confirm the theoretic estimate proposed in 1973 by Henderson (11), who reasoned that the functional surface area of the peritoneum must be substantially less than the SA. It could also be hypothesized that, in humans, the SC is a dynamic dialysis membrane affected by various parameters, some mechanical (such as agitation), others pharmacologic (such as surfactant), and still others related to the prescription (such as an optimized fill volume). In fact, Chagnac (6) was able to demonstrate the effect of increased IPV on membrane surface in PD patients: increasing the IPV by 50% (to 3 L from 2 L) results in a significant increase in SC to 0.67 ± 0.04 m² from 0.57 ± 0.03 m² (18% ± 2.3%), and a significant increase in MTACcreat to 13.6 ± 1.2 mL/min from 10.6 ± 0.7 mL/min (28% ± 2.4%).

Altogether, the PD prescription—and especially the fill volume—has a direct impact on SC, allowing for optimized dialysis exchanges.

**Exchange surface area**

The peritoneal membrane is not only an anatomic area and a contact area, it is also of course an exchange area. Those areas together result in a patient-specific “effective peritoneal surface area” (3,6).

The SE is a complex structure. It might be simplified this way: on the one hand, it has an anatomic part (capillaries, extracellular matrix, and mesothelial cells); on the other hand, it has a functional part (the peritoneal microvasculature). The degree of microvascular perfusion has a direct impact on the exchange (6,7). For example, in the case of reduced SA secondary to old infections or prior abdominal surgery, or in the case of reduced SC secondary to a small fill volume prescription (4,5), the direct effect is a reduction in the exchange area (3).

In the past decade, our knowledge of the transport processes across the peritoneal membrane has expanded considerably. In particular, the three-pore model introduced by Rippe and co-workers (12) has been most successful in predicting the transperitoneal exchange of fluid and solutes. (The model seems to be universal for microvascular beds in general.) According to the theory, the peritoneal membrane contains three populations of functional pores: the water-exclusive aquaporins, the small-pore pathways,
and the large-pore pathways. The frequency of the pores is inversely related to their size.

Those physiologic concepts have been used to estimate the PD capacity of individual patients (7,12). The most important parameter describing exchange across the peritoneal membrane is the “area parameter” (total pore area / diffusion). It determines the rate of diffusion (the MTAC) for any hydrophilic solute, and it seems mainly to reflect the number of capillaries available for exchange (the density of the functional pores of the perfused capillaries).

Using the three-pore model (7), we demonstrated that factors such as IPV, posture, and dwell time all dynamically affect the total pore area available for exchange (the vascular surface area of the peritoneal membrane, “effective peritoneal surface area”). In fact, the SE—as determined from the available pore area—increased to 24,000 ± 1,450 cm² · (cm/1.73 m²)–1 from 19,900 ± 1,200 cm² · (cm/1.73 m²)–1 as IPV increased to 1400 mL/m² BSA from 800 mL/m² BSA. A further increase to 2000 mL/m² did not result in any change in the available pore area: a plateau of maximum membrane recruitment was reached (7).

Our results support the view of Keshaviah (13) that IPV indeed affects the area available for exchange until functional recruitment reaches a plateau. They also agree with findings from a study of iohexol uptake from the abdominal cavity (14). The results of a calculated exchange area based on capillary pores varying with IPV can be confirmed by measurements of contact surface area from computed tomography imaging of the peritoneal membrane (6; Table I). In children, a fill volume of approximately 1,400 mL/m² BSA seems to be optimal to ensure maximum recruitment of peritoneal capillaries as an exchange surface area (3,7).

However, factors other than membrane area may affect the increased transport associated with an increase in IVP. One of those factors might be the differential increase in the contact area of PV and PP. In fact, the low efficiency of the PV might be attributable to the presence of unmixed or poorly mixed fluid trapped in the many pouches formed by the complex shape of the peritoneal space (8,6). Increasing IPV or applying agitation or vibration to the abdomen of experimental animals improved SC (8) and solute clearance (9), suggesting that a lack of mixing is a main factor limiting solute transport by the PV. In the same way, Flessner (8) demonstrated that surfactant enhanced SC in mice and rats, probably by increasing the surface tension between PP and PV surfaces.

An increase in IPV increases SE. However, the associated increase in intraperitoneal pressure would be expected to increase fluid absorption by peritoneal tissues and lymphatic vessels, thus reducing net ultrafiltration (9) and, consequently, solute removal. The use of surfactants in human subjects (if such treatment is proved to be nontoxic) might provide an alternative or combined approach for enhancing SC without increasing intraperitoneal pressure (8,6).

### Effective surface area

The effective surface area of the peritoneal membrane is related to the SA, the SC, and SE [mainly the capillaries recruited for dialysis exchange: density of and the more constant functional pores of the capillaries (7,12)]. Peritoneal vascular perfusion affects the number of perfused capillaries (15). The composition of the PD fluid (15,16) also directly affects capillary recruitment. Altogether, the PD fluid—in terms of both composition and fill volume—appears to be a main determinant of the dynamic changes of the peritoneal membrane as a dialysis membrane.

### References

1. Putiloff PV. Materials for the study of the laws of growth of the human body in relation to the surface areas of different systems: the trial on Russian subjects of planigraphic anatomy as a means for exact anthropometry—one of the problems of anthropol-

### Table I

<table>
<thead>
<tr>
<th>IPV in children [mL/m² (7)]</th>
<th>800</th>
<th>1400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surface area [cm² · (cm²/1.73 m²)⁻¹]</td>
<td>19,900±1,200</td>
<td>24,000±1,450</td>
</tr>
<tr>
<td>Contact surface area (computed tomography)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>IPV in adults [mL (6)]</td>
<td>2000</td>
<td>3000</td>
</tr>
<tr>
<td>Vascular surface area</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Contact surface area (computed tomography)</td>
<td>0.57±0.03</td>
<td>0.67±0.04</td>
</tr>
</tbody>
</table>

ND = not determined.
ogy. Report at the meeting of the Siberian Branch of the Russian Geographic Society, 1884.


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In this retrospective study, we evaluated the causative factors, outcomes, and complications of therapy in 35 patients (16 girls, 19 boys) started on chronic peritoneal dialysis (CPD) between 1997 and 2002. Average age at initiation of CPD was 9.3 ± 4.4 years. All patients started on continuous ambulatory peritoneal dialysis (CAPD). Nine patients switched to ambulatory peritoneal dialysis (APD) during the follow-up period.

The most common cause leading to end-stage renal disease (ESRD) in the patients was reflux nephropathy (22.9%). The major complication during therapy was peritonitis, with 41 episodes seen in 17 patients (1 episode per 18 patient-months). Of the children on APD, 7 developed 17 episodes of peritonitis (1 episode per 8.3 patient-months); of the children on CAPD, 10 developed 24 peritonitis attacks (1 episode per 24.9 patient-months). The other complications were inguinal hernia in 3 patients, subcutaneous leak in 2 patients, pericardial effusion in 1 patient, umbilical hernia in 1 patient, hydrothorax in 1 patient, and cuff protrusion in 3 patients. During the follow-up period, 4 patients died owing to sepsis or cardiopulmonary complications. Only 1 patient was transferred to hemodialysis (owing to persistent Candida peritonitis).

We think that CPD therapy is a good choice of treatment modality in the management of children with ESRD.

Key words
Causes of end-stage renal disease, children, complications

Introduction
End-stage renal disease (ESRD) occurs in all age groups. Children with ESRD differ from adults with respect to the causes of renal failure (1–3). The introduction of continuous ambulatory peritoneal dialysis (CAPD) to the pediatric ESRD population occurred in the late 1970s. The advantages of CAPD are simple application in infants and young children, ability to attend school for school-age children, and ability of adolescents to perform their own therapy. The CAPD procedure is relatively simple to learn, and home dialytic therapy can therefore be started quickly. Unlike hemodialysis (HD), CAPD requires no specialized, complex equipment. Also, the therapy results in continuous steady-state biochemical and fluid states, avoiding seesaw fluctuations that occur with intermittent HD (2,4). Continuous ambulatory peritoneal dialysis is better suited to children than is HD. However, the main disadvantages of chronic peritoneal dialysis (PD) are infections and mechanical and metabolic complications (1,2,5).

The aim of the present retrospective study was to evaluate the causative factors, outcomes, and complications of therapy in children treated with chronic PD.

Patients and methods
Between July 1997 and August 2002, 35 children (16 girls, 19 boys) diagnosed with ESRD at the department of Pediatric Nephrology, Medical Faculty of Uludag University, were dialyzed with chronic PD. The average age at initiation was 9.3 ± 4.4 years (range: 3 days – 16 years). We determined the causative factors leading to ESRD.

At the start of PD, 6 patients received double-cuff Tenckhoff catheters and 29 patients received double-cuff, swan-neck coiled catheters. Catheter insertion was performed by percutaneous trocar (n = 5), laparotomy (n = 19), or laparoscopy (n = 11). In 29 of our patients (82.9%), the catheter exit-site orientation was downward; in the others, it was lateral.

All patients started on CAPD. Nine patients switched to automated peritoneal dialysis (APD) during the follow-up period. The follow-up period was 15.1 ± 5.1 months (range: 7 – 23 months). The dialysate exchange volumes used by our patients were determined as 30 – 50 mL/kg. All CAPD patients used the UltraBag twin-bag system (Baxter Healthcare Corporation, McGaw Park, IL, U.S.A.). The cycler machines used by the APD patients were
Pac-Xtra, HomeChoice (Baxter Healthcare). Patients on chronic PD were evaluated at 5 stages during follow-up (start, <12 months, 13 – 24 months, 25 – 36 months, >36 months).

Serum biochemical and hematologic parameters were measured monthly from blood samples. The measured values included sodium, potassium, chloride, urea, creatinine, uric acid, calcium, phosphorus, alkaline phosphatase, triglycerides, total cholesterol, glucose, albumin, and hematocrit. Body weight, blood pressure, and height were recorded at each control visit. Dialysate, exit-site, and nasal cultures were performed each month.

The frequency of infectious and noninfectious complications was analyzed. The criteria for peritonitis was cloudy peritoneal fluid and increased dialysate white cell count (>100 cells/mL) with >50% polymorphonuclear cells. Facultative findings were abdominal pain or fever. Every 3 months or 6 months, daily urine output and drained dialysate volume were obtained to estimate creatinine clearance (CCr) and Kt/V urea. Creatinine and urea levels were measured in serum, urine, and peritoneal dialysate. The PD Adequest program (Baxter Healthcare) was used for calculations of adequacy (6).

Statistical analysis
The data are given as mean ± standard deviation. The differences in the various parameters during dialysis treatment were compared using analysis of variance. Values of p less than 0.05 were accepted as significant.

Results
The average follow-up period was 21.1 ± 17.1 months. The average duration of CAPD was 17.1 ± 14.5 months (range: 1 – 62 months) and of APD, 15.7 ± 15.0 months (range: 1 – 47 months).

The causes of ESRD were reflux nephropathy [n = 8 (22.9%)], chronic interstitial nephritis [n = 3 (8.6%)], chronic glomerulonephritis [n = 2 (5.7%)], membranoproliferative glomerulonephritis [n = 3 (8.6%)], focal segmental glomerulosclerosis [n = 6 (17.1%)], hemolytic uremic syndrome [n = 2 (5.7%)], Alport syndrome [n = 2 (5.7%)], renal tubular acidosis [n = 1 (2.9%)], nephroptithis [n = 1 (2.9%)], primary hyperoxaluria type I [n = 1 (2.9%)], polycystic kidney disease [n = 1 (2.9%)], and unknown [n = 5 (14.3%)]. Five children had hereditary familial nephropathy (14.1%) as the underlying cause for ESRD, 2 of whom had Alport syndrome; 1, oxalosis; 1, polycystic kidney disease; and 1, nephronophthisis.

The major complication during therapy was peritonitis. During the study, 41 episodes of peritonitis occurred in 17 patients. The overall frequency of peritonitis was 1 episode per 18 patient–months. Of the children on APD, 7 developed 17 peritonitis attacks (1 episode per 8.3 patient–months), including 1 child who developed peritonitis 10 times. Of the patients on CAPD, 10 developed 24 peritonitis attacks (1 episode per 24.9 patient–months). During the study, 51% of the patients had no episodes of peritonitis. No tunnel or exit-site infections occurred. Of all peritonitis episodes, 43.9% were caused by gram-positive bacteria, 24.4% by gram-negative bacteria, and 2.3% by Candida albicans. In 29.3% of the episodes, cultures were negative.

Table I presents hematologic and biochemical parameters, total CCr, and dialysate Kt/V for the patients. During follow-up, mean serum urea levels were significantly decreased from baseline; however, the reduction in mean CCr was not significant. The mean hemoglobin and hematocrit increased significantly during follow-up. The average dialysate Kt/V was greater than 1.9. After the 3rd year, the average CCr decreased to less than 70 L/week/1.73 m2. The mean CCr over 4 years was 66.6 L/week/1.73 m2, as compared with 70 L/week/1.73 m2 in the first 3 years. Mean serum albumin levels were above 3.3 g/dL. Values of serum total cholesterol and triglycerides increased during follow-up, but the difference was not significant.

All patients received human recombinant erythropoietin (rHuEPO). The rHuEPO dosage was individually adjusted according to hemoglobin values.

We also recorded noninfectious complications during follow-up. The overall rate of subcutaneous leak was 11.4% (n = 4). In those cases, conservative management did not help the leaks to regress, and the catheters had to be replaced. The overall rate of dialysate leak was 5.7% (n = 2). In those 2 patients, conservative management did not stop the leakage, and the catheters had to be replaced. A hydrothorax and a pericardial effusion regressed with conservative management. Inguinal hernia developed in 3 patients (8.6%) and umbilical hernia in 1 patient (2.9%). Those complications were treated surgically. Two patients (5.7%) experienced drainage problems. In 1 of those patients, the catheter had to be replaced. Three pa-
tients (8.6%) had problems with catheter cuff protrusion. Medical treatment for hypertension was given to 22 patients (62.9%) at some time during the study. Hypertension was controlled with 1 antihypertensive drug in 8 patients, with 2 drugs in 10 patients, and with 3 or more drugs in 4 patients.

By the end of the follow-up, 4 patients had died of sepsis or cardiopulmonary complications. One case was transferred to HD because of resistant Candida peritonitis.

Discussion and conclusions

In our study, reflux nephropathy was the most common primary renal disease, and focal segmental glomerulosclerosis was the second most common. Among the preventable causes of chronic renal failure, reflux nephropathy was reported at 22.9% among our patients, as compared with 12.5% in France (7), 0% in Sweden (8), 16.7% in Chile (9), and 32.4% in Turkey (10). The differences may be attributable to early detection of renal disease. The high incidence of reflux nephropathy in our patients was similar to that reported by Sirin et al. (10). We think that reflux nephropathy is one of the most important causative factors of chronic renal failure in children.

The incidence of peritonitis still has a significant impact on the success of chronic PD. The overall peritonitis rate of 1 episode per 18 patient–months in our patients compares with a frequency of 1 episode per 7.1–28.6 patient–months in recent reports (5,11–13). The frequency of peritonitis in our CAPD patients was found to be 1 episode per 24.9 patient–months. That result is similar to the findings of Honda et al. (13).

The incidence of peritonitis in our APD patients was higher than that in our CAPD patients. In the literature, the peritonitis incidence with APD is reported to be lower than the incidence with CAPD (14). On the other hand, some authors reported that the incidences were not different between the modalities (15,16). In our patients on CAPD, the peritonitis incidence was similar to those reported in the literature; but, in our patients on APD, the incidence was higher. We think that the 10 recurrent peritonitis episodes in 1 patient on APD affected the result.

Swan-neck double-cuff catheters and a downward exit-site orientation are reported to reduce peritonitis and tunnel and exit-site infections (5). The lack of tunnel or exit-site infections and the low incidence of peritonitis seen in our CAPD patients may be the result of our use of swan-neck double-cuff catheters and a downward orientation in 82.9% of our patients. In our patients, the most common exit-site orientation was downward; we therefore think that choosing that orientation reduced the peritonitis attacks in our study.

A literature review revealed that, during chronic PD, gram-positive bacteria cause peritonitis more frequently than do gram-negative bacteria (1). In our study, we found that gram-positive bacteria caused peritonitis 43.9% of the time. That result is similar to results reported in the literature. The incidence of Candida albicans observed in our study (2.3%) was slightly lower than in other reports (12,17).

We targeted weekly Kt/V urea clearances of >2.0 and CCr > 60 L/week/1.73 m². The guideline for the

<table>
<thead>
<tr>
<th>Duration of chronic PD (months)</th>
<th>Start &lt;12</th>
<th>13–24</th>
<th>25–36</th>
<th>&gt;36</th>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>35</td>
<td>35</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>194.5±74.1</td>
<td>111.9±28.7</td>
<td>96.9±21.9</td>
<td>98.2±12.6</td>
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<td>Creatinine (mg/dL)</td>
<td>6.6±2.1</td>
<td>6.0±1.7</td>
<td>6.2±1.6</td>
<td>6.4±1.9</td>
</tr>
<tr>
<td>Weekly Kt/V</td>
<td>2.4±1.2</td>
<td>1.9±0.4</td>
<td>2.1±0.3</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>Weekly CCr (L/1.73 m²)</td>
<td>71.3±14.2</td>
<td>70.6±11.4</td>
<td>71.6±5.4</td>
<td>66.6±6.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.4±1.8</td>
<td>10.3±1.8</td>
<td>10.8±2.2</td>
<td>9.9±0.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>24.8±5.5</td>
<td>30.9±4.9</td>
<td>32.4±6.2</td>
<td>32.8±4.6</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.5±0.8</td>
<td>3.5±0.7</td>
<td>3.6±0.7</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>231.9±82.4</td>
<td>230.9±85.2</td>
<td>225.1±59.5</td>
<td>208.7±84.5</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>235.6±115</td>
<td>211.3±133</td>
<td>218.6±102</td>
<td>191.8±134</td>
</tr>
</tbody>
</table>

* p < 0.05 as compared with the preceding follow-up period.
target value of weekly Kt/V is 1.7 – 2.2 and for CCr is 70 L/week/1.73 m² (18). The mean weekly Kt/V urea and CCr values in our patients were within the acceptable range.

Complications related to the catheter are an important cause of morbidity (1,5). The most common problems are subcutaneous leaks, dialysate leaks, cuff protrusion, inguinal hernia, and obstruction. The frequency of those complications reported in the literature ranges from 12% to 73% (19). We observed such problems in 17 of our 35 patients (48.6%). Those results are similar to the results reported in the literature.

According to the 1995 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), 49% of PD patients were given antihypertensive drugs (11). The overall incidence of hypertension in our patients was 62.9%. Hypertension was an important complication in our patients.

Four (11.4%) patients died. That mortality rate is similar to the rates given in previous reports (5,11,12). One patient was transferred to HD because of resistant Candida peritonitis. Thirty patients are still on chronic PD (22 CAPD, 8 APD).

We suggest that chronic PD is a good choice of renal replacement therapy in children with ESRD.

References

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Outcomes for pediatric peritoneal dialysis (PD) patients are closely related to dialysis adequacy and nutrition, which need to be measured frequently using a number of laboratory parameters. Although the critical meaning of adequacy and nutrition in the long-term prognosis of dialyzed children is well-documented, PD prescriptions are still largely empirical. Our objective was to evaluate nutritional and dialytic parameters in PD children (urea, creatinine, and albumin excretion in dialysate and urine, and daily protein intake); to measure peritoneal equilibration test (PET) results, Kt/V, normalized equivalent of protein nitrogen appearance (nPNA) and nitrogen balance; and to study the correlations between those variables. We performed 59 prospective laboratory measurements in 15 stable PD patients (7 boys; mean age: 6.7 years; age range: 1.1 – 14.8 years) during 6 months of follow-up. Creatinine, urea, total protein, and albumin were measured in plasma, urine, and dialysate. We calculated PET, Kt/V, daily dietary protein intake (DPI), protein catabolic rate (PCR), and nPNA. All statistical comparisons used the paired t-test, and correlations were calculated by two-way analysis of variance for repeated measures. A value of \( p < 0.05 \) was considered significant.

The mean 4-hour dialysate-to-plasma ratio (D/P) of creatinine was 0.78 ± 0.02 at month 0 and 0.74 ± 0.13 at month 6 \( [p = \text{nonsignificant (NS)}] \). The mean final-dialysate-to-initial-dialysate ratio (D/D) of glucose was 0.35 ± 0.11 and 0.34 ± 0.08 at the same intervals \( (p = \text{NS}) \). The D/P creatinine showed an inverse correlation with patient age and body surface area, and the D/D glucose ratio showed a positive correlation with both of those parameters \( (p < 0.05) \). Weekly total and residual Kt/V urea were 3.41 ± 0.86 and 1.49 ± 1 respectively. The daily DPI was 3.32 ± 1.05 g/kg, and the daily PCR was 1.32 ± 0.47 g/kg, showing a positive net protein balance \( \text{DPI} - \text{PCR} = +2 \text{ g/kg daily} \), which was negatively correlated with age and body surface area \( (p < 0.001) \). The mean daily nPNA was 0.94 ± 0.33 g/kg, which was negatively correlated with age and body surface area \( (p < 0.05, \ r = -0.51) \), and positively correlated with daily DPI and total and residual Kt/V \( (p < 0.0001) \).

Our patients could be classified as high-average transporters, with low-average ultrafiltration. The high transport state was associated with greater peritoneal albumin losses, a point of concern at younger ages. Total Kt/V and nPNA were higher for the youngest patients, suggesting a favorable nutrition status, but more studies are needed to determine the best value for both parameters in clinical practice.

Key words
Adequacy, nutrition, Kt/V, nPNA

Introduction
Growth retardation is an important complication in children with chronic renal failure (CRF). A large proportion of pediatric patients show signs of protein-energy malnutrition. In pediatric dialysis, malnutrition has been considered to be a major determinant of morbidity as well as mortality, and good nutrition remains one of the most important goals in the management of children on chronic peritoneal dialysis (PD) therapy (1,2). The data suggest that outcomes for pediatric PD patients are closely related to dialysis adequacy and nutrition (3–5), which need to be measured using a number of laboratory parameters, looking not only for isolated results, but also for correlations. For example, when measuring urea kinetics or serum albumin levels, it would be appropriate to ask about their relationship with daily dietary protein intake (DPI) or peritoneal protein losses.

For pediatric patients on PD, studies of protein catabolic rate (PCR) and nitrogen balance have been used to evaluate nutrition status. Recently, however, the Dialysis Outcomes Quality Initiative (DOQI) guidelines suggested that the equivalent of protein nitrogen appearance (PNA) is the best tool for evaluating nutrition (6). The end-product of protein catabolism is urea,

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and nitrogen intake comes almost entirely from protein. Therefore, in steady-state conditions, protein intake can be estimated from urea kinetics studies. In clinical practice, most of those studies are performed by measuring daily excretion of nitrogen in urine, dialysate, and feces and then multiplying the total nitrogen excretion by 6.25, because 6.25 g protein results in 1 g nitrogen. However, the true PCR is about 6 times higher than that estimated from the urea appearance rate, because most of the protein is not catabolized to urea, but is reused for protein synthesis. As a result, PNA has been suggested to be more accurate than PCR for protein balance studies (6,7). The modified Borah equation has been recommended by DOQI for PNA evaluation, normalized (nPNA) to grams per kilogram of body weight per day (3,6).

The relationship between nutrition, dialysis adequacy, and morbidity and mortality has been shown by several multicentric studies. The CANUSA study (4) in adults reported that a 5% decrease in patient survival was associated with every 0.1 decrease in total weekly Kt/V urea, for weekly Kt/V values between 1.5 and 2.3. A decrease in Kt/V from more than 1.9 to less than 1.4 has been shown to increase mortality by a factor of 3, and a low serum albumin and a low Kt/V were found to be predictive of death in adult patients (8). A weekly Kt/V urea equal to or greater than 2 is the DOQI recommendation. That value approximates a renal urea clearance of 7 mL/min, and a renal creatinine clearance (CCr) of between 9 mL/min/1.73 m² and 14 mL/min/1.73 m². The DOQI work group suggested that the target dialysis dose for children should always meet or exceed the adult recommendations, and that the target should be maintained, together with a protein intake greater than the recommended dietary allowance.

Although the growing evidence about the critical meaning of dialysis adequacy and nutrition in the long-term prognosis of dialyzed children is well-documented, PD prescriptions are still largely empirical. Some reasons for the limited interest in performing such studies in clinical practice arise from the short average dialysis time in pediatric patients, the small number of patients using PD as renal replacement therapy, and the low morbidity and mortality as compared with the adult population. But the peritoneal equilibration test (PET), dialysis dose (Kt/V), nitrogen balance studies, and nPNA should be objects of routine measurement in pediatric PD patients.

The aim of the present prospective study was to evaluate nutritional and dialytic parameters (urea, creatinine, and albumin excretion in dialysate and urine, and DPI) in children on PD; to measure PET, Kt/V, nPNA, and nitrogen balance; and to study the correlations between those variables.

Patients and methods
We performed 59 prospective laboratory measurements in 15 stable PD patients (7 boys; mean age: 6.7 years; age range: 1.1 – 14.8 years). Mean duration of PD was 9 months (range: 2 – 23 months). Underlying renal disorders included renal dysplasia (n = 9), reflux nephropathy (n = 3), hemolytic uremic syndrome (n = 1), obstructive uropathy (n = 1), and chronic glomerulonephritis (n = 1). At the start of the study, 8 patients were on continuous ambulatory PD, and 7 were on automated PD. Three patients had no residual renal function. No patient was studied within a month after a peritonitis episode. Patients with fever, infections, nephrotic syndrome, gastrointestinal absorption disturbances, steroid treatments, endocrine diseases, genetic syndromes, and compliance or behavioral disturbances were excluded. At study entry, and every month for 6 months of follow-up, 24-hour dialysate and urine samples, together with blood samples, were collected on an outpatient basis. Thimerosal was added to the urine and dialysate samples to avoid urea generation secondary to bacterial activity. All samples obtained under conditions of noncompliance were discarded. Creatinine (Jaffe reaction), urea (enzyme assay), total protein, and albumin (turbidimetric assay) were measured in plasma, urine, and dialysate. The PETs were performed according to a previously published protocol (9,10). Briefly, a standardized volume [1,100 mL/m² body surface area (BSA)] of Dianeal 2.5% solution (Baxter Healthcare Corporation, McGaw Park, IL, U.S.A.) was instilled into the peritoneal cavity, and dialysate samples were taken from the overnight exchange bag and at 0, 30, 60, 120, 180, and 240 minutes of the standardized exchange. A serum sample was taken at 120 minutes. Results analyzed were the equilibration ratios dialysate-to-plasma (D/P) creatinine and final-dialysate-to-initial-dialysate (D/D₀) glucose after a 4-hour dwell. Each patient was categorized as a high, high-average, low-average, or low transporter according to pediatric values published by Warady et al. (9).
Weekly Kt/V urea—peritoneal (Kt/Vp) and residual (Kt/Vr)—were calculated using this equation:

$$\text{Kt/V urea} = \left[ \frac{24\text{-}h \text{ dialysate volume (L)}}{\text{D/P urea} \times 7} \right] / \left[ 0.60 \times \text{weight (kg)} \right]$$

Dialysis dose was prescribed in consideration of a minimum weekly Kt/V value of 2 according to the DOQI guidelines (11), but no attempt was made to define a maximum Kt/V value in our patients.

**Nitrogen balance studies**

Once per month, patients were evaluated by a renal dietician. The dietician monitored for an adequate protein–energy intake that met pediatric (12) and DOQI recommendations (3). A weekly nutrition follow-up was performed by telephone to correct any deviations from the protocol. Daily DPI was registered by our dietician during the follow-up period.

Urea nitrogen appearance (UNA) is the net production (appearance) of urea nitrogen in body fluids and all measurable outputs (for example, urine and dialysate) and is usually expressed in grams of nitrogen per day. Total nitrogen appearance (TNA) is the sum of all outputs of nitrogen from the body (dialysate, urine, and feces) in the form of urea, protein, peptides, amino acids, and all other nitrogen-containing products.

In the adult-dialysis literature, daily DPI estimated from the UNA has been called the PCR, and PCR has been used as an indirect method of estimating DPI. The PCR is a useful concept but a misleading one, because intact proteins, peptides, and amino acids lost in dialysate and urine comprise a portion of the PCR, but they are not catabolized to urea. The PNA (formerly PCR) expresses TNA in terms of protein, multiplying TNA by 6.25. Regression equations that relate UNA to PNA have been defined for hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients. We performed the PNA calculation as proposed for children by the DOQI guidelines, using the modified Borah equation:

$$\text{PNA (g/d)} = (6.49 \times \text{UNA}) + (0.294 \times V) + \text{protein losses (g/24 h)}.$$  

After PNA was measured, it was normalized to body weight (g/kg), to define the nPNA.

Because PNA, TNA, and UNA do not include nitrogen from unmeasured respiratory and dermal losses, PNA can underestimate the actual DPI. To estimate total protein catabolism and losses in clinical practice, we use the sum of PCR, albumin (Alb) losses in urine (u 24 h) and dialysate (d 24 h), and unmeasured losses, so that the daily protein catabolism (DPC) in grams per day should be

$$\text{DPC} = (\text{UNA}_d^{24\text{ h}} \times 6.25) + (\text{UNA}_u^{24\text{ h}} \times 6.25 \times 1.25) + (\text{Alb}_d^{24\text{ h}}) + (\text{Alb}_u^{24\text{ h}}) + \left[ \text{weight (kg)} \times 0.045 \times 6.25 \right].$$

We recorded DPI – DPC (g/day) as the proteic (nitrogen) balance.

**Statistical analysis**

Data are reported as mean ± standard error. All statistical comparisons used the paired t-test, and $p < 0.05$ was considered significant. Two-way analysis of variance for repeated measures was used to calculate correlations.

**Results**

**Dialysis data**

The mean 4-hour D/P ratio for creatinine was $0.78 \pm 0.02$ at month 0 and $0.74 \pm 0.13$ at month 6 ($p = \text{non-significant (NS)}$). The mean D/D₀ glucose was $0.35 \pm 0.11$ and $0.34 \pm 0.08$ ($p = \text{NS}$) for the same observation periods (Table I). The 4-hour D/P creatinine showed an inverse correlation with patient age and BSA; D/D₀ glucose showed a positive correlation with the same two parameters ($p < 0.05$). The D/P creatinine

<table>
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<tr>
<th>Table I</th>
<th>Characteristics of dialysis and nutrition in 15 children on peritoneal dialysis</th>
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<tr>
<td>PET, 4-h D/P Cr</td>
<td>0.78±0.02</td>
</tr>
<tr>
<td>PET, 4-h D/D₀ Glu</td>
<td>0.35±0.11</td>
</tr>
<tr>
<td>Residual Kt/V urea</td>
<td>1.49±1</td>
</tr>
<tr>
<td>Total Kt/V urea</td>
<td>3.41±0.86</td>
</tr>
<tr>
<td>Daily protein intake (g/kg)</td>
<td>3.32±1.05</td>
</tr>
<tr>
<td>Protein catabolism (g/kg)</td>
<td>1.32±0.47</td>
</tr>
<tr>
<td>nPNA (g/kg)</td>
<td>0.94±0.33</td>
</tr>
</tbody>
</table>

PET = peritoneal equilibration test; D/P = dialysate-to-plasma ratio; Cr = creatinine; D/D₀ = final-dialysate-to-initial-dialysate ratio; Glu = glucose; nPNA = normalized equivalent of protein nitrogen appearance.
nine showed a positive correlation with dialysate albumin losses, but that relationship was not significant for D/D₀ glucose. Mean plasma, dialysate, and urine creatinine were 4.54 mg/dL, 4.21 mg/dL, and 16.02 mg/dL respectively, showing almost complete equilibration between dialysate and plasma creatinine.

Measured weekly total and residual Kt/V urea were 3.41 ± 0.86 and 1.49 ± 1 respectively, and weekly total and residual CCR were 4.4 ± 2.3 mL/min and 2.24±1.33 mL/min (Table I). The Kt/V urea was positively correlated with CCR (p < 0.05), and negatively correlated with age and BSA.

**Nutrition data**

Plasma albumin and bicarbonate showed mean values of 3.57 ± 0.37 g/dL and 23.6±3.4 mmol/L respectively. Daily peritoneal and urinary albumin losses were 153±84 mg/kg and 25.7 ± 11.8 mg/kg. Total daily peritoneal protein and albumin losses were 4.8±2.6 g and 3.06±1.6 g. Albumin in plasma was strongly correlated with urine losses (p < 0.05, r = -0.72), but weakly correlated with peritoneal losses (p = 0.65). A positive correlation existed between D/P creatinine and peritoneal albumin losses (p < 0.05). Peritoneal albumin losses showed a negative correlation with age (p < 0.0001, r = -0.56). The daily urea nitrogen excretion in urine and dialysate was 34.8 ± 34.8 mg/kg and 29.5±15.9 mg/kg, and both values were positively correlated with daily DPI (p < 0.05, Table II).

The mean daily DPI was 3.32 ± 1.05 g/kg, and the daily PCR was 1.32 ± 0.47 g/kg, showing a net daily protein balance (DPI – PCR) of +2 g/kg. Protein balance showed a negative correlation with age and BSA (p < 0.001), and daily DPI was inversely correlated with plasma bicarbonate.

The mean daily nPNA was 0.94 ± 0.33 g/kg and showed a negative correlation with age, BSA, and plasma bicarbonate (p < 0.05, r = -0.51) and a positive correlation with daily DPI and total and residual Kt/V (p < 0.0001).

**Table II**

| Peritoneal albumin loss (mg/kg daily) | 153±84 |
| Urinary albumin loss (mg/kg daily)   | 25.7±11.8 |
| Peritoneal UN excretion (mg/kg daily) | 29.5±15.8 |
| Urinary UN excretion (mg/kg daily)   | 84.9±34.8 |

**Discussion**

Optimal PD in children requires a prescription appropriate to each patient’s age, size, residual renal function, and metabolic and nutritional needs. Our results demonstrate clearly that quantitative measures of PD and nutrition delivery can be used to measure dialysis adequacy in stable, chronic pediatric PD patients.

The PET is crucial to prescription management in dialyzed children. It characterizes the patient’s peritoneal membrane transport capacity, and that characterization in turn serves as a significant influence on the prescribed dialysis modality. First published by Twardowskli (10) for adults, and later studied in children (9,13,14), transport rate is categorized as high, high-average, low-average, or low. Patients with high peritoneal solute transfer rates are likely to have inadequate ultrafiltration on standard CAPD, doing much better on dialysis regimens with short-dwell exchanges, such as automated PD.

The Mid European Pediatric Peritoneal Dialysis Study Group (15) demonstrated that a high transport state in children had a negative correlation with longitudinal growth and a positive correlation with body mass index. They observed a slight rise in individual peritoneal transport rates during follow-up, with an annual increase in the 4-hour D/P creatinine ratio of 0.04 ± 0.12 (p < 0.05). We observed no change in creatinine and glucose PET values during the 6 months of the study, and the same observation was made during a longer period of follow-up by Warady et al. (13), who showed a delta of 0.02 ± 0.12 for D/P creatinine (n = 19) and 0.33 ± 0.13 for D/D₀ glucose (n = 26) during 19 months of follow-up. A previous report concerning 24 children on PD at our hospital (14), with a 12-month follow-up period, showed a delta of 0.01 for D/P creatinine and 0.04 for D/D₀ glucose, suggesting that peritoneal transport rates remain stable in clinical practice.

In our study, the mean 4-hour D/P creatinine was 0.78 ± 0.02 and the mean 4-hour D/D₀ glucose was 0.35 ± 0.11—almost the same values reported by the European group (0.71 ± 0.20 and 0.36 ± 0.12 respectively). However, that group found that peritoneal transport rate was independent of age and body size, in contrast with other experiences that showed a higher D/P in small infants (16,17), but similar to data published by Bouts et al. (18), who found no significant changes in D/P and mass transfer area coefficient (MTAC) according to age.
The MTAC is an additional measure of solute transport capacity, essentially independent of dialysis mechanics such as exchange volume and dialysate dextrose concentration. It has been defined as the area available for solute transport divided by the sum of resistances to peritoneal diffusion. A few clinical experiences with MTAC instead of D/P have been published (9,18). Using MTAC, Warady et al. (9) studied 83 children and showed that a nonlinear decrement of that parameter for creatinine, glucose, and potassium occurred with age—indicative of higher peritoneal permeability in the youngest children. However, the group did not find the same correlation with D/P creatinine and D/D₀ glucose. We found a negative correlation between age and BSA and D/P creatinine, and a weak positive correlation with D/D₀ glucose, suggesting—as did the findings of others (17,18)—that higher peritoneal permeability is found in the youngest PD patients.

Residual and total Kt/V were found to be 1.49 ± 1 and 3.41 ± 0.86 respectively. The DOQI recommendations suggest a minimum total Kt/V of 2, but no agreement exists concerning the best Kt/V in pediatric practice. Our total dialysis dose is higher than the total Kt/V of 2.3 (range: 1 – 4.41) reported by the European group (15), but the range of our results showed that we have no patients with a weekly Kt/V of less than 2. Our results are quite similar to the values published by Holtti et al. (19) of 3.2 ± 0.5, and Chadha and Warady (20) of 3.39 ± 0.71, suggesting that, in pediatric clinical practice, the total Kt/V is far from the minimum value recommended by DOQI.

Warady (21) recently published an experience showing that delta height velocity in 24 pediatric patients at 1 year of follow-up was positively correlated with residual Kt/V and total CCr, which shows the relationship between growth and dialysis dose. The relationship between dialysis dose and nutrition is an area of particular interest, and a correlation between Kt/V urea and nPNA has been suggested by previous studies (22–24). The relationship has often been criticized as being the result of mathematical coupling; but, in some experiences, nPNA tends to increase after Kt/V urea has been increased (6), and Aranda et al. (25) found that 7 children with a mean Kt/V urea of 3.0 ± 0.4 had a significantly higher nPNA than other children with a lower total Kt/V urea. The mean nPNA of 0.94 ± 0.33 g/kg in our patients is quite similar to the DOQI recommendations (6) and to the results from the European group (15). Moreover, it was significantly correlated with daily DPI (p < 0.05), as was daily nPNA with residual (p < 0.0001, r = 0.79) and total Kt/V (p < 0.0001, 0.75).

The analyses of dialysis dose as compared with age in our group of patients showed a negative correlation between Kt/V and BSA or age, and between daily nPNA and those same two variables. The same relationship between Kt/V and age was reported by Brem et al. in the End Stage Renal Disease Clinical Indicators Project (26), suggesting that smaller children tend to have a greater Kt/V as well as a greater daily nPNA. That finding should be of great importance, because of the higher protein requirements in the youngest patients (6,12) secondary to growth and (in our experience) to a greater loss of albumin in dialysate.

Finally, evidence is increasing that metabolic acidosis is an important stimulus for net protein catabolism and that protein intake means an acid load for the metabolism (7). The persistent negative correlation (p < 0.001, r = 0.51) found between daily DPI, daily nPNA, and plasma bicarbonate in our patients should be pointed out. Those observations correlate closely with a significant negative relationship found between daily DPI and dual-energy X-ray absorptiometry (DEXA) in this group of patients (Unpublished data) and make clear that full correction of acidosis should be attempted when treating children on PD.

Conclusions
The roles of good nutrition and dialysis adequacy as determinants of outcome in dialyzed children are well known. A positive protein balance, together with an adequate dialysis dose, requires close supervision of several laboratory parameters. The PET, Kt/V, DPI, and nPNA are invaluable tools that appear to be the best indexes for following children on PD. Long-term studies with a greater number of patients will allow us to determine the impact of those variables on growth and development.

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