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IMPROVEMENT IN PERITONEAL DIALYSIS TREATMENT IN CHILDHOOD, WITH EMPHASIS ON SMALL CHILDREN

by

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ACADEMIC DISSERTATION

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SUMMARY

Since 1986, most Finnish children with terminal uremia or congenital nephrosis have been treated with chronic ambulatory peritoneal dialysis (PD) prior to transplantation. This study was designed to characterize and improve the management of pediatric patients on PD, with special emphasis on children under 5 years of age.

The outcome in 34 children under 5 years of age on PD during 1986-1994 was analyzed from patient files. A total of 30 patients were followed prospectively up to 12 months in 1995-1999. Clinical outcome was analyzed and compared with the results obtained before 1995, and peritoneal equilibration tests and measurements of dialysis adequacy were performed every 3 months. Utilization of tidal peritoneal dialysis (TPD) was studied and compared with continuous cycling peritoneal dialysis (CCPD). Blood pressure was measured with an automatic oscillometric device and with 24-h ambulatory blood pressure monitoring. Cardiopulmonary status was evaluated and blood atrial natriuretic peptide (ANP) levels were measured to find correlates with hypertension and with high blood volume.

Length of hospitalization decreased during the study from 150 days to 95 days/patient-year in children under 5 years of age (60 days in all children). The peritonitis rate decreased from 1 per 7.4 dialysis months to 1 per 9.4 months (difference not significant) in children under 5 years of age. The need for antihypertensive medication also decreased, and complications, such as seizures (26% of the patients in 1986-1994) and pulmonary edema (41% of the patients in 1986-1994), did not appear during the study period. Catch-up growth was seen in most of the patients treated between 1986-1994, but was more evident during the prospective study period. Growth was significantly better in the younger patients than in the older ones.

No significant difference in peritoneal membrane transport was found between children under and over 5 years of age. The mean weekly urea clearance (Kt/V) was similar and stable in the two age groups (3.1 vs. 3.2 at baseline). At baseline, the mean weekly creatinine clearance (C_{Cr}) was significantly lower in the younger patients (59 vs. 78 L/wk/1.73m^2, p=0.004). During the study period, C_{Cr} increased in the younger children. All patients reached the mean weekly urea Kt/V target of >2.0. The mean C_{Cr} target of >60 L/wk/1.73m^2 was more difficult to reach, especially in the younger, nephrectomized patients. The target C_{Cr} was not reached by 79% and 29% of these children at baseline and at 9 months, respectively.

In most children, TPD and CCPD provided adequate dialysis, but in patients with high peritoneal membrane permeability TPD provided clearly better small-solute clearances than CCPD. Thus, the ideal candidates for TPD are children with high peritoneal permeability and ultrafiltration problems and children with mechanical outflow

problems or outflow pain. TPD is, however, more expensive than CCPD, since more dialysis fluid is needed.

High blood pressure was found in 52% and left ventricular hypertrophy (LVH) in 45% of the patients. Both were more common in the nephrectomized patients under 5 years of age. This may have been due to the difficulty in estimating the exact dry weight in these patients. Blood ANP levels correlated significantly with the severity of hypertension and LVH, especially in the nephrectomized patients. Thus, ANP was found to be a valuable measure for facilitating the diagnosis of hypervolemia.

These studies show that PD outcome in children can be improved by knowing peritoneal transport kinetics and by increasing dialysis adequacy in addition to good clinical care. With such interventions, the dialysis outcome in children under 5 years of age may be as good as in children over 5 years of age.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals.

I Hölttä T, Rönnholm K, Jalanko H, Ala-Houhala M, Antikainen M, Holmberg C. Peritoneal dialysis in children under 5 years of age. Perit Dial Int 17:573-580, 1997.

II Hölttä T, Rönnholm K, Holmberg C. Influence of age, time, and peritonitis on peritoneal transport kinetics in children. Perit Dial Int 18:590-597, 1998.

III Hölttä T, Rönnholm K, Jalanko H, Holmberg C. Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control. Pediatr Nephrol 14:889-897, 2000.

IV Hölttä T, Rönnholm K, Holmberg C. Adequacy of dialysis with tidal and continuous cycling peritoneal dialysis in children. Nephrol Dial Transplant 15:1438-1442, 2000.

V Hölttä T, Happonen J-M, Rönnholm K, Fyhrquist F, Holmberg C. Hypertension, cardiac state and the role of volume overload during peritoneal dialysis in children. Submitted.

ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ANP	atrial natriuretic peptide
ANP-C	carboxy-terminal atrial natriuretic peptide
ANP-N	amino-terminal atrial natriuretic peptide
AOD	aortic diameter in end-diastole
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CAPD	continuous ambulatory peritoneal dialysis
CCPD	continuous cycling peritoneal dialysis
C_{Cr}	creatinine clearance
CNF	congenital nephrotic syndrome of the Finnish type
CNS	congenital nephrotic syndrome
CRF	chronic renal failure
dBP	diastolic blood pressure
D/D_0 glucose	ratio of dialysate glucose at a given time to dialysate glucose at time 0
DOQI	Dialysis Outcome Quality Initiative
D/P	dialysate-to-plasma ratio
EDTA	European Dialysis and Transplant Association
EF	ejection fraction
ESI	exit-site infection
ESRD	end-stage renal disease
GFR	glomerular filtration rate
H	high peritoneal membrane permeability
HA	high average peritoneal membrane permeability
HD	hemodialysis
hSDS	height standard deviation score
IPP	intraperitoneal pressure
Kt/V	urea clearance
L	low peritoneal membrane permeability
LA	low average peritoneal membrane permeability
LAS	left atrial diameter in systole
LVEDD	left ventricular end-diastolic diameter
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVPWD	left ventricular posterior wall thickness at end-diastole
MTAC	mass transfer area coefficient
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
NIPD	nightly intermittent peritoneal dialysis
NPHS1	nephrotic syndrome type 1
NPHS1	the nephrin gene
PD	peritoneal dialysis

Peak E wave	peak velocity during rapid ventricular filling (early filling)
Peak A wave	peak velocity at atrial contraction (late filling)
PET	peritoneal equilibration test
PTH	parathyroid hormone
RDA	recommended dietary allowance
rhGH	recombinant human growth hormone
rHuEPO	recombinant human erythropoietin
sBP	systolic blood pressure
Sept D	interventricular septal diameter at end-diastole
TI	tunnel infection
TPD	tidal peritoneal dialysis
UF	ultrafiltration

INTRODUCTION

Chronic ambulatory peritoneal dialysis (CAPD) was adopted for use in pediatric patients in 1978 (1). CAPD became popular in pediatric patients, because the continuous dialyzing allows more freedom and provides steady control of blood volume and blood purification. Even infants can be kept in acceptable clinical condition with CAPD while waiting for a new kidney, which has allowed renal transplantation to become a standard therapy for end-stage renal disease (ESRD) in childhood. Previously, all children with ESRD died. In Finland, active medical treatment for uremia was started in 1967 for pediatric patients. During the first 10 years, however, only a few small children were treated and most of the older ones were treated in adult hemodialysis (HD) units. Some older children were transplanted in adult units as early as in the 1960s. The first child was transplanted at the Children's Hospital, University of Helsinki, in 1971, after being treated with HD for a longer period. CAPD treatment for Finnish pediatric patients was started in 1982, and for infants in 1986. After 1987, CAPD was gradually replaced by continuous cycling peritoneal dialysis (CCPD).

In Finland, there are more small children on renal replacement therapy than in most other countries because of the high incidence (14.2 per 10^5 live births (2)) of the severe type of congenital nephrotic syndrome type one (NPHS1), which is also called the congenital nephrotic syndrome of the Finnish type (CNF) (3). In Europe as a whole, the annual incidence of new ESRD patients per million children is 4.6, but in Finland 12.5 (4).

Since 1986, Finnish children with CNF have been treated actively. Today, optimal therapy includes bilateral nephrectomy at the age of 6-10 months (5). Prior to renal transplantation, these children are maintained on PD to improve their nutritional status and to correct coagulation abnormalities (5). Because we have more small children on PD than in other centers, and because small children have more complications during PD, it is important for us to characterize the PD outcome in our patients and try to improve their treatment.

Earlier studies on peritoneal membrane permeability in pediatric patients demonstrated higher permeability in younger children (6-11). More recent studies have found similar membrane permeability through the pediatric age range (12, 13). In infants and young children on peritoneal dialysis (PD), determination of blood volume is difficult because of growth. Measurements of weight and blood pressure (BP) and clinical investigations, although important, are insufficient to estimate the exact dry weight of a growing child, and approximately 50% of all children treated with PD are on antihypertensive drugs (14). Maintenance of normal growth is difficult to achieve, and mortality and the number of

infectious complications are higher in small children than in older children and adults (14-17). New, more efficient PD regimens, such as tidal peritoneal dialysis (TPD), were developed and studied in children aged 5-16 years (18-20), but their applicability to small children was not known.

The present study was undertaken to evaluate the outcome in children treated with PD with intensified clinical care and a controlled dialysis dose. Measurements of peritoneal membrane permeability and dialysis adequacy were introduced and studied to enable better control of the dialysis dose. In a prospective study, the results in children under 5 years of age were compared with those in children over 5 years of age. The outcome in children under 5 years of age treated with CPD before 1995 was analyzed from patient files and used as control material. TPD was studied in order to characterize its possible benefits as compared with CCPD. Hypervolemia in the etiology of high blood pressure was also studied, since it is a common and serious complication of PD in childhood.

REVIEW OF THE LITERATURE

END-STAGE RENAL DISEASE

More than half of the renal mass must be destroyed before the serum creatinine concentration rises above normal or glomerular filtration rate (GFR) falls below 80% of normal. Chronic renal insufficiency is present when the GFR decreases permanently to less than 25% of normal and, at this stage, clinical abnormalities are often present. Acidosis, growth failure, renal osteodystrophy, hypertension, and anemia are common, and require medical treatment. But, despite medical treatment, prolonged anemia, acidosis, and azotemia lead to the multisymptom complex known as uremia. When renal dysfunction has progressed to the point at which dialysis or renal transplantation is required, the term ESRD is used. According to the registry of the European Dialysis and Transplant Association (EDTA), the incidence of ESRD in pediatric patients in Europe is about 500 patients annually, which is about 4.5 children per year per million children under 15 years of age (4). Of these patients, 10% are less than 1 year of age, 15% are 2-5 years of age, and 75% 6-14 years of age. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), 6% of ESRD patients are less than 1 year old, 17% 2-5 years of age, and 77% 6-17 years of age (21). However, in Finland there are 12.5 new ESRD cases per million children, and 50% of them are less than 1 year of age (4).

The congenital nephrotic syndrome (CNS) is defined as proteinuria leading to nephrosis soon after birth. NPHS1 includes all patients with a mutation in the nephrin gene (*NPHS1*) (3), and CNF comprises all patients with the severe type of NPHS1, which is unresponsive to medication lowering perfusion pressure. The main problem in CNF is severe loss of protein, 90% of which is albumin (22), leading to severe hypoalbuminemia with generalized edema. Patients with CNF are treated with albumin infusions (5). Nevertheless, they develop muscular hypotonia, which hampers their motor development. Because of urinary losses of gamma globulin and complement factors B and D, CNF patients are especially prone to severe infections, despite the use of immunoglobulin infusions and prophylactic antibiotics (23, 24). In order to prevent the loss of important proteins, CNF patients are bilaterally nephrectomized and dialyzed at an early age. These children differ from other ESRD patients, since they are not uremic before nephrectomy and PD.

The most common renal diseases leading to ESRD in Finland and in the rest of Europe are listed in *Table 1*. In Europe, the most common renal diseases in children less than 2 years of age are congenital anomalies (4), but in Finland CNF predominates in patients

under 5 years of age. However, in older children the diagnoses in Finland and in other European countries are similar.

Table 1. Distribution of primary renal diseases according to the registry of European Dialysis and Transplant Association (EDTA, 1976-1989) and the Finnish Registry for Kidney Diseases (FRKD, 1967-1997).

	EDTA		FRKD			
	<2 yrs	2-15 yrs	<5 yrs		5-14 yrs	
hypoplasia / dysplasia	24%	14%	8%		19%	
cystic kidney disease	10%	7%	2%		9%	
hereditary dis. (CNF[a], CNS[b])	4%	10%	84%	(75%)[c]	19%	(1%)[c]
pyelonephritis / anomal.[d]	15%	24%			17%	
glomerulonephritis	14%	23%	3%		25%	
hemolytic uremic syndrome	17%				1%	
other	16%	22%	3%		9%	

[a] congenital nephrotic syndrome of the Finnish type
[b] congenital nephrotic syndrome
[c] percentage of all patients with CNF or CNS
[d] pyelonephritis, including urinary tract anomalies

MANAGEMENT OF UREMIA IN PEDIATRIC PATIENTS

Nutrition

Pediatric diets for uremic patients are generally liberal in order to achieve optimal growth and to improve compliance. Restrictions are imposed only when there is a clear indication of need. An energy intake of at least 100% of the recommended dietary allowance (RDA) (25) for children of the same gender and height-age is recommended. High-calorie formulas should be used, if needed, in order to meet energy requirements. Protein requirements are high, especially in the youngest patients, because of losses of amino acids and protein in the dialysate (26, 27).

Pharmacological treatment

Anemia is a common finding in PD patients. It is caused by decreased production of erythropoietin (28, 29). To maintain adequate hemoglobin levels, blood transfusions were

previously required by almost all patients, but are now rarely necessary because of the use of recombinant human erythropoietin (rHuEPO) (30).

In chronic renal failure, renal production of 1,25-dihydroxyvitamin D_3 (calcitriol) and renal phosphorus excretion decrease. Renal and intestinal calcium reabsorption decreases because of decreased circulating 1,25-dihydroxyvitamin D_3, resulting in low serum ionized calcium. Reduced ionized calcium concentration stimulates secretion of parathyroid hormone (PTH) by the parathyroid glands (31), which in turn increases osteoclastic activity and the release of calcium from bone. High serum phosphorus also exerts a direct stimulatory effect on PTH secretion, with the result that renal excretion of phosphorus increases (32). Without vitamin D_3 substitution and phosphate restriction, these complex interactions lead to secondary hyperparathyroidism and bone destruction (33-35).

Today calcium carbonate is used for hypocalcemia, and as a phosphate binder. Sodium polystyrene sulfonate resin is used for hyperkalemia. Water-soluble vitamins should be added, and fat-soluble vitamins, except vitamin D, should in general be avoided (36). Antihypertensive drugs are given if needed.

Dialysis treatment

Hemodialysis

Hemodialysis uses extracorporeal perfusion to transfer low-molecular-weight solutes into and out of the body, and to remove water by ultrafiltration. It has been used to treat children with acute and chronic renal failure for over 25 years. HD is used more commonly in older children than younger ones. In 1996, 37% of all pediatric ESRD patients, compared with 12% of patients under 5 years of age, were treated with HD in North America (37). The proposed advantages of chronic HD include the successful long-term use of treatment, minimal technical assistance required by the patient and parents, and relatively low hospitalization rates with 11- 26 hospital days per patient-year at risk (38, 39). In contrast to the arteriovenous fistulas used in adult patients, the most common type of vascular access in children is a dual-lumen venous catheter, usually in the subclavian or jugular vein (14). The most frequent cause of morbidity in HD patients is the need for access revision, caused by infection, clotting, or malfunction (37). Catheterization should therefore be replaced as quickly as possible by fistulas or grafts, which are not without complications in small children, on account of the small caliber of their blood vessels (40). In general, however, there is no difference in the longterm outcome of HD and PD (41). Although PD is today the preferred treatment form for infants and small children, HD treatment has been developed to become more suitable for small children also. Overall

survival rates as high as 52% have been reported for infants weighing less than 5 kg (42). Thus, in experienced hands, HD can also be successfully used for infants with ESRD.

Peritoneal dialysis

PD takes place across the peritoneal membrane between the blood in the capillaries of the peritoneum and the infused dialysis solution. The peritoneal membrane is a semipermeable membrane which allows small molecules and water to pass through faster than larger molecules. PD is an important renal replacement therapy for pediatric patients because of its safety and simplicity. The first child was treated with CAPD in Canada in 1978 (1). CAPD was originally designed for adult patients, and lack of equipment and other supplies suitable for use in children hindered its spread in pediatric patients. However, the time interval between the adoption of CAPD in North America and in Europe was short, and the breakthrough of PD in pediatric ESRD patients began in the 80s (43). The introduction of CCPD, the first automated PD modality, in the early 80s (44, 45) was an important milestone in increasing the use of PD. CCPD was originally developed to reduce the frequency of peritonitis and the complications caused by high intra-abdominal pressure (44, 45). The first experiences with CCPD in pediatric patients were encouraging (45, 46), and it gradually became the most popular PD modality, although daily CCPD clearances of small and middle-sized molecules were not better than those given by CAPD with the same quantity of dialysate (45). TPD was introduced in 1990 to increase the efficacy of dialysis without sacrificing the advantages of CCPD and CAPD (47). Preliminary results in schoolchildren showed that TPD was able to provide a dialysis outcome equal to that of CCPD within a shorter time (18, 19). In recent studies, however, TPD has been shown to be superior only when high dialysis flow is used in patients with high average / high peritoneal membrane permeability (20, 48, 49). For most infants with ESRD, the first treatment modality has become automated PD, and for example in Italy, during 1986-1993, no infants were treated with CAPD or chronic HD (50).

The most common PD techniques are illustrated in *Figure 1*. CAPD treatment is given continuously. Three exchanges are performed manually during the day and one before bedtime. The overnight exchange time is usually 8-10 hours. The dialysate volumes for day and night exchanges are usually the same (about 1000 ml/m^2). CCPD treatment is also given continuously. Usually 5-6 exchanges are made with the help of a cycler machine during the night, combined with a long daytime exchange. It is also possible to perform extra daytime exchanges manually. The nightly dialysis time is 8-12 hours, the night exchange volume usually being 1000-1200 ml/m^2, but the day exchange volumes are

smaller (about 500 ml/m^2). The nightly intermittent peritoneal dialysis (NIPD) is provided with the help of a cycler machine every night, lasting for 8-12 hours. The daytime is free of treatment. There are usually more cycles performed during the night with NIPD than with CCPD. The exchange volume is about 1000-1200 ml/m^2. In TPD, a constant volume of dialysis solution (reserve volume) is maintained in the peritoneal cavity throughout the treatment session. Over and above this reserve volume, rapid fixed tidal volume exchanges are carried out with the help of a cycler machine. The nightly dialysis time is usually 8-10 hours. The initial fill in children is about 1000-1200 ml/m^2, and the tidal volume exchanges are usually made with a volume which is 50% of the initial fill. Day exchanges are optional. With all treatment modalities, the glucose concentration is chosen according to the patient's ultrafiltration (UF) needs.

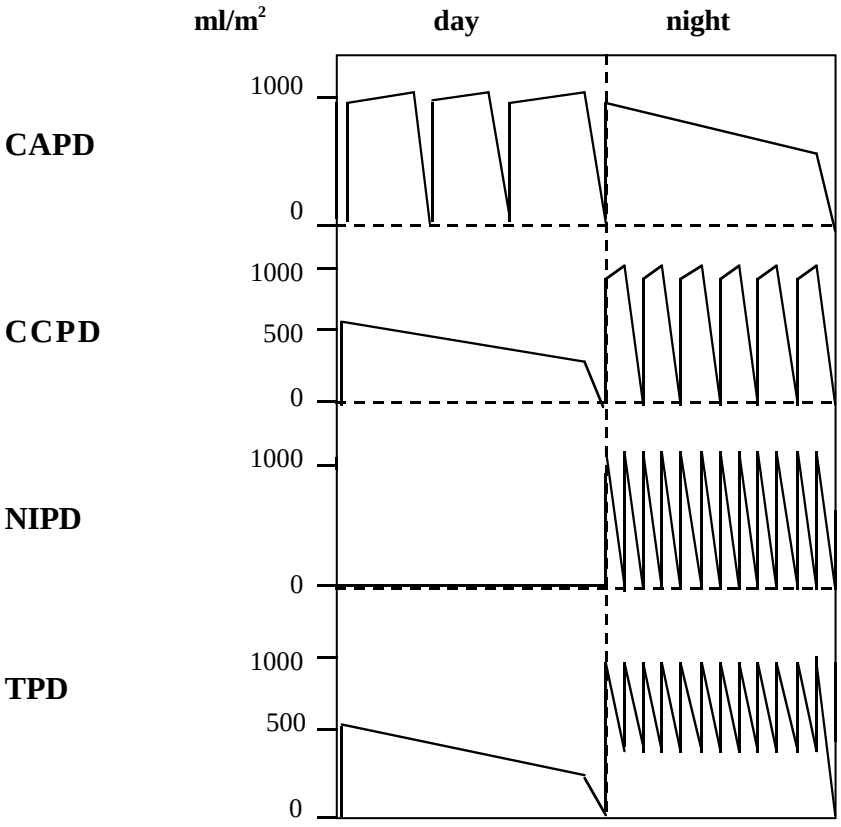

Figure 1. The most common regimens of peritoneal dialysis. The vertical line represents the change from day to night, and the horizontal lines the dialysate volume of 0 ml/m^2.

PERITONEAL TRANSPORT KINETICS

Peritoneal equilibration test

The peritoneal equilibration test (PET) was developed to investigate peritoneal membrane function (51), so as to be able to individualize and optimize the patient's PD regimen. PET is based on ratios of dialysate-to-plasma solute concentrations (D/P) to define the rate of solute transport across the peritoneal membrane. Similarly, the ratio of glucose in the dialysate at a given time to the initial glucose concentration immediately after instillation of dialysate into the peritoneal cavity (D/D_0 glucose) is used to predict the likelihood of achieving ultrafiltration. The D/P and D/D_0 glucose ratios of an individual patient are plotted against standard curves, thereby permitting categorization of the patient's membrane transport as rapid (high; H), slow (low; L) or average (high average; HA, low average; LA) (*Figure 2*). PET should be performed at earliest 4 weeks after an acute episode of peritonitis. At least 4 weeks are required, because peritonitis induces a hyperpermeable state in the peritoneum, which normalizes within 2 to 4 weeks (52).

PET has been used in pediatric patients, but its application has been controversial and problematic, since the test was initially introduced for use in adult patients. Early studies have demonstrated a trend toward higher membrane permeability in young children as compared to older children and adults (6-11). However, in these studies the test volume was related to body weight instead of body surface area (BSA), which has been later recommended for calculation of the test volume (53), since BSA is proportional to the surface area of the peritoneal membrane (54). Despite calculating the test volume according to BSA (1000-1100 ml/m^2), reports about peritoneal membrane transport were inconsistent (13, 55, 56). In 1996, the most comprehensive report with 95 patients was published (12). In this multicenter study, peritoneal membrane transport was found to be similar across the pediatric age range, and pediatric reference curves were defined (12).

Very few studies have measured alterations in the peritoneal equilibration rate over time in pediatric patients and the short follow-up times in children have hindered interpretation of the results. Peritonitis has been assumed to be a risk factor for deterioration of peritoneal membrane function in children (57). Latterly, however, peritoneal membrane permeability has been shown to be relatively stabile in patients with no history of peritonitis and to increase in patients who have experienced one ore more peritonitis episodes (58, 59). Increased microvascularization of the peritoneal membrane, in response to infections and chronic exposure to a high glucose concentration, has been suggested to explain the increased membrane permeability (59). Peritonitis, especially that caused by

Pseudomonas and alpha streptococcal organisms, may increase the risk of peritoneal membrane failure (60, 61).

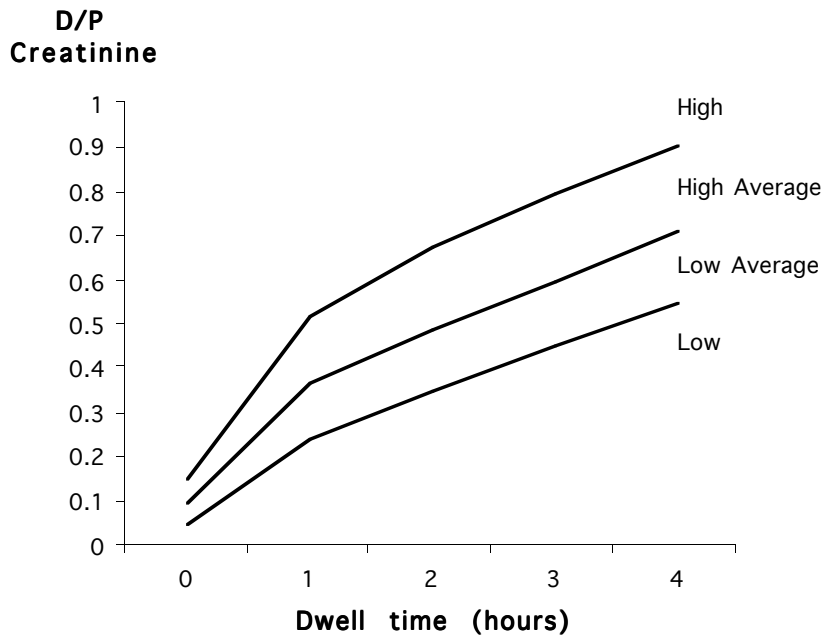

Figure 2. PET reference curve for creatinine. Lines represent mean ± 1SD. High, high average, low average, and low represent the peritoneal membrane transport categories.

Mass transfer area coefficient

In the absence of an osmotic gradient between the blood and the dialysate, the rate of solute movement is directly proportional to the solute concentration gradient, the membrane size, and the diffusive permeability of the membrane for the solute. For small solutes, the concentration gradient decreases exponentially and for larger solutes almost linearly. The surface area and the diffusive permeability are combined into a single parameter, the mass transfer area coefficient (MTAC). MTAC represents the maximal clearance of the membrane for a solute at the point when the dialysate concentration of the solute is zero. MTAC has been assumed to be constant in a specific patient from exchange to exchange (62).

DIALYSIS ADEQUACY

Since the introduction of dialysis treatment, efforts have been made to define the appropriate dose for purification. Urea and creatinine clearances have been used as markers of small solute clearance. Kt/V represents the urea clearance normalized for the volume of urea distribution. Kt means the urea clearance during the sampling period and V is the urea distribution volume, which is considered equivalent to total body water. C_{Cr} represents the creatinine clearance, which is measured similarly to Kt/V over 24 hours, but is expressed as liters of clearance per week. Dialysis adequacy has been used to describe the minimally acceptable dose of dialysis, below which a significant increase in morbidity and mortality would occur. In adult patients, mortality is often used as a criterion for dialysis adequacy (63), but it is more difficult to define adequate dialysis in children, because of the small number of dialyzed children, the short duration of dialysis, and the difficulty of normalizing the measured dialysis doses across the range of body sizes. The Dialysis Outcome Quality Initiative (DOQI) guidelines published in 1997 were based on a review of 260 published articles (63). For adult patients, the CAPD doses delivered should be a total of weekly urea Kt/V >2.0 and a total of weekly C_{Cr} >60 L/1.73 m^2. According to mathematical calculations, the equivalent delivered doses for CCPD and NIPD should be 2.1 and 2.2 for urea Kt/V, and 63 and 66 L/wk/1.73m^2 for C_{Cr}. Since no data linking PD dose with clinical outcome were available for children, the use of the adult recommendations as the lower limit of PD adequacy was proposed for children (63).

CLINICAL OUTCOME OF PEDIATRIC PD

Hospitalization

Hospitalization is an important aspect of morbidity in pediatric PD patients. Pediatric PD patients spend 13-100% more days in hospital than HD patients (38, 39). Hospitalization rates of 15-30 days per year at risk have been reported in children (17, 39), but the numbers of hospital admissions and hospital days have been shown to be much higher in younger children than in older children (38). Peritonitis is the most frequent cause of hospitalization in pediatric PD patients (33% of admissions), followed by catheter-related problems (19% of admissions) (64).

Dialysis access

The median survival time for PD catheters has been reported to be 1-3 years (37, 65). According to 1996 NAPRTCS data, about 20% of catheters need to be replaced, mostly because of catheter malfunction (47%), peritonitis (18%), or exit-site/tunnel infection (17%) (37). The most common combination of PD access in pediatric patients is a Tenckhoff curled catheter with a single cuff, a straight tunnel and a lateral exit-site (37, 66).

Dialysis adequacy

Published information on dialysis doses delivered in children is limited. However, initial studies in pediatric patients have shown that C_{Cr} targets of >60 L/wk/1.73m^2 are difficult to achieve (67, 68); in fact, only Walk et al. have succeeded in showing, in 19 patients (median age 9 years), a mean C_{Cr} of 74±47 L/wk/1.73 m^2, achieved with CAPD and NIPD therapies (69). In contrast, the target weekly urea Kt/V clearances are achieved in most pediatric patients (67-70). There are only a few studies correlating clinical outcome and dialysis adequacy in pediatric patients. In 1997, Walk at el. reported urea Kt/V and C_{Cr} to correlate weakly with serum albumin and protein intake (69), but Schaefer et al. could not confirm this (68). In 1999, however, Schaefer et al. reported that the peritoneal transporter state was an independent determinant of growth, and suggested that high transporters were at risk of poor growth and of becoming obese (68).

Growth

Malnutrition, acidosis, anemia, and renal osteodystrophy are believed to impair growth in children on RRT (71-73). Because one third of a child's growth occurs during the first 2 years of life, infants are at greatest risk of loosing growth potential (74, 75). Thus, growth retardation in children whose disease begins after infancy usually is less than that seen in children with congenital disease (76). In some children with chronic renal failure (CRF), optimal nutrition and medical care have been shown to provide normal growth velocity (77, 78). However, significant catch-up growth to correct the height lost has not been obtained without recombinant human growth hormone (rhGH) during conservative therapy (77, 78). At transplantation, according to the NAPRTCS registry, the mean height deficit for pediatric patients was –2.16 SDS (14). Younger recipients had a greater height deficit at the time of transplantation (14). Early studies showed better growth in children treated with PD than with HD (79, 80), but recently growth has been shown to be comparable under PD and HD (81), and even catch-up growth has been reported in children treated

with HD (82). However, optimization of nutritional support and medicinal therapy with vitamin D, rHuEPO, and mineral supplements has not uniformly improved growth during PD treatment (17, 37, 83-85). Caloric supplementation far beyond 100% of RDA (25) has been suggested to lead to obesity rather than to improved growth (86, 87). However, some recent studies have suggested that a high energy intake correlates with better growth (84, 88, 89). Catch-up growth has been achieved in pediatric PD patients mostly only with rhGH therapy, which is recommended during PD to prevent further loss of height (17, 90).

Complications

Peritonitis

Peritonitis is the major cause of morbidity and technique failure in PD patients. The incidence of peritonitis is higher in children than in adults (15, 91-93), and within the pediatric population, infants and children up to 5-6 years of age develop peritonitis more frequently than older children (37, 65, 66, 94). Reported incidences of peritonitis range from one episode per 8 to one per 29 treatment months (14, 17, 64, 65, 95, 96), but recent data from the NAPRTCS registry, involving more than 2000 patients, gives an overall incidence of one episode for every 13 patient-months (37). The peritonitis rate for infants under 1 year of age was one per 9.9 months, for children 2-5 years of age one per 12.7 months, and for children over 6 years of age one per 14.3 months (37). The exact etiology of the higher peritonitis rate in infants is unclear, but potential predisposing factors might be hypogammaglobulinemia (97), upper respiratory tract infections (61), and a shorter subcutaneous tunnel with its exit-site near the diaper area.

The recommended definition of peritonitis during PD is a dialysate white blood cell count of at least 100/μl, of which over 50% should be polymorphonuclear leukocytes (92). Other signs include abdominal pain, and/or cloudy peritoneal fluid, fever, and identified organisms in culture and/or Gram stain (92). The predominant pathogens are Gram-positive organisms (50-60%), followed by Gram-negative organisms (10-30%) and fungi (<5%) (14, 64). The commonest Gram-positive organism is *Staphylococcus aureus* followed by *Staphylococcus epidermidis*, and the commonest Gram-negative organisms are *Enterobacter* and *Pseudomonas* (64, 98). The recommended initial treatment for peritonitis includes vancomycin and ceftazidime or aminoglycoside intraperitoneally (99), adjusted later according to the microbial findings. In the 1993 guidelines, intermittent intraperitoneal therapy with vancomycin (once a week) and aminoglycosides (once daily) were included in the recommendations, but only for adult patients (99). In the most recent updated guidelines in 1996, limited usage of vancomycin and return to first-generation

cephalosporins instead of vancomycin was recommended, because of the increasing prevalence of vancomycin-resistant microorganisms (92). In a recent study, however, vancomycin, administered intermittently to pediatric patients in two doses 7 days apart, was found to be as effective as when administered continuously (100).

Exit-site infections and tunnel infections

The most common definition of exit-site infection (ESI) is redness and/or skin induration, and purulent discharge at the catheter sinus, and for tunnel infection (TI) purulent outflow from the tunnel, and redness and induration above the tunnel. The most common organisms causing ESI in pediatric PD patients are *Staphylococcus aureus* (46%), *Staphylococcus epidermidis* (26%), and *Pseudomonas aeruginosa* (10%) (101). Because of lack of standardized criteria for the diagnosis of ESI and TI, studies reporting their incidences in pediatric patients are sparse. Levy et al. reported an incidence of ESI of one episode per 6 months (101), and, according to NAPRTCS data, 28% of patients have had ESI at 12 months of PD (37). Microbial analysis of the causative agent is mandatory in the diagnosis of ESI and TI. Gram-positive bacteria should be treated with penicillinase-resistant penicillin or with first-generation cephalosporins orally for 7-10 days (92). For Gram-negative organisms, ceftazidime is recommended (92). Catheter removal is indicated in case of chronic ESI or TI, and if ESI or TI is associated with Gram-negative peritonitis, especially when due to *Pseudomonas*, or with *Staphylococcus aureus* peritonitis or fungal peritonitis (102).

Hypertension

About 50% of all children on PD are receiving antihypertensive drugs (14). BP studies in pediatric PD patients are sparse. Lingens et al. reported hypertension in 47% of their pediatric PD patients aged over 6 years and, when measured with an ambulatory BP monitor (ABPM), 70% were found to be hypertensive (103). ABPM has also been used in pediatric patients to measure the BP profile. Patients with renal diseases have been shown to have altered BP profiles with increased nocturnal BP as compared with healthy children (103, 104).

Estimation of the exact dry weight of infants and young children on PD is difficult. Weight gain may be interpreted as growth, although it may have been caused by retention of sodium and water. A normal blood volume is, in general, reached in ESRD patients with residual renal function through both dialysis and residual renal function. In contrast, in nephrectomized children, blood volume is regulated only by dialysis. Therefore it is

difficult to avoid hyper- or hypovolemia. However, normal volemia is aimed at limiting the use of antihypertensive medication.

Vasoactive hormones such as atrial natriuretic peptide (ANP), cyclic guanosine monophosphate, and plasma catecholamines have been studied with the aim of correlating them with blood volume (105, 106). ANP is a cardiac hormone that is secreted primarily by atrial myocytes in response to local wall stretch. ANP reduces systemic BP and intravascular volume through relaxation of vascular smooth muscle, through increasing salt and water excretion, and through facilitating trassudation of plasma water to the interstitium (107). Pro-ANP 1-126 is cleaved by a membrane protease to release a vasoactive carboxy-terminal peptide (ANP-C) and amino-terminal ANP (ANP-N) (108). The plasma level of ANP-C in healthy children more than 4 weeks of age has been shown to be similar to that of healthy adults (109). Plasma levels of ANP-C are known to increase in renal failure (110, 111), in association with hypervolemia in adult patients on HD and PD (105) and in pediatric patients on HD (111, 112), as well as in association with cardiac dysfunction in adult PD patients (106). However, there are not many studies dealing with ANP in pediatric PD patients. In one pediatric study, the plasma level of ANP-C was found to be increased in PD patients with fluid overload, but not in those with an apparently normal blood volume (113). ANP-N has been found to be more stable ex vivo than ANP-C, which makes its use in clinical work easier and more reliable (114, 115). Since 1993, a few clinical studies dealing with ANP-N have been published, showing a significant correlation with the decrement in relative blood volume in adult patients on HD (116), and an even better correlation with LVH and LV dysfunction than with ANP-C (117-119). Recently, similar results have been shown in pediatric patients with heart disease (120).

Cardiac complications

Chronic volume overload, systemic hypertension, and anemia predispose to left ventricular hypertrophy (LVH) and diastolic dysfunction (121). According to echocardiographic studies, increased left ventricular mass (LVM) and impaired left ventricular diastolic function are common in both adult and pediatric PD patients (122-125). In a few studies, however, the cardiac state has been shown to improve as a result of better control of volemia, blood purification, BP, and anemia during PD (126, 127).

Other complications

Inguinal and abdominal wall hernias are common in children treated with PD and 23 - 40% of the patients have been reported to develop hernias (128, 129). Young males are at greatest risk for inguinal hernias. A dialysate volume of more than 1200 ml/m^2 (over 800 ml/m^2 in neonates) has been shown to increase the intraperitoneal pressure (IPP) in children from 8 to 12 cm of water, but substantial intra-individual variations for IPP were found after the same amount of fluid (130). The effect of high IPP on the development of hernias was demonstrated in a recent study (131). Hydrothorax is an uncommon complication of PD, which is found more often in small children (132, 133). The leak has been suggested to be the result of raised intraperitoneal pressure due to small defects in the pleuroperitoneum covering the diaphragm (134).

Mortality

The overall mortality rate for the pediatric PD population is 9-11% (37, 65). Mortality rates for children less than 6 years of age are reported to be greater than for older children (37, 50, 65). According to the NAPRTCS database, the mortality rate for children less than 2 years of age was 22.5% and for children 2-5 years of age 11.5%, as compared with 5-7% for children 6-17 years of age (37), the most common causes of death being cardiopulmonary disease and infection (66).

AIMS OF THE STUDY

Because of the relative abundance of young children on PD in Finland, the PD outcome was studied for children under and over 5 years of age. The main objective of the present study was to investigate whether the PD outcome in small children differs from that in older children and whether the outcome could be improved through intensified clinical care and PD adequacy control. The specific aims of the study were:

1. to retrospectively analyze the clinical PD outcome in children under 5 years of age (I),

2. to evaluate peritoneal transport kinetics and its changes over time, and any differences between children under and over 5 years of age (II),

3. to study the clinical PD outcome under PD adequacy control, and to compare the outcomes of the age groups under and over 5 years of age with one another and with previous results (III),

4. to compare PD adequacy and outcome of CCPD and TPD therapies (IV), and

5. to specify the impact of hypervolemia in the etiology of hypertension (V).

PATIENTS AND METHODS

ETHICAL CONSIDERATIONS

The study design was approved by the Ethical Committee of the Hospital for Children and Adolescents, University of Helsinki. Informed consent was obtained from the patients and/or their parents or guardians after the design and purpose of the study had been explained.

PATIENTS

The diseases of the patients included in studies I-V are listed in *Table 2*.

Table 2. Demographic data of patients included in studies I-V.

	I	**II**	**III**	**IV**	**V**
Patient number	34	28	21	17	21
Renal disease					
CNF (*NPHS1* mutation)	27	10	10	9	11
CNS	3	-	-	-	-
obstructive uropathy	1	3	3	3	2
cystic kidney disease	1	3	2	-	3
reflux nephropathy	-	1	1	1	1
RPGN[a]	-	1	1	1	1
prune-belly syndrome	-	2	1	1	2
Alport syndrome	-	1	1	1	-
Wegener's granulomatosis	-	2	1	-	-
Denys-Drash syndrome	-	1	1	1	1
other[b]	2	4	-	-	-
Age at baseline, years	1.6±1.0	7.8±5.5	5.5±5.0	5.1±5.0	5.3±5.3
(range)	(0.6-4.3)	(0.3-16.6)	(0.3-14.4)	(0.3-14.4)	(0.2-14.8)
<5 years	1.6±1.0	1.7±1.3	1.0±0.6	1.0±0.7	0.9±3.4
≥5 years	-	11.2±3.8	9.6±3.4	9.7±3.3	10.2±3.4
Nephrectomy (<5/≥5yr)	29 (29/-)	12 (8/4)	12 (9/3)	10 (8/2)	13 (10/3)

[a] rapidly progressive glomerulonephritis

[b] neuroblastoma, dysplasia renis, IgA nephropathy, lupus erythematoides disseminatus (LED), dysplasia fibromuscularis arterialis, and optic nerve coloboma with renal disease.

Study I: The study included all children under 5 years of age who had been placed on chronic peritoneal dialysis at the Hospital for Children and Adolescents, University of Helsinki before 1995. The patient records were analyzed from initiation of dialysis to renal transplantation (0.8±0.4 years).

All pediatric patients treated at the Hospital for Children and Adolescents with maintenance peritoneal dialysis were potential candidates for the prospective studies (II-V). Between 1995 and 1998, all patients being maintained on or starting peritoneal dialysis were asked to participate in the study, with the aim of obtaining equal numbers of patients for the groups under and over 5 years of age. A total of 30 patients were included; 15 were under 5 years of age. Two patients aged over 5 years were followed twice: one patient was without PD for 1 year, and the other for 4 months, after their first kidney transplantation. In seven patients (three patients were under 5 years of age) the follow-up time was less than 3 months because of early renal transplantation. Twelve patients were studied during the entire follow-up period of 12 months, six of whom were under 5 years of age. The remaining 11 patients were followed for 3–9 months. The mean dialysis time prior to examination was 0.38±0.49 years (0.02-1.86 years), and the mean follow-up time in the study was 0.70±0.37 years (0.06-1.08 years).

Study II: The PET results for 24 patients were analyzed. In addition the results for four other patients were available. In the latter patients, only the regular PETs and adequacy measurements were performed. Baseline PETs were analyzed for all patients, and control PETs for 21 patients after 0.8±0.4 years. The latest available PET served as a control for the study of long-term changes in peritoneal membrane function. In some patients, PETs were performed every 3 months even after the 12-month study period. Accordingly, in these patients the latest available PET was performed after 12 months. The mean dialysis time before the study was 0.39±0.42 years. At the start, the mean age of the 10 children under 5 years of age was 1.7±1.3 years and of the 18 children over 5 years of age 11.2±3.8 years.

Study III: All the patients followed for at least 3 months were included in the study. For the analysis of clinical outcome under adequacy control, the final number of patients was 21. The patients were divided into two groups according to age; under 5 years of age (n=10, 1.0±0.6 years) and over 5 years of age (n=11, 9.6±3.4 years). The mean follow-up period was 0.8±0.2 years.

Study IV: Seventeen patients were enrolled in the study comparing the efficacies of CCPD and TPD therapies. However, four patients tested only with one modality were excluded from further analysis. The remaining 13 patients were dialyzed for at least 6

months with one modality and for 3-6 months with the other, to allow comparison. The patients were seen every 3 months. Thus, if the patient was followed for 6 months on the first modality and for less than 6 months on the second, the mean of the two measurements obtained during the first modality was compared with the single measurement during the second modality. At the start of the study, nine patients were under 5 years of age (1.0±0.7 years).

Study V: Twenty-one patients were enrolled in the study of hypertension. Baseline data were available for all these patients, and control data for nine patients (after 0.9±0.2 years). Eleven patients were under 5 years of age (0.9±3.4 years).

METHODS

A retrospective analysis was made from data collected from the patients' files (I). The following data were collected: characteristics of PD, medication, laboratory data, peritonitis data, and measurements of height and weight. In the prospective studies the observation period was up to 12 months unless renal transplantation was performed earlier. All patients were seen every 3 months for clinical and dietary examination, laboratory tests, BP measurements, dialysate collection, and PETs. Between these visits, the patients visited their local hospitals every 2-4 weeks.

Peritoneal dialysis (II-V)

The dialysate volume was calculated according to the patient's BSA; a nightly exchange volume of 1000 ml/m^2 of BSA, and a last fill of 500 ml/m^2 were targeted in all the prospective studies. All patients received nightly automated peritoneal dialysis and a long daytime exchange. In the anephric children, two additional exchanges were performed in the late afternoon to avoid hypertension. The target volume of the additional daytime exchange was 500 ml/m^2 of BSA per exchange. The glucose concentration used varied according to the estimated dry weight of the patient at every check-up. None of the children in the prospective studies were treated with CAPD. CCPD therapy consisted of approximately 9 (8-14) exchanges throughout the night. The initial TPD prescription consisted of a fill volume of 1000 ml/m^2 and 21-24 tidal exchanges with 50% of the initial fill, leading to a nightly dialysate flow rate of approximately 50 ml/kg/h. Curled, single cuff Tenckhoff catheters (Quinton Instruments, Seattle, WA, U.S.A.) were used. In most patients, the tunnel was straight and lateral and the exit-site pointed upward. The cycler

machines used were PAC X, PAC Xtra, Home Choice (Baxter Healthcare, Illinois, U.S.A.), PD 100 (Gambro, Lund, Sweden), and PD-Night (Fresenius AG, Schweinfurt, Germany).

Collection of dialysate and urine (III, IV)

A complete 24-h collection of dialysate and urine was obtained from each patient every 3 months. This was modified to make it possible to keep the patients in hospital only 2 days. A modified 24-hour dialysate collection was started at noon on day 1 with replacement of the last fill volume after a complete dwell; if there were day exchanges, they were performed as usual. Night dialysis was performed 2-4 hours earlier than for the patient's normal dialysis program. After the night dialysis, an 8-hour dwell was performed with 1000 ml/m^2 of 2.27% glucose dialysate.

Peritoneal equilibration test and mass transfer area coefficient (II-IV)

Immediately after dialysate collection, a 4-hour PET was performed with 1000 ml/m^2 of 2.27% glucose dialysate. Blood samples were taken immediately after completing the dialysate collection, and again after 2 hours (during PET). Dialysate samples were taken immediately after completion of the infusion, and after 1, 2, and 4 hours. To achieve a physiologically consistent relationship between the blood and dialysate concentrations of the particular solute, all serum values, except albumin, were expressed as concentrations per unit volume of plasma water. This was achieved by dividing the serum values, except that of albumin, by a factor 0.93, thereby correcting the plasma volume for protein and lipid contents (135). Dialysate and serum creatinine assays were further corrected for glucose interference, as suggested by Twardowski et al. (51), using a correction factor of 0.51 specific to our laboratory. Peritoneal transport was estimated from the dialysate-to plasma ratios at 0, 1, 2, and 4 hours, and glucose transport from dialysate to patient was estimated from dialysate glucose at a given time to dialysate glucose at time 0. In study IV, pediatric reference values of 4-h D/P for creatinine (12) were used to determine the type of peritoneal membrane transport.

Calculation of the MTAC, characterizing the diffusive permeability of the peritoneal membrane, was based on the two-pool Pyle-Popovich model (136), and was further expressed as a weighted average (II).

Dialysate collection and kinetic studies were performed at least 1 month after completing antibiotic therapy for peritonitis. The 1.4 version of the PD ADEQUEST program (Baxter Healthcare, Deerfield, IL, U.S.A.) was utilized to calculate the MTAC values (II), and total weekly C_{Cr} and urea Kt/V from the modified 24-hour collection (III, IV). For the clearance calculations, total body water was estimated from height and body weight, using the child-specific equation of Friis-Hansen (137). BSA was calculated, using the child-specific equation of Haycock et al. (138). In 1995, we used a urea Kt/V of >1.7 and a C_{Cr} of >40 L/wk/1.73m^2 as target clearances (139). In 1997, we adopted new raised targets: a urea Kt/V of >2.0 and a C_{Cr} of >60 L/wk/1.73m^2 (140) (III, IV). The PD ADEQUEST program was further used to obtain mathematical simulation of the results of the patient's usual 24-hour dialysis regimen, and of changes planned in the PD prescription.

Diagnosis and treatment of peritonitis (II, III)

As criteria of peritonitis, we used cloudy peritoneal fluid and an elevated dialysate white cell count >100/μl with >50% polymorphonuclear cells. Facultative findings were abdominal pain and/or fever. Peritonitis therapy outside our institution consisted of loading doses of vancomycin (15 mg/kg) and netilmycin (1.8 mg/kg) intraperitoneally for 2 hours, followed by 8 to 12 daily exchanges of dialysate containing 30 mg/L vancomycin and 8 mg/L netilmycin. Patients treated at our institution received intermittent intraperitoneal antibiotic treatment: vancomycin in a dose of 30 mg/kg in one 6-hour exchange, and netilmycin 20 mg/L using one dose daily. The serum vancomycin concentration was followed, and the dose was repeated after one week or earlier if the serum concentration fell below 5 μg/ml. Antibiotics were later adjusted according to the microbial findings and continued until the peritoneal fluid leukocyte count and C-reactive protein had normalized after 8 to 10 days. Heparin (500 U/l) was added to the dialysate until the effluent was clear.

Nutrition and dietary examination (III)

Nasogastric tube feeding was used if spontaneous protein and energy intakes were clearly below our target for chronological age. Tube-feeding was based on infant milk and cereal formulas, supplemented with a casein-based protein product and glucose polymers. Rape seed oil and glucose polymer were added to the diet if additional energy was needed. The protein allowance was restricted only if blood urea nitrogen (BUN) rose above 40 mmol/L. Additional changes in diet were made if the serum phosphorus concentration rose above the reference values. Adherence to diet was checked using a 3-day food record.

Nutritional intakes were analyzed using a computer program (Unidap SFO4a, van den Berg Foods).

Medication (II-IV)

Water-soluble vitamins were added to the diet and vitamin D was given as oral alphacalcidol pulse therapy two to three times weekly (141). The alphacalcidol dose was adjusted to keep the serum intact PTH concentration between 80 and 150 ng/L. Calcium carbonate was used as a calcium supplement and phosphate binder. Sodium polystyrene sulfonate resin was given, if needed, for hyperkalemia. All patients received rHuEPO subcutaneously; the starting dose was 50 U/kg three times weekly. The dose was later adjusted to keep the blood hemoglobin concentration at about 110 g/L. During rHuEPO therapy, the patients received oral iron (Fe^{++}) supplementation, with a starting dose of 5 mg/kg per day. One patient was given recombinant human growth hormone (III).

Auxological measurements (I, III)

Height and weight were measured by the same trained nurse. Height was measured in the supine position until 2 years of age (Holtain LTD, Crymych, Pembs, United Kingdom), and later with a Harpenden stadiometer (Holtain LTD, Crymych Dyfed, United Kingdom). The height standard deviation score (hSDS) was calculated according to the following equation: hSDS = (observed value – mean value) / SD, where SD represents the standard deviation for the normal population of the same chronological age and gender (142, 143). In study I, the ΔhSDS was calculated from height measurements performed 6 months before and after the dialysis began, and in study III nine months after the study began. The patients' height percentiles were calculated according to the Finnish reference data (V) (144).

Blood pressure measurement (V)

Mean daytime systolic and diastolic blood pressures were calculated from serial blood pressure measurements obtained with an automatic oscillometric Dinamap device (Vital Signs monitor 1846 and 8100, Criticon inc., Tampa, FL, USA). Blood pressure was also measured with an ambulatory blood pressure monitor over 24 hours. An auscultatory device (QuietTrak, Tycon-Welch-Allyn, Arden, NC, USA) was used, the validity of which has been confirmed (145). The monitor was programmed to measure blood pressure every 20 minutes during the daytime and every 30 minutes during the night. The updated 1987

Second Task Force reference values, giving the age, gender, and height-percentile-specific 95th percentile values for systolic and diastolic daytime blood pressure, were used to define hypertension (146). For correlation analysis, the grade of hypertension was calculated as the difference between the patient's BP and the 95th percentile. ABPM data were not used to define hypertension, since the available 95th percentile values are not applicable for patients with a body height <120 cm (104). Nocturnal declines ("dips") in systolic and diastolic BP were calculated from ABPM data as (mean daytime BP – mean nightly BP) / mean daytime BP. A decline of at least 10% from the daytime BP was considered to be normal nocturnal dipping (104, 147).

Cardiological investigation (V)

M-mode and Doppler echocardiography were performed, using an Acuson 128 XP ultrasound unit with 4.0, 5.0, and 7.0 MHz transducers or an Acuson Sequoia ultrasound unit with 5.0 and 7.0 MHz transducers (Acuson Corp., Mountainview, CA, USA). Measurements were made by the same investigator (J-M.H) on an average of three consecutive cycles, according to the recommendations of the American Society of Echocardiography (ASE). LVM was determined by M-mode echocardiography, using the formula for anatomic LV mass determined by the ASE-cube method (148). The following echocardiographic data were collected: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal diameter at end-diastole (Sept D), left ventricular posterior wall thickness at end-diastole (LVPWD), aortic diameter at end-diastole (AOD), left atrial diameter in systole (LAS), ejection fraction (EF), diastolic mitral inflow measuring the peak E wave flow (early filling), and the peak A wave flow (late filling).

Linear dimensions (LVEDD, LVESD, Sept D, LVPWD, AOD, and LAS) were recalculated in relation to $BSA^{0.5}$, as recommended by Gutgesell and Rembold (149), to permit comparisons between the results for the age groups. Reference ranges (95th percentile) for the echocardiographic measurements in the Dutch population were used for the upper limit of normal (150), because they represent European reference values. For the peak E and peak A waves, the 95th percentile values according to Schmitz et al. were chosen (151). LVM was related to body height$^{2.7}$, which produces a linear relationship and allows comparison between the age groups (152). LVH was defined as LVM above the 95th percentile related to body height$^{2.7}$ (152). We calculated the LVM (%), for correlation analysis, as the difference between the actual LVM related to body height$^{2.7}$ and 95th percentile for LVM related to body height$^{2.7}$ divided by the actual LVM related to body height$^{2.7}$.

Atrial natriuretic peptide (ANP) measurements (V)

For ANP determinations, venous blood was taken into ice-cold tubes containing Na_2 EDTA, 6 g/L of blood. Plasma was separated at 4°C and stored at –20°C until analyzed. The ANP-C concentration was determined by radioimmunoassay without extraction (153). The ANP-N concentration was measured from plasma with an in-house immunoradiometric assay, using two monoclonal antibodies (Mabs). One (Mab 7801, Medix Biochemica, Kauniainen, Finland) was used for coating maxisorp star tubes (Nunc, Denmark), and the other (Mab 7901, Medix Biochemica) was iodinated by the Chloramine-T method and was used as a tracer. Incubation was carried out overnight at 4-8 °C. Calibration was made against a radioimmunoassay (RIA) method, with pro-ANP 1-30 (Peninsula, England) as standard. Since 1999, ANP-N has been measured from serum by immunofluorometric assay, using two monoclonal antibodies (Mab 7901 labeled with Europium and Mab 7801 coated microtiter plates (FB plates, Delfia-graded, LabSystems)). Calibration was made against the RIA method, with synthetic pro-ANP 1-30 (Peninsula, England) as standard. The ANP-N levels assayed with the two methods were comparable.

Statistical analysis

All data are expressed as means ± 1SD, or medians (range). Comparisons of the two groups were performed using the unpaired t test and the Mann-Whitney U test for nonparametric data. The paired t test was used for comparison of paired measurements from the same individual. The Wilcoxon signed rank test was used for paired comparison of nonparametric data. Analysis of variance with repeated measures was used to determine whether time affected the parameters studied (III), and Bonferroni's method was used for correction of simultaneous multiple comparisons with the baseline values within the groups. For significant interactions, paired tests were used (III). Pearson's correlation coefficient was used to evaluate linear correlations between parametric data, and the Spearman rank correlation coefficient for correlations between nonparametric data. Simple regression analysis was used to identify the independent predictors MTAC (II), hSDS, C_{Cr}, and urea Kt/V (III). Statistical association was considered significant at $p < 0.05$.

RESULTS

CLINICAL OUTCOME (I, III)

The main clinical outcome measures are summarized in *Table 3*. The results for children under 5 years of age, treated between 1986 and 1994 (I), and the results for children under 5 and over 5 years of age treated between 1995 and 1999 (III) are given separately to allow comparison. CCPD therapy consisted of 6±2 (4-12) exchanges, with a mean volume of 730±97 ml/m^2 per exchange in 1986-1994, and 9±2 (6-12) exchanges with a mean volume of 855±188 ml/m^2 per exchange in 1995-1999. The volume was lower in the younger children; 716±95 and 982±161 ml/m^2 for children under and over 5 years of age, respectively (III). Thus, the dialysate volume per dwell was similar in children under 5 years of age treated in 1986-1994 and after 1995, but more night dwells were performed after 1995. The total 24-h dialysate volume was significantly higher in children under 5 years of age treated after 1995 than in those treated in 1986-1994 (9.3±1.5 L/m^2 vs 5.3±1.1 L/m^2, $p<0.0001$, unpaired t test). The general outline of treatment for uremia and the guidelines for nutrition were not changed between 1986-1994 and 1995-1999, the essential difference being the regular use of adequacy measurements, knowledge of peritoneal transport characteristics, and the regular use of rHuEPO. The doctors responsible for the patients were the same in 1986-1994 and after 1995.

Hospitalization

In the 1980s, the length of hospitalization in the patients under 5 years of age was very high, 270 days/patient-year, but decreased to 150 days/patient-year in the 1990s, after experience with PD had increased (I). The hospitalization rate was later significantly higher for patients under 5 years of age, as compared with older ones (III). The higher rate of hospitalization in the younger patients was due largely to two patients with social problems: one patient had to spend the whole dialysis period (11.2 months) in hospital, and the other, half of the week for over 12 months. If these two children are excluded, the length of hospitalization is reduced to 55 days/patient-year in the younger patients, and the total length of hospitalization from 60 to 40 days/patient-year. The most common reasons for hospitalization were dialysis control (37%) and peritonitis/ESI (15%) (III).

Table 3. PD outcome measures at 6 months follow-up in patients <5 years of age (1986-1994 and 1995-1999) and in patients ≥5 years of age (1995-1999). Percentages represent the proportions of patients with antihypertensive medication (hypertension), seizures or pulmonary edema during at least one 3-month observation period. P^1 represents the significance level in children <5 years of age, and P^2 that between children <5 and ≥5 years of age.

	<5 years		≥5 years		
	1986-1994	1995-1999	1995-1999	P^1	P^2
	(n=27)	(n=10)	(n=9)		
Age at onset	1.6±1.0	1.0±0.6	9.6±3.4		
Hospitalization (days/pt.yr)	150[a]	95	30		0.02
Peritonitis frequency	1 : 7.3 mo	1 : 9.4 mo	1 : 15.8		
Hypertension	64%	50%	44%		
Seizures	26%	0%	0%		
Pulmonary edema	41%	0%	0%	0.02*	
Nutrition and growth					
Protein intake (% RDA)	140 - 200%[b]	209±42%	178±72%		
Energy intake (% RDA)	110 - 120%[b]	93±16%	101±41%		
hSDS (6 months)	-1.7±1.5	-1.1±1.1	-0.6±0.9		
ΔhSDS (0-6 months)	+0.6±0.6	+0.8±0.6	-0.1±0.2		<0.01
Laboratory parameters					
Hemoglobin (g/L)	91±12[c]	104±11	118±12	0.009	0.03
Hematocrit (%)	0.27±0.04[c]	0.32±0.03	0.36±0.03	0.009	0.02
BUN (mmol/L)	47±15	40±6	36±8		
Creatinine (μmol/L)	515±77	451±126	801±181		<0.01
Prealbumin (mg/L)	391±80	449±77	431±70		
Albumin (g/L)	29±5	30±4	34±4		0.03
Protein (g/L)	54±8	60±2	63±5	0.06	
Ionized Calcium (mmol/L)	1.27±0.07[d]	1.24±0.05	1.27±0.06		
Phosphorus (mmol/L)	2.01±0.42	1.51±0.48	1.73±0.34	0.004	
Intact parathyroid hormone (ng/L)[e]		389±345	163±202		
Medication					
Alphacalcidol (μg/wk)	1.1±2.0[f]	1.8±1.5	1.7±2.5		
Calcium substitute (mg/kg/d)	339±163	86±48	72±17	<0.01	

* Fisher's exact test

[a] Hospitalization (days/patient-year) between 1990-1994
[b] Analyzed for 1989-1992
[c] Patients without rHuEPO were excluded
[d] Analyzed in eight patients
[e] Data for 1986-1994 not available
[f] Used since 1991 in eight patients

Peritonitis

The peritonitis rate was one episode per 7.3 patient-months during 1986–1994, and one to 9.4 patient-months during 1995–1999 for the children under 5 years of age. The frequency for the older children was lower (one to 15.8 patient-months). Before 1995, the culture was negative in 51% of the peritonitis episodes, and Gram-positive bacteria were found in 26% (I). Since 1995, Gram-positive bacteria accounted for 72% of the episodes, Gram-negative bacteria for 22%, and only 6% were culture-negative (III). The most common bacteria both before and after 1995 was *Staphylococcus aureus*. Thirty-one percent of the episodes were treated with intermittent intraperitoneal antibiotic therapy, and the rest was treated continuously. No relapses were documented after intermittent intraperitoneal antibiotic therapy.

Blood pressure control

Complications related to blood pressure control were clearly less numerous during the prospective study with PD adequacy control (III) than before 1995 (I). The need for antihypertensive medication decreased slightly as well (III). In the patients treated in 1986-1994 and analyzed retrospectively, pulmonary edemas and seizures, related to poor blood volume control, were numerous, but during the prospective study disappeared in both age groups (*Table 3*).

Laboratory results and medication

Since the end of 1989, all patients have received rHuEPO. Prior to rHuEPO, the patients received 12 erythrocyte transfusions per patient per year (range 8-60). The mean rHuEPO dose was lower in the patients treated in 1989-1994 than in the younger patients treated in 1995-1999 (124±47 vs. 202±91 U/kg/wk), and accordingly their hemoglobin and hematocrit values were lower. The younger patients needed more rHuEPO (202±91 vs. 139±101 U/kg/wk) (III). When the results in children under 5 years of age are compared, BUN, serum creatinine, prealbumin, protein, and phosphorus levels are seen to have improved (*Table 3*). With intensified clinical care and PD adequacy control, the laboratory results did not differ significantly between the age groups, with the exception of serum albumin, which remained significantly lower in the younger patients ($p<0.05$ at 3, 6 and 9 months, unpaired t test) (III). Although the younger patients had higher alphacalcidol substitution (2.2 vs. 1.3 μg/week), their intact PTH concentration was higher (difference not significant) after the baseline (III). The need for calcium substitution decreased

significantly in the younger patients after 1995 (from 339 to 86 mg/kg/d), and did not differ later between the age groups under and over 5 years of age.

Nutrition and growth

In the retrospective analysis, between 1989-1992, the protein and energy intakes of some patients were analyzed (154). Protein intake was higher during the prospective study, but energy intake was lower, as seen in *Table 3*. No significant difference in nutrition was found between the age groups (III). During 1986-1994, most of the children showed catch-up growth: the mean 6-month change in height decreased by –0.12±068 SDS prior to dialysis, and increased by +0.59±0.64 SDS after dialysis began ($p<0.001$, Wilcoxon signed rank test). The increase in hSDS was better in the 29 nephrectomized patients between 1986–1994 (*Figure 3*). One of the nephrectomized and one of the non-nephrectomized patients, studied retrospectively, were treated with rhGH. During the prospective study, all the younger patients and 33% of the older patients (one patient was treated with rhGH) showed catch-up growth. The nine-month change (baseline to 9 month follow-up) in hSDS was +0.97±0.71 for the children under 5 years of age, and –0.04±0.23 for the children over 5 years of age ($p=0.002$, Mann-Whitney U test) (*Figure 3*). In simple regression analysis hSDS was not significantly predicted by urea Kt/V, C_{Cr}, energy, or protein intake (/kg, /m^2, or as a percentage of RDA), serum albumin, serum protein, phosphorus, BUN, intact PTH, or serum alkaline phosphatase (III). However, trends toward positive prediction of hSDS by C_{Cr} and negative prediction by alkaline phosphatase were observed.

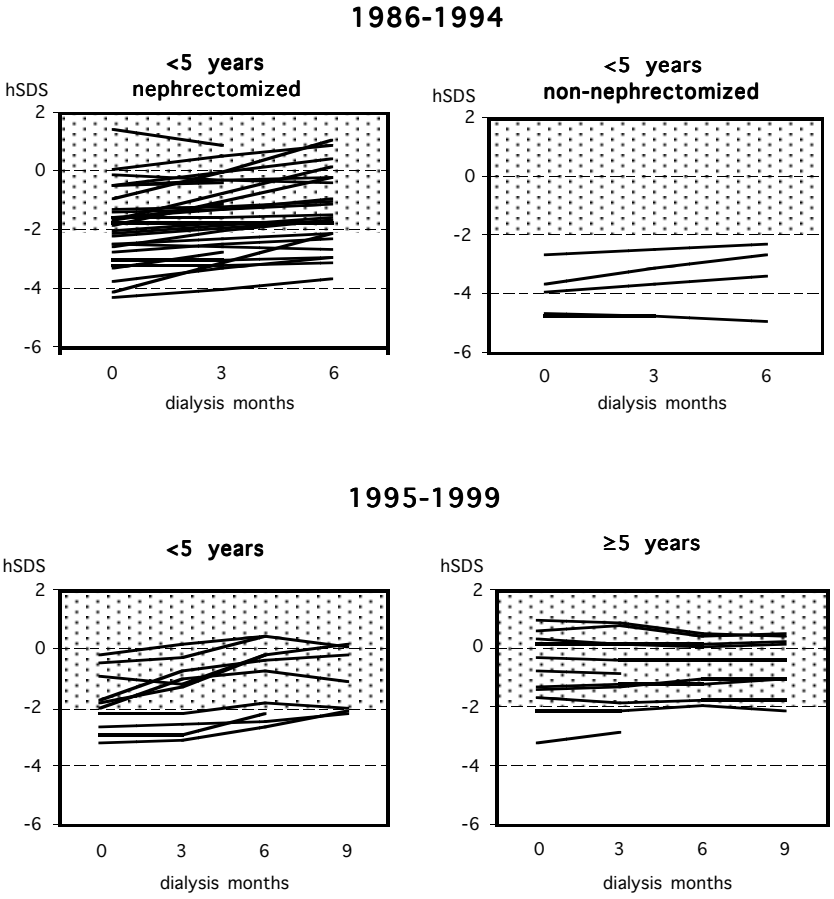

Figure 3. Height standard deviation score (hSDS) in 1986-1994 for 29 nephrectomized and 5 non-nephrectomized patients <5 years of age, and in 1995-1999 for 10 patients <5 years and 11 patients ≥5 years of age. Dialysis months represents the observation period in months, and the shaded area the normal growth range (±2SDS) for Finnish children.

PERITONEAL TRANSPORT KINETICS (II)

Peritoneal transport kinetics were studied in 28 patients, 10 of whom were under 5 years of age. Seven children had histories of peritonitis 2.8±1.6 months prior to their initial PET. The mean dialysis time prior to initial PET did not differ significantly between the age groups, or between children who had had or had not had peritonitis. No significant difference in equilibration was found between children who had had or had not had peritonitis. Therefore, all initial PETs were pooled. In *Table 4*, D/P and D/D_0 glucose values at 1 and 4 hours are given for all patients and subgroups of children under 5 and

over 5 years of age. No significant difference in membrane transport was found between the two age groups. The mean test volume was 967±31 ml/m^2 in the younger age group (n=10) and 994±23 ml/m^2 in the older age group (n=18) (p=0.03, Mann-Whitney U test).

Table 4. Initial PET data at 1 and 4 hours (mean D/P±1SD) for the total of 28 children, and for children <5 and ≥5 years (yrs) of age (n=10 and n=18, respectively).

		1 hour	4 hours
Urea	Total	0.49±0.08	0.92±0.05
	<5 yrs	0.50±0.07	0.93±0.03
	≥5 yrs	0.49±0.09	0.91±0.06
Creatinine	Total	0.32±0.08	0.70±0.12
	<5 yrs	0.34±0.04	0.70±0.09
	≥5 yrs	0.31±0.09	0.70±0.14
Glucose	Total	0.69±0.07	0.32±0.10
	<5 yrs	0.67±0.05	0.30±0.08
	≥5 yrs	0.70±0.08	0.33±0.11
Sodium	Total	0.84±0.04	0.86±0.04
	<5 yrs	0.86±0.04	0.86±0.05
	≥5 yrs	0.83±0.04	0.86±0.04
Potassium	Total	0.50±0.11	0.85±0.11
	<5 yrs	0.49±0.06	0.83±0.10
	≥5 yrs	0.50±0.12	0.85±0.12
Phosphate	Total	0.26±0.09	0.57±0.12
	<5 yrs	0.26±0.04	0.59±0.13
	≥5 yrs	0.26±0.10	0.56±0.12
Albumin	Total	0.005±0.003	0.014±0.007
	<5 yrs	0.005±0.002	0.014±0.006
	≥5 yrs	0.005±0.003	0.014±0.008

Longitudinal changes in peritoneal membrane transport

A final PET was performed in 21 patients (nine patients were under 5 years of age and 12 over 5 years of age) at a mean of 0.8±0.4 years after the initial PET. The mean test volume in the final PET was 1005±20 ml/m^2, (1009±56 and 1002±13 ml/m^2, difference not significant, respectively). No significant difference was found in membrane transport when the initial and final PETs were compared (*Figure 4*).

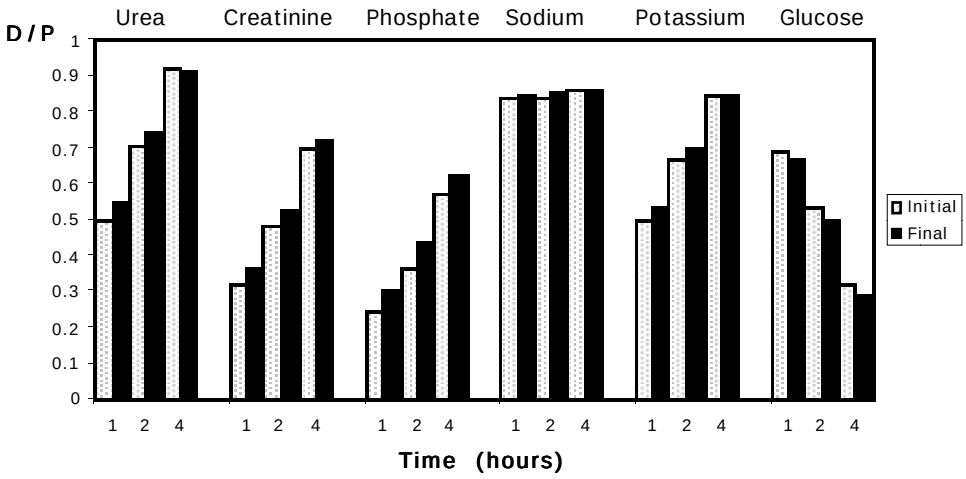

Figure 4. Mean initial and final 1-, 2-, and 4-hour D/P ratios for urea, creatinine, phosphate, sodium, and potassium, and the D/D_0 glucose ratio, respectively. The gray bars represent initial PET of 28 patients, and the black bars the final PET of 21 patients.

No significant changes in equilibration rates were observed in patients who had experienced one or more peritonitis episodes between the initial and final PET (n=8), and in those without peritonitis (n=13). The time interval between the PETs did not differ significantly between the groups. In the peritonitis group, the equilibration ratio decreased only in one patient with two peritonitis episodes caused by *Pseudomonas aeruginosa* (her initial and final 4-h D/P creatinine values were 0.76 and 0.60).

Baseline peritoneal membrane permeability was slightly higher in the patients with CNF (n=10) than in the non-CNF patients. However, this difference was significant only for the baseline 4-h D/D_0 ratio for glucose (0.26±0.06 and 0.35±0.10, p=0.03, unpaired t test) and the 4-h D/P ratio for phosphate (0.65±0.12 and 0.53±0.11, p=0.01, unpaired t test). In the final PET, these differences in membrane transport were reduced or had disappeared. Patients with CNF did not differ from other patients in respect of test volume or dialysis time prior to the study.

Mass transfer area coefficient

The MTAC data for urea, creatinine, glucose, and albumin are given in *Table 5*. No difference was found in MTAC between the children under and over 5 years of age, nor was any correlation found between MTAC and age. When all MTAC values were pooled,

no significant longitudinal changes were observed, but the children with a history of peritonitis tended to have higher MTACs.

Table 5. Mass transfer area coefficients (mean±1SD, ml/min/1.73m^2) calculated for 28 children and for the subgroups of children <5 years of age (n=10) and ≥5 years of age (n=18).

	Urea	Creatinine	Glucose	Albumin
Total	22.3±4.8	10.9±4.1	11.1±3.3	0.07±0.03
<5 years	22.5±2.4	10.4±2.8	11.5±2.9	0.07±0.02
≥5 years	22.2±5.8	11.3±4.7	10.9±3.5	0.08±0.03

DIALYSIS ADEQUACY (III)

Adequacy was measured from 24-h dialysate and urine collection. If the clearance targets (Kt/V >2 and C_{Cr} >60 L/wk/1.73m^2) were not reached, the dialysis prescription was optimized with the help of the PD ADEQUEST computer program and knowledge of the peritoneal transport characteristics, in order to increase clearances. The mean urea Kt/V and C_{Cr} values at baseline and at 9 months are listed in *Table 6*. Urea Kt/V did not change during the 9-month observation period, nor was any significant difference found between the two age groups. Every patient reached urea Kt/V >2.0. The mean C_{Cr} increased slightly during the 9-month period. It differed significantly between the age groups only at baseline (*Table 6*). At baseline, C_{Cr} was <60 L/wk/1.73 m^2 in 70% of the patients under 5 years of age, and at 9 months in 29%. All the older patients attained a C_{Cr} >60 L/wk/1.73 m^2. Residual renal clearance decreased slightly during the study period (from 2.9 to 2.4 ml/min/1.73 m^2). Urea Kt/V and C_{Cr} were correlated significantly ($r=0.61$, $p<0.05$ at baseline, Spearman rank correlation). In simple regression analysis, neither urea Kt/V nor C_{Cr} were predicted by age, BUN, serum albumin, protein intake, or energy intake. The total daily dialysate volume (ml/m^2) gave a weak positive prediction of urea Kt/V and C_{Cr}.

Table 6. Mean weekly urea Kt/V and C_{Cr} (mean ±1SD) at the beginning of the study, and after 9 months on PD for 21 children and for the subgroups of children <5 years of age (n=10) and ≥5 years of age (n=11).

	All	<5 yr	≥5 yr	p*
Kt/V				
baseline	3.2±0.5	3.1±0.6	3.2±0.4	
9 months	3.2±0.5	3.3±0.5	3.0±0.4	
C_{Cr} (L/wk/1.73m^2)				
baseline	68.8±16.6	58.7±11.9	78.0±14.9	0.004
9 months	71.3±14.0	71.2±19.9	71.5±7.3	

* Comparison of different age groups, Mann-Whitney U test.

TIDAL PERITONEAL DIALYSIS (IV)

Dialysis efficacy with CCPD and TPD was analyzed in 13 patients, five of whom were under 5 years of age. In most of the patients, in contrast to our initial expectations, prediction of UF during TPD was relatively easy and alarms caused by volumes that were too low diminished within 2 to 4 weeks. Patients and parents felt safe and familiar with TPD after a few weeks, and no patients reported dialysis-induced pain during TPD, in contrast to three patients (23%) during CCPD.

Table 7. Description of dialysis regimens in 13 patients with continuous cycling peritoneal dialysis (CCPD) and with tidal peritoneal dialysis (TPD).

	CCPD	TPD	p
Number of dwells/night	9±1	22±2	0.005
Dialysis time/night (h)	9.7±0.9	9.4±0.9	
Volume/dwell period (ml/m^2)	888±128	951±129	
Night volume (ml/m^2)	7956±924	11365±1165	0.001
Dialysate flow rate/night (ml/kg/h)	32.7±4.6	46.4±3.7	<0.001
Ultrafiltration rate/night (ml/m^2)	495±251	447±215	
Glucose content (%)	1.8±0.4	1.6±0.2	0.01

Dialysis prescriptions with CCPD and TPD are listed in *Table 7*. Both the total nightly dialysate volume (ml/m^2) and the nightly dialysate flow rate (ml/m^2/h) were significantly higher with TPD than with CCPD.

The mean total C_{Cr} was significantly higher with TPD than with CCPD (p=0.02, Wilcoxon signed rank test), while the mean total urea Kt/V did not differ significantly (*Table 8*). With TPD, the mean total weekly C_{Cr} and urea Kt/V were clearly higher in patients with high than in those with high average membrane permeability for creatinine (*Table 8*), although there were no significant differences in dialysis prescriptions between high and high average transporters during TPD and CCPD. During CCPD, no such difference was found.

Table 8. Total weekly urea Kt/V and creatinine clearance (C_{Cr}) in 13 patients on CCPD and TPD. Urea Kt/V and C_{Cr} were also analyzed for high (H; n=3 and n=2 with CCPD and TPD, respectively) and high-average (HA; n= 10 and n=11 with CCPD and TPD) membrane transporters (based on 4-h D/P of creatinine).

	Kt/V			C_{Cr}		
	CCPD	TPD	p	CCPD	TPD	p
All patients	3.3±0.4	3.5±0.5		72.5±16.0	79.3±18.5	0.02
HA transporters	3.3±0.4	3.3±0.5		73.9±17.0	74.8±16.0	
H transporters	3.4±0.6	4.1±0.01		68.0±15.0	103.8±11.3	

In patients under and over 5 years of age, no significant difference was found between CCPD and TPD either in total C_{Cr} or in total urea Kt/V. No difference was found between the age groups either, when clearances achieved with CCPD or TPD were compared. During both CCPD and TPD, the nightly dialysis time was significantly longer and the nightly dialysate volume significantly lower in the children under 5 years of age (*Table 9*), which can be attributed to the larger number of nephrectomized CNF patients in this age group (80% vs. 25%). The dialysate volume was increased slowly in these patients, as CNF patients are more prone to fluid leaks because of muscular hypotonia. However, regardless of the lower fill volume and longer nightly dialysis time, the number of cycles per hour and the total dialysis volume per night (ml/m^2) did not differ significantly between the age groups during either CCPD or TPD.

Table 9. Description of dialysis regimen and total weekly urea Kt/V and creatinine clearance (C_{Cr}) for patients under and over 5 years of age with CCPD and TPD.

		<5 years (n=5)	≥5 years (n=8)	p
Dwells/night	CCPD	10.2±1.1	8.4±1.1	0.02
	TPD	22.4±1.7	21.7±2.3	
Dialysis time	CCPD	10.5±0.6	9.2±0.6	0.01
(h)	TPD	9.9±0.7	9.1±0.9	0.05
Volume/dwell	CCPD	773±61	961±102	0.003
(ml/m^2)	TPD	869±81	1003±130	0.04
Kt/V	CCPD	3.4±0.6	3.2±0.4	
	TPD	3.4±0.6	3.5±0.6	
C_{Cr}	CCPD	63±16	79±13	
($L/wk/1.73m^2$)	TPD	68±17	86±16	0.06

Albumin and phosphate losses into the dialysate did not differ significantly between CCPD and TPD (data obtained from five patients). The total albumin loss was 2.2±0.5 g/m^2 during CCPD and 2.3±0.7 g/m^2 during TPD, and the phosphate losses 6.0±1.6 and 5.9±2.3 $mmol/m^2$, respectively. Patients under 5 years of age lost more albumin both during CCPD and TPD than the older patients (difference not significant). The phosphate loss did not differ between the age groups during CCPD or TPD.

HYPERVOLEMIA AND HYPERTENSION (V)

Hypertension

The cardiopulmonary status, ANP, and the prevalence of high BP were analyzed in 21 patients (11 patients were under 5 years of age), the aim being to specify the impact of hypervolemia on the etiology of high blood pressure and to facilitate the diagnosis of hypervolemia. The role of hypervolemia in the etiology of high blood pressure was especially studied in 13 nephrectomized patients, as renal causes of hypertension could be excluded. ANP-C and ANP-N were measured as possible additional markers of hypervolemia.

Of all patients, 52% were treated with antihypertensive drugs at baseline (54% of the younger and 50% of the older patients). Calcium channel blockers and ß-adrenergic blockers were the drugs most commonly used, followed by ACE inhibitors. Of the treated patients, 82% had the mean daytime systolic BP (sBP) and the mean daytime diastolic BP (dBP) above the 95th percentile, and their BP was significantly higher than that of patients without antihypertensive treatment (p=0.003 for sBP and p=0.0004 for dBP, Mann-Whitney U test).

The mean daytime BPs (Dinamap vs. ABPM) for all patients are given in *Table 10*. In 52% of the patients the mean sBP and in 43% the mean dBP were above the 95th percentile (73% and 100% were receiving antihypertensive medication, respectively). In these hypertensive patients, the mean difference between sBP and the 95th percentile was 31±19 mmHg (range 3-58 mmHg), and between dBP and the 95th percentile 24±11 mmHg (range 5-35 mmHg). More patients under 5 years of age had hypertension than those over 5 years of age. In the younger patients daytime sBP and dBP were above the 95th percentile in 73% and 54%, respectively, as compared with 30% and 30% in the older patients. However, the mean differences between the BP and the 95th percentile were higher in the older patients (35±16 and 29±21 mmHg for sBP, difference not significant, and 26±14 and 22±11 mmHg for dBP, difference not significant, respectively). The nightly decline in BP ("nocturnal dip") for all patients and for the age groups separately are also presented in *Table 10*. The nocturnal dip was less in the nephrectomized than in the non-nephrectomized children (5±10% vs 13±6% in sBP, difference not significant, and 10±14% vs. 14±11% in dBP, difference not significant, respectively). If a nightly decline of 10% or more is considered normal, 53% were nondippers for dBP, and 40% for sBP.

Atrial natriuretic peptide

The mean plasma level of ANP-C at baseline, measured in the morning after PD, was 135±120 pg/ml (8.5-448 pg/ml) for all patients. The corresponding values for patients under and over 5 years of age were 147±151 pg/ml and 122±79 pg/ml (difference not significant, Mann Whitney U test). The mean ANP-N was 3.6±3.2 nmol/L (0.4-12.0 nmol/L) for all patients. The values for the two age groups were 4.3±3.7 nmol/L and 2.7±2.4 nmol/L (difference not significant, Mann Whitney U test), respectively. ANP-C and ANP-N correlated significantly (r=0.60, p=0.01, Spearman rank correlation).

Table 10. Mean daytime blood pressures (BPs) measured with an automatic oscillometric device (Dinamap) and with an ambulatory blood pressure monitor (ABPM) in 21 patients on chronic peritoneal dialysis. Nocturnal decline is given in % for 15 patients. The number of patients is given in parentheses.

	All patients	<5 years	≥5 years
Systolic BP			
Dinamap, *mmHg*	118±30 (21)	114±35 (11)	123±23 (10)
ABPM, *mmHg*	120±18 (16)	121±19 (7)	119±19 (9)
Nocturnal decline, %	10±10 (15)	7±14 (6)	12±6 (9)
Diastolic BP			
Dinamap, *mmHg*	67±24 (21)	61±25 (11)	74±23 (10)
ABPM, *mmHg*	73±14 (16)	70±12 (7)	75±15 (9)
Nocturnal decline, %	13±12 (15)	14±16 (6)	12±10 (9)

Cardiac findings

Cardiac measurements are listed in *Table 11*. None of the patients had structural cardiac abnormalities. Left ventricular and atrial internal dimensions were above the 95th percentile in less than 20% of the patients, and no difference was found between the age groups. In contrast, wall thickness measurements (Sept D and LVPWD) and also AOD were above the 95th percentile in approximately 30% of the patients, more often in the younger patients. When related to BSA$^{0.5}$, Sept D and LVPWD were significantly greater in the younger patients. Forty-five percent of the patients had LVM related to body height$^{2.7}$ above the 95th percentile. LVH was significantly greater in the younger patients. Left ventricular systolic function (EF,%) and diastolic function (peak E and A wave) were not significantly impaired.

Table 11. Baseline cardiopulmonary status of 21 patients on chronic peritoneal dialysis. Values are also given as means ±1SD separately for 11 patients <5 and 10 patients ≥5 years of age.

	all	< 5 years	≥ 5 years	p *
LVEDD				
> 95th centile, *%*	5	9	0	
LVEDD / BSA$^{0.5}$	40.0±5.4	40.2±6.9	39.8±3.4	
LVESD				
> 95th centile, *%*	19	18	20	
LVESD / BSA$^{0.5}$	26.1±5.8	27.0±7.1	25.1±4.0	
Sept D				
> 95th centile, *%*	35	70	0	
Sept D / BSA$^{0.5}$	7.4±1.6	8.4±1.5	6.5±1.2	0.007
LVPWD				
> 95th centile, *%*	24	36	10	
LVPWD / BSA$^{0.5}$	7.3±1.8	8.3±1.7	6.3±1.3	0.01
AOD				
> 95th centile, *%*	31	60	12	
AOD / BSA$^{0.5}$	22.5±2.4	23.1±1.9	22.1±2.6	
LAS				
> 95th centile, *%*	0	0	0	
LAS / BSA$^{0.5}$	27.5±4.4	30.2±4.0	25.7±3.9	
LVM				
> 95th centile, *%*	45	60	30	
LVM / height$^{2.7}$, *g/m$^{2.7}$*	53.5±28.2	70.5±30.7	36.5±9.9	0.008
EF, %	65±9	63±11	66±7	

* p, when results for patients under and over 5 years of age are compared.

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; Sept D, interventricular septal diameter at end-diastole; LVPWD, left ventricular posterior wall thickness at end-diastole; AOD, aortic diameter in end-diastole; LAS, left atrial diameter in systole; LVM, left ventricular mass; EF, ejection fraction

Correlations between hypertension, ANP, and cardiac findings

LVM (%) correlated significantly with the severity of hypertension, calculated from the mean systolic daytime BP (r=0.79, p<0.001, Spearman rank correlation), and with ANP-N (r=0.66, p=0,005, Spearman rank correlation). ANP-N correlated significantly with the severity of hypertension (r=0.82, p<0.001, Spearman rank correlation). ANP-C also correlated significantly with the severity of hypertension (r=0.66, p=0.005, Spearman rank correlation), but less strongly than ANP-N.

In 61% of the 13 nephrectomized patients, the difference between BP and the 95th percentile for BP was positive, indicating hypertension. A clear association was seen between LVH, ANP-N, and the severity of hypertension (mean daytime sBP) in the patients with ANP-N >3.0 nmol/L (*Table 12*).

Table 12. Characterization of the 12 of the 13 nephrectomized patients. Post-nephrectomy (Post-nephr) represents the time in years between nephrectomy and the study. Hypertension represents the difference between a patient's mean daytime systolic BP and the reference BP (95th percentile).

	Age (years)	Post-nephr (years)	LVM (%)	ANP-C (pg/ml)	ANP-N (nmol/L)	Hypertension (mmHg)
1.	1.85	0.91	+57.0	378	9.70	+52
2.	0.61	0.01	+37.1	85	3.80	+11
3.	0.73	0.05	+37.0	448	12.00	+47
4.	0.52	0.01	+25.6	46	3.50	+15
5.	1.66	1.06	+21.7	197	5.10	+58
6.	0.69	0.03	+21.7	76	3.74	+29
7.	8.63	0.02	+16.1	178	3.40	+43
8.	1.68	1.01	-23.5	29	1.70	+ 3
9.	7.25	2.78	-24.4	118	1.80	-10
10.	0.51	0.02	-24.4	142	1.45	-26
11.	0.87	0.01	-55.7	33	1.60	-38
12.	8.21	0.25	-63.6	8.5	2.10	-11

LVM, left ventricular mass; ANP-C, C-terminal atrial natriuretic peptide;
ANP-N, N-terminal atrial natriuretic peptide

Echocardiography as well as BP and ANP measurements were repeated in nine patients after 0.9±0.2 years. In the repeated echocardiography, the prevalence of LVH decreased from 50% to 11%. BP also decreased (sBP from 127 to 115 mmHg, and dBP from 80 to 63 mmHg), as well as ANP-C (from 150 to 128 pg/ml) and ANP-N (from 3.4 to 2.4 nmol/L). However, none of these changes were significant. At baseline, seven of the nine patients were being treated with antihypertensive drugs, but, when the measurements were repeated, only three.

DISCUSSION

The present study was undertaken to evaluate the outcome in children treated with chronic PD with intensified clinical care and a controlled dialysis dose, and further to compare the results with those of patients under 5 years of age treated previously. Additionally, utilization of TPD in children and the role of hypervolemia in the etiology of high blood pressure were studied. The efficacy of PD did not differ significantly between TPD and CCPD. Peritoneal transport kinetics were comparable in children under and over 5 years of age. The clinical outcome of patients under 5 years of age, studied after 1995, improved under PD adequacy control, compared with the previous results in children of the same age. According to the literature, the outcome of PD in young children is not as good as in older children or adults. However, the outcome in the patients under and over 5 years of age in this study did not differ significantly, although the frequency of peritonitis and the prevalence of high blood pressure, mainly caused by increased blood volume, remained somewhat higher in the younger patients. For the first time, catch-up growth was achieved without rhGH in most children during PD.

CLINICAL OUTCOME AND ADEQUACY OF DIALYSIS

Information about the effects of PD adequacy measurements on clinical outcome in children is scanty. In most dialysis centers, PD prescription is still empirical and mainly aimed at optimizing daily ultrafiltration and correcting uremia. To improve the outcome, we optimized the PD prescription with the help of knowledge of the peritoneal membrane capacity and dialysis adequacy in our patients. Since mortality in pediatric PD patients is low, we measured the more sensitive parameters of patient morbidity, such as growth, nutritional parameters, and serum albumin, as indicators of patient well-being. Dialysis adequacy differed between the age groups only at baseline with respect of C_{Cr}. Neither urea Kt/V nor C_{Cr} predicted serum albumin or nutritional parameters, but there was a trend toward positive prediction of hSDS by C_{Cr}.

Values of urea Kt/V and C_{Cr} in the patients studied were approximately 13% and 15% higher than during the patients' regular dialysis program, because we modified the 24-h dialysate collection to make it possible to keep the patients only 2 days in hospital during the PET and adequacy studies. Thus, after recalculation, our urea Kt/V approximates 2.8, and C_{Cr} 61 L/wk/1.73 m^2. Especially in our young nephrectomized patients the DOQI target C_{Cr} of >60 L/wk/1.73 m^2 was hard to achieve. Schaefer et al. found C_{Cr} and urea Kt/V values similar to ours in their patients, and also reported that it

was difficult to achieve C_{Cr} targets. Recently, van der Voort et al. reported that only 45% of their 20 pediatric patients had a dialytic Kt/V and 10% dialytic C_{Cr} above the DOQI guidelines (155). All their patients were well dialyzed. They had a dwell volume >1000 ml/m^2 and a nightly dialysis time of at least 10 hours, and 17 patients had an additional long day dwell. In contrast to our findings and those of Schaefer et al. and van der Voort et al., Walk et al. reported a mean total C_{Cr} of 74±47 L/wk/1.73m^2 and a mean total urea Kt/V of 2.3 in their 19 children on PD (69). The high C_{Cr} in their patients can be explained by the relatively high residual renal function (<10 ml/min/1.73m^2 compared with <3 ml/min/1.73m^2 in our patients) in their 12 non-nephrectomized patients; in their nephrectomized patients the mean C_{Cr} was only 42 L/wk/1.73m^2. Thus, it seems that in most nephrectomized patients the DOQI target of C_{Cr} >60 L/wk/1.73m^2 is hard to reach.

Growth is one of the most important end points of PD outcome in children. Despite improved control of nutritional intakes, acidosis, disturbed calcium/phosphorus balance and uremia, poor growth has remained a major problem during PD treatment (14, 17). Catch-up growth has mostly been reached only with rhGH therapy (17, 90). The first prospective pediatric report on the effects of PD adequacy control was published in 1999, and included 51 children followed for 18 months (68). In that study, growth was slightly retarded, although 37% of the patients were treated with rhGH. In contrast to previous reports, both our retrospectively and prospectively studied patients showed significant catch-up growth. Growth was significantly better in the younger patients, partly because of normalization of the protein balance after nephrectomy in the patients with CNF. Compared with our retrospective study of patients treated between 1986 and 1994 (I), the hSDS at 6 months and the 6-month ΔhSDS in patients under 5 years of age were better after 1995 (III), when strict dietary control and PD adequacy studies were included, although the numbers of nephrectomized patients with CNF were similar. There was a trend toward prediction of hSDS by C_{Cr}. Thus, our findings suggest a positive effect of strict dietary and PD adequacy control on growth, bearing in mind that the number of patients and the follow-up period are limited. Schaefer et al. (68) reported a weak positive effect of dialytic small solute clearance on statural growth, which supports our results.

The number of culture-negative findings in peritonitis diagnoses decreased from 51% between 1986-1994 to 6% after 1995. The high proportion of negative cultures may have been due to the prompt antibacterial treatment in suspected cases of peritonitis before 1995. Since 1995, we have centrifuged an aliquot of the dialysis sample before examining with Gram's stain and before culturing the effluent. This may further have improved the diagnosis in patients treated for peritonitis at the Hospital for Children and Adolescents, University of Helsinki (31% of the study patients).

The overall frequency of peritonitis and exit-site infections decreased slightly in children under 5 years of age treated after 1995 under PD adequacy control. However, the frequency of peritonitis was higher in the younger patients, which agrees with previous reports on peritonitis frequency (37, 65, 66, 94). In Italy and in Japan, lower incidences of peritonitis (one to 26–28 patient-months) have been reported (64, 65). However, according to the 1996 NAPRTCS registry data (37), the overall frequency of peritonitis was one per 13 patient-months in North American PD patients. Our results are similar (one per 11.6 patient-months), although most of our patients had single-cuff Tenckhoff catheter with exit-site pointed up, which has been found to increase the risk of peritonitis (66).

Since, in PD patients, the peritoneum is an immunocompromised site, with access to an external world filled with different organisms, complete avoidance of peritonitis episodes will not be possible. It has been suggested that the low pH of fresh dialysis fluid reduces opsonic activity, and that the combination of low pH, lactate, and the hyperosmolality of peritoneal dialysis solutions impairs immune cell function, at least *in vitro* (156). Dialysis fluid also has a diluting effect on macrophages, opsonins, and immunoglobulins, which further attenuates the host defense. Thus, PD forms with long dwells have been suggested to decrease peritonitis frequency because of the reduced diluting effect, bearing in mind the importance reducing the risk of touch contamination (64). As our patients are on CCPD with frequent exchanges and with 1-3 exchanges per day, the short dwells with a large amount of fresh dialysis fluid might be a risk factor increasing the peritonitis rate. Another risk factor might be the manual day exchanges, which increase the risk of touch contamination in our patients. To lower the peritonitis frequency, the use of a downward exit-site and two cuffs in the catheter has been suggested (37). Prophylactic control with a *Staphylococcus aureus* nasal carriage might also be beneficial in preventing ESI and peritonitis in our patients (157, 158), as *Staphylococcus aureus* is the most common bacterium causing peritonitis in our patients.

PERITONEAL TRANSPORT KINETICS

The possibility of differences in peritoneal transport kinetics was evaluated over time and between children under and over 5 years of age. No changes were found in peritoneal membrane transport function during the follow-up period, and peritoneal transport kinetics (D/P and MTAC) was found to be independent of age. There was neither a significant difference between the patients under and over 5 years of age nor a correlation with age. Peritoneal membrane transport has been reported to be higher in small children when the test volume is related to weight instead of BSA (6-11). Even when relating the PET

volume to BSA, the initial studies reported a tendency toward more rapid transport in the youngest patients (55, 56). Since 1996, findings similar to ours have been reported (12, 13). Warady et al. showed that the peritoneal equilibration rate did not differ between children of different ages, but MTACs for glucose and creatinine were higher in infants than in older children (12). They suggested that higher MTACs might be the result of maturational changes in the peritoneal membrane or differences in the effective peritoneal membrane surface area. Since 1996, the PET results reported by them have been used as pediatric reference values. Recently, Bouts et al. found neither any correlation between D/P or MTAC and age in 18 pediatric PD patients nor any differences between pediatric and adult results (159). MTAC should be independent of differences in dialysate volume (160) and in the glucose content of dialysis fluids (161). Thus, the variable test volumes (910-1500 ml/m^2 vs. 1100 ml/m^2) and lower glucose content of the fluid (1.36% vs. 2.27%) used by Bouts et al. as compared with that used by Warady et al. do not explain the discrepancy in MTAC related to age between these two studies (12, 159). The results of Bouts et al. can be interpreted to support our findings.

Compared with the reference data of Warady et al. (12), our patients had higher membrane transport for urea, potassium, and creatinine at 4 hours (0.91±0.05 *vs*. 0,82±0.09 and 0.85±0.11 *vs*. 0.75±0.10 and 0.70±0.12 *vs*. 0.64±0.13, respectively). Our higher D/P values could partly be explained by the higher peritoneal membrane transport and the slightly lower test volume at baseline PET in our patients with CNF. It should also be noticed that the mean dialysis time prior to the PET measurements was clearly shorter in our patients (0.4±0.4 *vs*. 2.0±1.1 years) (12).

In the present study, the CNF patients showed higher peritoneal membrane permeability (D/P and MTAC) in the initial PET, but this difference disappeared in the final PET. However, there was no difference in the test volume or the dialysis time between the CNF patients and the other patients. CNF is caused by a defect in the *NPHS1* gene encoding a transmembrane protein, called nephrin (3), which appears to be expressed solely in glomerular podocytes. There is no evidence of expression of nephrin in the peritoneal membrane (J.Patrakka et al., unpublished data, 2000). Thus, the peritoneal membrane in these patients should be intact. In support of this, de Boer at al. found no size selectivity in peritoneal membrane transport in children with CNS as compared with non-CNS patients (162). CNF patients have low serum albumin, prealbumin, and protein levels prior to nephrectomy. They also have cholesterol, lipoprotein, and phospholipid abnormalities. Prealbumin normalizes after 1 month on PD, and albumin, protein, cholesterol, and lipoprotein levels improve substantially within 3 months, but do not reach normal values (154). In addition, children with CNF, in contrast to other patients, become uremic only after nephrectomy. These metabolic differences may have an impact on membrane permeability, especially during the first months on PD, which could partly

explain the higher peritoneal equilibration rate in our patients compared to the reference data (12).

TIDAL PERITONEAL DIALYSIS

Preliminary results indicated that TPD was able to provide a dialysis outcome equal to that of CCPD within a shorter time (18, 19). We started the study by comparing dialysis adequacy in the same patients treated with CCPD and TPD, with the aim of discovering whether TPD could provide better dialysis adequacy than CCPD. Our results showed that TPD is an adequate method for dialysis in pediatric patients, including infants, with ESRD. No significant difference in adequacy of dialysis was found between the age groups under and over 5 years of age during TPD. However, TPD, because of the better osmotic gradient (163), provided similar UF with a lower glucose content than CCPD. When the results for all patients or for the different age groups were compared, it appeared that, despite a 42% higher flow rate during TPD, albumin and phosphate losses were not higher during TPD than during CCPD. However, we must emphasize that TPD was performed with a moderate dialysate flow rate (<50 ml/kg/h) and albumin and phosphate losses were studied only in five patients.

In the initial TPD studies, Flanigan et al. showed that, when dialysate flow rate was increased from 30 to 50 ml/kg/h, urea Kt/V and C_{Cr} increased, but the dialysate pattern did not alter TPD efficacy (48). To achieve solute removal equal to CCPD, some of their patients needed a TPD flow rate as high as 60-70 ml/kg/h. They suggested that, when a dialysate volume sufficiently large to cover the peritoneal membrane was used, the dialysis efficacy was determined by peritoneal membrane permeability and the dialysate flow rate (48). Thus, to achieve the same solute removal in a patient with low peritoneal membrane permeability, a higher flow rate is needed. In 1996, Durand et al. defined the maximal effective dialysate flow rate (MEDF) as the hourly dialysate flow rate giving the maximum peritoneal creatinine clearance, beyond which peritoneal clearances decrease when the flow rate is further increased (164). In six adult patients, they showed that MEDF depends strictly on peritoneal permeability: MEDF was 1.8 L/h with TPD for a low transporter (4-h D/P creatinine 0.50) and 4.2 L/h for a high transporter (4-h D/P creatinine 0.80). For an adult weighing 60 kg, these rates correspond to approximately 30 ml/kg/h and 70 ml/kg/h. Thus, MEDF is higher for the high transporters than for the low transporters. Accordingly, after MEDF is reached in low transporters, it is possible to obtain clearances equal to those of high transporters only by increasing the dialysis time (164).

In our study, both CCPD and TPD were performed with a moderate flow (<50 ml/kg/h). TPD, with a moderate, 42% higher dialysate flow rate and slightly shorter

nightly dialysis time, was superior to CCPD only in the high transporters, which is in accord with the findings of Durand et al. (164). Several recent studies have also confirmed these findings. In 1995, Edefonti et al. showed TPD with a high flow rate (68 ml/kg/h) to be superior to NIPD with a low flow rate (29 ml/kg/h) (20). Patients with H/HA membrane permeability seemed to be more suitable for TPD than those with L/LA peritoneal membrane permeability (20), as we also found. In 1999, Vychytil et al. showed, that in adult patients TPD did not provide better small-solute or middle-molecule clearances than intermittent peritoneal dialysis up to a dialysate flow rate of 3 L/h (which approximates 50 ml/kg/h in an adult patient with a body weight of 60 kg) (49).

Thus, TPD, besides CCPD is a good option in pediatric PD patients. Both TPD and CCPD provided adequate dialysis in our patients, but less drainage-induced pain was reported during TPD. But whether TPD is superior to CCPD depends on the patient's transporter state, and because of its higher costs (about $400 higher per month in our study), TPD should be saved for patients with high membrane permeability and reduced ultrafiltration, and for patients with mechanical outflow problems or outflow pain.

BLOOD VOLUME CONTROL

As high blood pressure was common in our patients, we initiated the hypertension study to assess the cardiopulmonary status and the prevalence of hypertension in our PD patients, and to further specify the impact of hypervolemia in the etiology of high BP. ANP was measured as a possible additional marker of hypervolemia.

Hypertension was found in 52% of our patients. It was more common in our younger and nephrectomized patients. In previous reports, about 50% of pediatric PD patients, according to their need for antihypertensive medication, have been defined as having hypertension (14). There are few reports of BP measurements in pediatric PD patients. Lingens et al. (103) reported a similar prevalence of hypertension (47%) in their 17 pediatric PD patients aged over 6 years, and an even higher prevalence (70%) when measured with ABPM. In contrast to us, they did not find a significant difference in BP between their nephrectomized and non-nephrectomized patients. The higher prevalence of high blood pressure in our nephrectomized patients, even though most of them were on antihypertensive medication, as compared with that of Lingens et al., can be explained by the lower age of our patients, which hampers determination of normal dry weight and increases the risk of hypervolemia. The BP profile seems also to be altered in pediatric PD patients. Both in our study and in a few previous studies, the mean nocturnal decline in BP was less than in healthy children (103, 165).

BP was measured with an automatic oscillometric Dinamap device. Dinamap has been studied in neonates, infants, and young children, and has been shown to provide an accurate BP determination as compared with direct arterial measurements (166, 167). Lingens et al. used the European normal values for BP, obtained with a mercury column manometer (168), both for casual BP measurements and for ABPM, because European ABPM normal values (104) were not available in 1995. However, we were not able to use either the European normal values for casual BP (168) or for ABPM (104), as both are available only for older children.

LVH may be due to uremia, hypertension, chronically elevated cardiac output induced by anemia, or extracellular fluid volume overload (121). Sixty percent of our younger, mostly nephrectomized patients had LVH, and 70% had interventricular septal hypertrophy. LVH and the severity of hypertension were correlated significantly. Systolic and diastolic function, however, were not impaired. Johnstone et al. reported less LVH and normal diastolic function in their pediatric PD patients (125), and Morris et al. found more LVH in addition to diastolic dysfunction (124). The cardiac impairment in the latter patients can be partly attributed to anemia, and Morris et al. have subsequently shown reduction of the left ventricular mass, and a trend toward improvement in diastolic ventricular function following treatment with rHuEPO (127). All our prospectively studied patients received rHuEPO and their mean hemoglobin was 110 g/L. Their BUN and creatinine were also stable. Even so, 58% of our nephrectomized patients had LVH. The patients with congenital nephrosis are not uremic before nephrectomy (5), and LVH did not correlate with the mean time elapsed since nephrectomy. Thus, it is unlikely that LVH was present before nephrectomy or was caused by uremia. In nephrectomized patients, renal hypertension can be excluded. LVH was later reduced during dialysis with improved blood volume control (decreased BP and ANP-N). Thus, the most important factor causing hypertension and cardiac hypertrophy in our younger nephrectomized patients seemed to be hypervolemia.

In adults, ANP-N has been shown to correlate with the decrement in relative blood volume (116), and even better with LVH and LV dysfunction than ANP-C (117-119). In children, ANP-N has been shown to be significantly higher in patients with congenital heart disease than in healthy controls (120), but no data about ANP-N in pediatric PD patients are available. As LVH usually is a consequence of chronic volume and/or pressure overload, our observation of increased ANP-N levels correlating with BP and LVM (%) may reflect changes in the regulation of ANP secretion through blood volume changes during PD. ANP-N correlated better with BP than with LVM (%), and ANP-N levels in our patients were higher (3.6 nmol/L) than in the cardiac patients of Holmström et al. (1.06 nmol/L) (120). Together, these suggest even stronger stimulation of ANP release in response to increased cardiac load through hypervolemia. This claim is

supported by the decreased ANP-N and BP in three of our hypertensive patients after fluid removal.

Pulmonary edema was more common before 1995. During the 80s, rHuEPO was not used and the patients were more anemic, which would have influenced their cardiac function. In addition, they received a mean of 12 erythrocyte transfusions annually, increasing the risks for volume overload in a nephrectomized child. During recent years, with rHuEPO and intensified clinical care, complications such as pulmonary edema have been avoided. Even so, however, 52% of our patients were hypertensive. Thus, our findings confirm the difficulty of estimating the exact dry weight from the clinical status, weight, and BP measurements. ANP-N seems to be a better tool than ANP-C for facilitating the recognition of increased blood volume in PD patients. Another option for identifying increased blood volume could be bioelectrical impedance analysis (BIA) (169-173). However, the routine use of BIA measurements has been restricted by the expensive equipment and lack of cross-validation of the published prediction equations.

CONCLUSIONS

This study summarizes the peritoneal dialysis outcome in 34 children under 5 years of age treated at the Hospital for Children and Adolescents, University of Helsinki, during 1986-1994, and 30 children (15 of them under 5 years of age) followed prospectively during intensified clinical care and a controlled dialysis dose after the introduction of regular PETs and adequacy measurements in 1995-1999. The main conclusions of the study are:

1. PD outcome improved in the children under 5 years of age and did not differ significantly in the children under and over 5 years of age during intensified clinical care and PD adequacy control. However, peritonitis frequency in the children under 5 years of age remained higher than in the older children.

2. Peritoneal transport kinetics is age-independent. No significant difference was found in the dialysate-to-plasma ratios for urea, creatinine, glucose, sodium, potassium, phosphate, or albumin between the patients under and over 5 years of age, nor was any correlation found with age. The mass transfer area coefficients were also age-independent.

3. Catch-up growth occurred in most children in response to optimal nutrition, dialysis, and clinical care. Growth further improved after the PD adequacy controls were started.

4. Tidal PD provides adequate dialysis for children under and over 5 years of age, but is a more effective treatment modality than CCPD only in patients with high peritoneal membrane permeability. Because of the higher cost, it should be reserved for patients with high membrane permeability combined with reduced ultrafiltration, and for those with mechanical outflow problems or outflow pain.

5. A clear diminution of complications related to high blood pressure was observed during intensified clinical care and optimized peritoneal dialysis. However, the prevalence of hypertension was higher in the patients under 5 years of age, which was due to the difficulty of estimating the exact dry weight from clinical status, weight, and BP measurements in a growing child.

6. The most important etiological factor causing hypertension in the prospectively studied patients was hypervolemia. ANP-N is a better measure than ANP-C for the recognition of increased blood volume during PD. ANP-N over 3.0 nmol/L with hypertension was indicative of hypervolemia in pediatric PD patients.

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