J Am Soc Nephrol 12: 2418–2426, 2001

Improved Growth in Young Children with Severe Chronic Renal Insufficiency Who Use Specified Nutritional Therapy

RULAN S. PAREKH,* JOSEPH T. FLYNN,† WILLIAM E. SMOYER,‡ JOAN L. MILNE,‡ DAVID B. KERSHAW,‡ TIMOTHY E. BUNCHMAN,§ and AILEEN B. SEDMAN‡

**Departments of Pediatrics and Medicine, Johns Hopkins University, Baltimore, Maryland; †Department of Pediatrics, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York; ‡Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan; and §Department of Pediatrics, University of Alabama, Birmingham, Alabama.*

Abstract. Growth in children with chronic renal failure caused by polyuric, salt-wasting diseases may be hampered if ongoing sodium and water losses are not corrected. Twenty-four children were treated with polyuric chronic renal insufficiency (CRI; creatinine clearance <65 ml/min per 1.73 m^2) with low-caloric-density, high-volume, sodium-supplemented feedings. Subsequent growth was compared with that of children in two control groups: a national historic population control from the US Renal Data System database ($n = 42$), and a literature control ($n = 12$). Members of the three groups were 81 to 96% white, and 58 to 70% were boys. Obstructive uropathy and dysplasia were the cause of CRI in 92% of the treatment group, 75% of the literature control group, and 30% of the population control group. Treatment effect was assessed in a multivariate, retrospective analysis of the height standard deviation score (SDS), simultaneously controlling for the severity of disease by renal replacement therapy, primary cause of CRI, and initial height SDS. The change in SDS (ΔSDS) for height by regression analysis at 1 yr was significantly greater by +1.37 in the treatment group *versus* the population control ($P = 0.017$). The 2-yr height ΔSDS by regression analysis adjusted for creatinine clearance was significantly greater by +1.83 in the treatment group *versus* the literature control ($P = 0.003$). Nutritional support with sodium and water supplementation can maintain or improve the growth of children with polyuric, salt-wasting CRI. This inexpensive intervention may delay the need for renal replacement therapy, growth hormone treatment, or both in many of these children and may be used in any clinical setting.

The long-term prognosis of children with early-onset chronic renal failure has improved dramatically in the last decade as a result of technologic and pharmacologic improvements in dialysis and transplantation, aggressive nutritional support, correction of metabolic defects, and effective treatment of renal osteodystrophy. Despite these advances, however, growth failure continues to be a significant obstacle affecting children with renal failure. The greatest height deficit occurs in the first year of life (1), especially in the first 4 mo of life (2). Known factors contributing to growth failure include anorexia, caloric deficits, hyposthenuria, salt wasting, anemia, metabolic acidosis, mineral depletion, renal osteodystrophy, and growth hormone resistance (1,3–6).

Renal replacement therapy (RRT), irrespective of modality (dialysis or transplantation), does not always result in the correction of height deficits (7–9). This is especially true in children with congenital polyuric forms of end-stage renal disease (ESRD), most notably renal dysplasia and obstructive uropathy, the two most common forms of childhood ESRD (10). Children with these forms of ESRD commonly have height deficits >2 SD below the mean, despite aggressive, conservative management. The resulting height deficit frequently cannot be overcome, despite supplemented feedings (11,12), peritoneal dialysis (11), or even transplantation, which results in catch-up growth in <50% of younger children (7,9,13). Strategies are therefore needed to minimize pretransplant growth retardation.

Children with polyuric, salt-wasting forms of chronic renal failure whose sodium and water losses are not corrected may experience significant growth retardation related to chronic intravascular volume depletion and a negative sodium balance. We hypothesized that sodium and water supplementation in the form of low-caloric-density, high-volume, sodium-supplemented feedings could normalize the internal milieu in such children and promote normal growth. Our aim in this study was to evaluate the growth response to such feedings and to determine whether this nutritional intervention would result in improved growth compared with previously reported results.

Received June 1, 1999. Accepted May 25, 2001.
Correspondence to Dr. Rulan Parekh, Division of Pediatric Nephrology, Park 327, 600 N Wolfe Street, Johns Hopkins Hospital, Baltimore, MD 21287-2535. Phone: 410-955-2467; Fax: 410-614-3680; E-mail: rsparekh@jhmi.edu
1046-6673/1211-2418
Journal of the American Society of Nephrology

Materials and Methods

Specified Nutritional Therapy

The nutritional therapy we prescribed for the children consisted of an enteral formula diluted with water to a caloric density of 0.3 to 0.5 kcal/ml and supplemented with 2 to 4 mEq of sodium (as chloride, bicarbonate, or both) per 100 ml of formula (Appendix). Children who

received this formula all had chronic renal failure, defined as calculated GFR ≤65 ml/min per 1.73 m^2, at the time the specified feedings were initiated. Formulas used included Nepro, Suplena, Similac PM 60/40 (Ross Products Division, Abbott Laboratories, Columbus, OH), and SMA (Wyeth-Ayerst Laboratories, Philadelphia, PA). Feedings were prescribed in volumes of 180 to 240 ml/kg per 24 h (depending on urine output), which provided 100 to 160 kcal/kg per 24 h and approximately 2 to 2.5 g/kg protein per day. Initial caloric and protein intakes for the patients reported here were 120 kcal/kg per day and 2.0 to 2.5 g/kg per day. The corresponding recommended dietary allowances (RDA) for infants and toddlers <3 yr old are 98 to 108 kcal/kg per day and 1.2 to 2.2 g/kg protein per day (14).

Growth parameters, including initial length by infant stadiometer, standing height by stadiometer, and weight by standard balance were measured. Laboratory studies including electrolytes, acid base status, and intact parathyroid hormone level were performed on a regular basis (usually monthly). All patients received vitamin D therapy if they developed an elevation of the intact parathyroid hormone more than three times normal. A renal formulated multivitamin was prescribed (Iberet Abbott Laboratories, North Chicago, IL; Nephro-Vite, R&D Laboratories, Marina del Rey, CA; Nephrocaps, Fleming & Co., Fenton, MO) for all patients. No child received growth hormone.

Feeding volume and caloric intake were regularly adjusted on the basis of increases in height and weight. During regular monthly or bimonthly visits, fluid intake was increased according to gain in body weight, and calories were adjusted up or down depending on linear growth, head circumference, and albumin levels during the previous few months. The sodium was prescribed as milliequivalents per 100 ml of formula, and increases in formula volume were accompanied by proportional increases in supplemental sodium. Further adjustments in sodium concentration and protein content were made depending on the results of patients' serum biochemistries. To limit the osmolality of the feedings, the maximum concentration of supplemental sodium was set at 4 mEq/100 ml of formula. Supplemental bicarbonate was given if the serum bicarbonate level was <19 mEq/L and adjusted to achieve a target serum bicarbonate of 23 to 25 mEq/L.

Feedings were administered by spontaneous oral intake, supplemented by intermittent or continuous nasogastric or gastrostomy feeding tubes. Typically, infants were hospitalized at the time of initial diagnosis, and during this hospital stay, it was determined whether the patients were able to spontaneously achieve the target caloric and fluid intake. If they were not able to meet their target intake, a nasogastric tube was placed and used until the infant was able to receive a gastrostomy feeding tube. Infant formula Nepro, or Suplena with additives, was used until age 2 yr, at which time each patient was reassessed to determine the best individual diet.

Control Groups

Two control groups were used in this study: a historical population control and a literature control. The historical population controls were selected from the national Pediatric Growth Special Study of the US Renal Data Systems (USRDS) (15). The use of this national database allows for comparison of growth in the treatment group we assessed to a national standard of growth in children treated for ESRD. This special study reported on prevalent ESRD in pediatric patients followed from 1990 to 1991. The controls chosen from this large national cohort were children from all disease categories who were <1 yr of age at the time of RRT, who had received no growth hormone therapy, and who had height measurements obtained before their second birthday. The children were followed for a period of up to 1 yr from January 1990 to December 1990, and height measurements obtained 6 mo or more apart. Exclusion criteria for the control subjects included the use of growth hormone or death during the study period, or missing data regarding height measurements. More detailed information regarding the abstraction of data for this special study has been previously published (13). No information is available on the dietary management of this control group.

The literature controls were obtained from a report by Abitbol *et al.* (12), who described 12 infants with chronic renal failure diagnosed within the first month of life. The literature control was used to compare the effect of our nutritional approach on growth with that of a group of infants who received adequate nutrition, which is a weakness of the USRDS control group. Patients in this study were given high-caloric-density feeding regimens intended to provide ≥100% of the RDA for calories and protein. Feedings consisted of Similac PM 60/40 concentrated to 24 kcal/oz, with the addition of glucose polymers to increase the caloric density to 30 kcal/oz. Sodium supplementation was not provided. Seven of 12 patients received vitamin D therapy. All patients were followed for 2 yr. Only the final (2-yr) height change in SD scores (ΔSDS) were available for this group of patients.

Analysis of Growth

For the treatment group and the USRDS control group, height SDS was calculated by Growtrak 1.2 for Windows (Genetech, South San Francisco, CA). The height SDS was calculated by comparing the patient's height measurement to the mean US value for children of equal age and gender:

$$\text{SDS} = \frac{\text{(ESRD patient measurement)} - \text{(mean US value for age and gender)}}{\text{(SD of mean US value for age and gender)}}$$

The resultant SDS indicates how many SD the child is above or below the average height measurement for children of similar age and gender. A SDS of zero corresponds to the average height measurement of the general population adjusted for age and gender.

Statistical Analyses

Baseline demographic factors included race, gender, primary cause of chronic renal insufficiency (CRI), creatinine clearance (C_{cr}), and RRT as categorical variables. Race was classified as white, black, or other. Primary cause of CRI was divided into three broad categories: polycystic kidney disease, obstructive uropathy or dysplasia, and other causes. Obstructive uropathy or dysplasia included all causes of obstructive uropathy, renal dysplasia, and hypoplasia. C_{cr} in the treatment group was assessed at time of entry into study and was divided onto three groups for the purposes of analysis: <10 ml/min per 1.73 m^2, 10 to 50 ml/min per 1.73 m^2, and >50 ml/min per 1.73 m^2. RRT was also determined at the time of entry into the study and was categorized as no RRT, dialysis, or transplant.

Because of the observational and nonrandomized study design, the comparison of the 1- and 2-yr ΔSDS between groups was performed by multivariate linear regression. Adjusted comparisons of the treatment group to the two control groups were performed to further validate the data. The treatment group and control groups were compared by the baseline characteristics, and we adjusted for variables that were considered to be significant and clinically relevant in the multivariate linear regression analysis. The comparison of the USRDS and treatment group was adjusted for RRT, primary cause of ESRD, and initial height SDS, and the outcome of the 1-yr height SDS was assessed. Because the USRDS Pediatric Growth Study was limited to 1 yr, we made no adjustment for changes in renal replacement

modality, and correspondingly, in the treatment group, we made no adjustment for the institution of RRT. The comparison of the treatment group and literature control group was adjusted for the severity of disease by including C_{cr} as a covariate and evaluating the 2-yr height ΔSDS.

Statistical analyses were performed by SAS statistical software (version 6.12; SAS Institute Inc., Cary, NC). Dichotomous variables were analyzed by χ^2 test, and continuous variables were compared by *t* test. In all analyses, the tests of statistical significance were two-tailed. A *P* value of <0.05 was considered to be statistically significant.

Results

Patient Characteristics

The treatment group consisted of 24 children treated at the University of Michigan who were diagnosed between 1992 and 1999 with polyuric renal insufficiency before 1 yr of age. All children had a C_{cr} of <65 ml/min per 1.73 m^2 as calculated by the Schwartz equation (3). Twenty-one patients were followed for 2 yr, and 3 patients were followed for 1 yr. Data were collected regarding dialysis, transplantation, height, weight measurements, and renal function, and all data were available for all patients.

There were 12 patients in the literature control group and 42 patients in the USRDS control group. Characteristics of the groups are compared in Table 1. There were no statistical differences between the three groups with respect to race and gender. The percentage of patients with obstructive uropathy or dysplasia was similar in the treatment and literature control groups (92 *versus* 75%, P = NS) but was significantly less in the USRDS control group compared with the treatment group (30 *versus* 92%, $P = 0.001$).

A C_{cr} of <50 ml/min per 1.73 m^2 was present in 92% of the treatment group, *versus* just 75% of the literature control group ($P < 0.05$). C_{cr} for patients in the USRDS group was not reported; however, 83% of patients in the USRDS control group were on dialysis, and 17% received transplants. RRT was instituted in 29% of the treatment group, significantly less often than in the USRDS control group ($P = 0.001$). During the 2-yr follow-up period, two children in the treatment group underwent preemptive transplantation, six children on dialysis received transplants, one child remained on peritoneal dialysis, one child started dialysis in the second year of life, and one child recovered renal function and dialysis was discontinued. The remaining 13 children were able to be maintained without RRT throughout the entire follow-up period.

Nutritional Status

Nutritional intakes for the study population are shown in Table 2. The average energy intake for the entire treatment group was 104 kcal/kg per day (102% RDA), and the average protein intake was 2.45g/kg per day (153% RDA). By contrast, the mean nutritional intake of the patients in the study of Abitbol *et al.* (12) was just 87% of the RDA for energy (despite their intended goal of providing >100% of the RDA) and 141

Table 1. Patient characteristics of the treatment group and control groups[a]

Parameter	Treatment Group (%)	Literature Control Group (%)	*P* Value[b]	USRDS Control Group (%)	*P* Value[c]
No. patients	24	12		42	
Race					
white	23 (96%)	10 (83%)		34 (81%)	
black	1 (4%)	2 (17%)	NS	5 (12%)	NS
other	0	0		3 (7%)	
Gender					
female	7 (30%)	5 (42%)	NS	14 (33%)	NS
male	17 (70%)	7 (58%)		28 (67%)	
Disease					
polycystic kidney	1 (4%)	0		8 (20%)	
urologic causes	22 (92%)	9 (75%)	NS	12 (30%)	0.001
other causes	1 (4%)	3 (25%)		21 (50%)	
C_{cr}					
<10 ml/min per 1.73 m^2	10 (42%)	1 (8%)			
10–50 ml/min per 1.73 m^2	12 (50%)	8 (67%)	<0.05	NA	
>50 ml/min per 1.73 m^2	2 (8%)	3 (25%)			
RRT					
none	17 (71%)			0	
dialysis	7 (29%)	NA		35 (83%)	0.001
transplant	0			7 (17%)	

[a] USRDS, US Renal Data System; NS, not significant; C_{cr}, creatine clearance; RRT, renal replacement therapy; NA, data not available.
[b] Comparing the literature control group with the treatment group.
[c] Comparing the USRDS control group with the treatment group.

± 42% of the RDA for protein intake. Dietary data were not available for the USRDS pediatric population.

Calculated C_{cr} for the 13 children who did not require dialysis or transplantation and only received supplemented feedings during the study period are shown in Figure 1. Initial clearances were quite impaired, <60 ml/min per 1.73 m^2 in all but one child, whose clearance was 62 ml/min per 1.73 m^2. After the initiation of feeds, clearance improved in most children in the first year and declined during the second year.

The weight SDS for each subject is shown in Figure 2. The baseline mean weight SDS for the entire treatment group was −0.74, −0.61 at 1-yr and −0.3 at 2-yr follow-up. The literature control group had a mean weight SDS of −0.4 at birth and −1.5 at 2 yr. The weights of the USRDS group are not shown because of the variability of weights of children on dialysis.

Linear Growth

Height measurements for all three groups are shown in Table 3 as the mean and SD for each group. There was no difference between the 1-yr height measurements of patients in the treatment and USRDS control groups. However, when the height was converted to the 1-yr height SDS, the patients in the treatment group had a greater height SDS than did the patients in the USRDS group ($P = 0.001$). The unadjusted 1-yr height ΔSDS showed no difference between the treatment and USRDS control groups. The unadjusted 2-yr height ΔSDS of the literature control group was significantly lower than the treatment group ($P = 0.002$).

The initial multivariate analysis compared the treatment group with the USRDS control group at 1 yr (Table 4). This model simultaneously assessed the effect of treatment on growth while controlling for the severity of disease by RRT, primary cause of ESRD, and initial height SDS; the model accounted for 44% of the variance in the 1-yr ΔSDS by linear regression analysis. There was evidence of a treatment difference between the treatment and USRDS control groups in predicting the 1-yr height SDS while adjusting for the severity of disease, primary cause of ESRD, and initial height SDS ($P < 0.012$). The predicted 1-yr height ΔSDS was greater for the patients in the treatment group than the patients in the USRDS control group, with an increase in height ΔSDS of +1.37, assuming the RRT and diagnosis were the same (Table 4).

Children on dialysis who were not receiving RRT had significantly lower 1-yr height ΔSDS than did members of the transplant group, with the no-RRT group having the lowest predicted 1-yr height ΔSDS compared with children who had received a

Table 2. Average nutritional intake of fluid, calories, protein, and sodium supplements for the 2-yr study period

Patient	Feeding Regimen	Mean ml/kg per d	Mean kcal/kg per d	Mean g of Protein/kg per d	Mean Supplemental NaCl mEq/ 100 ml of Formula[a]	Mean Supplemental $NaHCO_3$ mEq/ 100 ml of Formula[a]
1	GT	184.6	87	1.85	3	1.3
2	Oral	87.5	106	1.3	0	1
3	GT	135	113	2.95	2	0
4	GT	135.5	90	2.2	2	0
5	GT	182.6	104	1.83	0	2.7
6	GT	125	83	2.2	2.9	0
7	GT	138	91.6	2	1	2.5
8[b]	GT	150	100	2.2	3.3	0
9[b]	Oral	130	130	2	Dose not specified	Dose not specified
10	GT	161.5	70	1.5	2	1
11[b]	Oral	200	136	3.2	1	2.5
12	GT	177.6	101.6	2.3	2	1
13	GT	185.5	95	3	2.4	0
14	Oral	175	115.6	2.6	0	2.6
15	GT/oral	226.3	98.3	2.13	2.1	2.2
16	GT	132	110	1.6	2	3
17	NG/oral	151	110	2.96	2.9	3
18	Oral	158.6	108	2.3	0	3
19	NG/oral	186	108.3	2.3	2	2
20	GT	212	118.3	2.4	1.5	2.4
21	Oral	225.5	119.5	2.65	1.5	1.8
22	GT	250	151.5	3.35	0	2.5
23	GT	143	72.3	1.62	1.6	1.7
24	GT	210	100	2.35	1	2

[a] Does not include the NaCl or $NaHCO_3$ in the formula.
[b] Limited dietary data available.

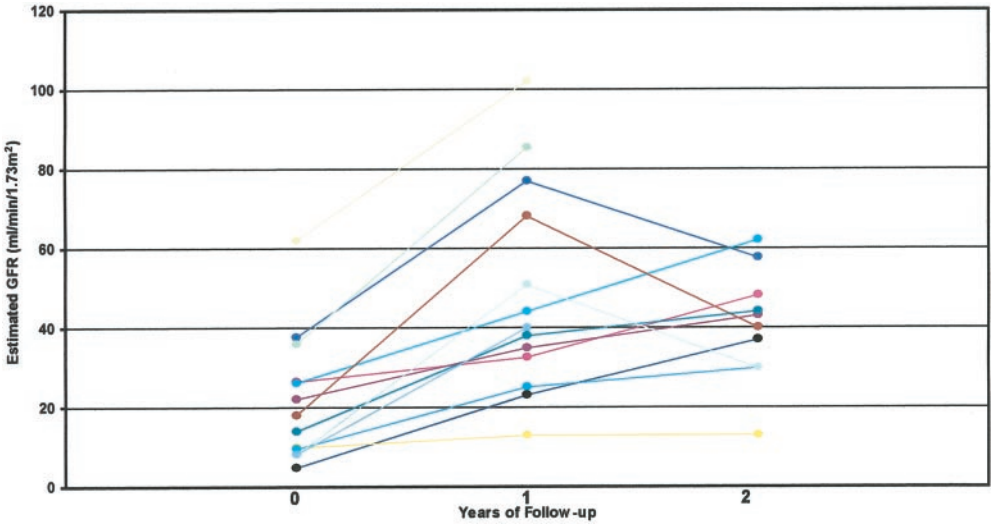

Figure 1. Estimated creatinine clearance (C_{cr}; estimated by the Schwartz equation) in 13 children treated only with nutritional prescription during the entire study period.

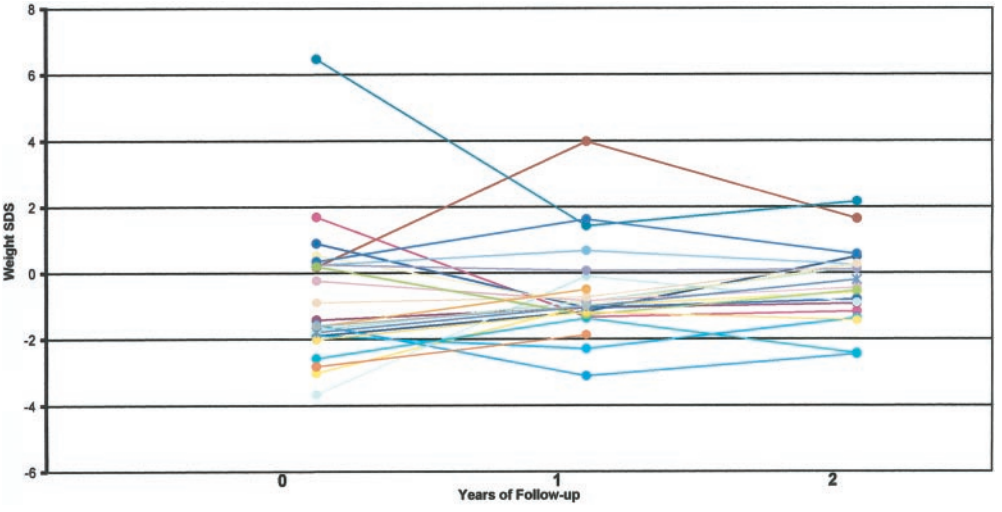

Figure 2. Weight standard deviation score (SDS) of all 24 children in the treatment group during the 2-yr study period.

transplant. Children with polycystic kidney disease and other causes of renal insufficiency had little difference in predicted 1-yr height ΔSDS compared with the referent group of children with obstructive uropathy. When only children with obstructive uropathy from the USRDS control group were used for analysis, we found a statistically significant difference in 1-yr height ΔSDS in the treatment group compared with the USRDS control group, with an increase in height ΔSDS of +1.74 in the treatment group compared with the control group, assuming similar RRT (Table 4). This model accounted for 47% of the variance in the 1-yr ΔSDS by linear regression analysis.

Additional analyses compared the treatment group with the literature control group at 2 yr. A linear regression model to assess the outcome of the 2-yr height ΔSDS (2-yr height SDS minus initial height SDS), while adjusting for the C_{cr}, revealed a statistically significant greater 2-yr height ΔSDS in the treatment group than the control group ($P < 0.03$). This model accounted for 34% of the variation of the 2-yr height ΔSDS. The literature control group had a decrease in the predicted 2-yr height ΔSDS by 1.83 compared with the treatment group (Table 3). In children with the lowest calculated C_{cr}, there was a small gain in 2-yr height ΔSDS among both treatment and control groups compared with those children with clearances >50 ml/min per 1.73 m^2, which was not statistically significant. The addition of primary cause of ESRD as a covariate had no additional effect on the model, with the treatment group continuing to have significantly greater height ΔSDS (data not shown).

Discussion

In this study, we describe the beneficial effect of a dilute, sodium-supplemented, high-volume feeding regimen on linear growth in young children with severe polyuric CRI. Patients treated with this specified nutritional regimen maintained their height SDS at 1 and 2 yr despite significant renal insufficiency. The treatment group was able to maintain a nearly normal

Table 3. Height measurements of the treatment and control groups[a]

Parameter	Treatment Group	Literature Control Group[b]	USRDS Control Group[c]
Initial height (mean cm ± SD)	53.2 ± 6.3		66.5 ± 9.8
Initial height SDS (mean SDS ± SD)	−0.93 ± 1.6	−0.7	−2.4 ± 1.3
One-yr height (mean cm ± SD)	74.8 ± 4.0		76.8 ± 8.6
One-yr height SDS (mean SDS ± SD)	−1.06 ± 1.3		−2.3 ± 1.3
Two-yr height (mean cm ± SD)	86.4 ± 3.6		
Two-yr height SDS (mean SDS ± SD)	−0.78 ± 1.2	−2	
One-yr ΔSDS (mean SDS ± SD)	−0.13 ± 1.7		0.13 ± 1.3
Two-yr ΔSDS (mean SDS ± SD)	0.12 ± 1.5	−1.59 ± 1.3	

[a] USRDS, US Renal Data System; SD, standard deviation; SDS, SD score; ASDS, change in SDS.
[b] Two-year ΔSDS unadjusted *P* value compared with the treatment group ($P < 0.05$).
[c] Initial height, SDS, and 1-y SDS unadjusted *P* value compared with the treatment group ($P < 0.05$).

height SDS, with the height SDS not decreasing over time, as is typical for children with ESRD. Instead, there was a net gain of height SDS of 0.15 during the 2 yr. These results were superior to those seen in two previously reported comparable groups of children, one group with CRI treated with high-caloric-density feedings, and the other with ESRD and RRT. This gain of height SDS is unusual in infants with CRI, who typically demonstrate a loss of height SDS over time (16).

The natural history of poor growth commonly seen in children with CRI is clearly illustrated by the initial and 2-yr height SDS of patients in the literature control group, who had poor growth despite supplementation with high-density feeds (12). The nutritional intake of the treatment group consisted of a higher volume of sodium-supplemented feeds with similar energy and protein intakes than the literature control group. Compared with this group, the patients we studied demonstrated stable growth during 2 yr, even though the mean C_{cr} was significantly lower than in the group reported by Abitbol *et al.* (12). The weight SDS of the treatment group was also higher at 2 yr than the literature control group. Some patients had been on dialysis or had received transplants, which may have affected the weight gain. The trend of the weight SDS, however, continued to improve during the 2 yr, so it is unlikely that this solely represents fluid gain.

The USRDS population control group was used to compare our results with the prevailing standard of care of young children with ESRD. The initial height SDS was lower in the USRDS control group than the treatment group. This difference in initial height SDS can be explained partly by the severity of renal disease, and also by primary cause of ESRD; however, we adjusted for these factors in the analysis. Height SDS of the USRDS group was maintained during the 1-yr follow-up period and represented the average height SDS among prevalent pediatric dialysis and transplant patients. The maintenance of the mean height SDS is partially explained by the contribution of a gain in height by transplant patients of 0.13 height SDS per year for this age group (13). However, the USRDS control group reflects an ESRD population treated with RRT that was able to maintain height SDS but demonstrated no catch-up growth, highlighting the need for a method to improve growth in children with chronic renal failure before they require transplantation.

This retrospective study of nutritional intervention adjusts for the clinically significant differences of severity of disease and the primary cause of CRI in the analyses. Demographic variables (race and gender) did not vary by group: the causes of congenital ESRD in this age group are similar throughout the United States (15). The internal validity of the study is further strengthened by the use of two control groups with follow-up for a 2-yr period. However, the center effect and the potential differences in the care of children in the USRDS database could not be taken into consideration in this analysis. We were also limited by our inability to retrospectively collect data on growth factors such as insulin-like growth factor, which might have given clues to possible biologic mechanisms of growth failure in this subset of young children with ESRD. Linear growth was routinely measured; however, skinfold thickness and midarm circumference were not routinely measured, so changes in muscle mass could not be assessed.

Sodium has been reported to be vital for growth in children, specifically very low birth weight infants, children with Bartter's syndrome, and children with salt-wasting gastroenteropathy (17–19). Sodium depletion is known to affect not only extracellular volume, but also growth and nitrogen retention (20). Sodium intake also promotes the normal expansion of extracellular fluid volume that is necessary for muscle development and mineralization of bone (18). Fine *et al.* (21) have shown in a rat model that the sodium requirements for growth are unrelated to body size because the sodium is primarily used for new tissue growth. They noted a decrease in extracellular fluid volume with severe salt restriction. The authors concluded that plasma volume expansion appears to be required for growth, and salt deprivation may in part affect growth by depleting extracellular fluid volume. We hypothesize that this same process occurs in children with polyuric, salt-wasting chronic renal failure and that the repletion of sodium and water losses is vital to promote normal growth in these children.

To our knowledge, this is the largest reported series of

Table 4. Multiple linear regression models for 1-yr and 2-yr height change in standard deviation score.[a]

Parameter	Coefficient	Standard Error	95% CI	*P*
Dependent variable				
1-yr height ΔSDS				
Independent variables				
intercept	1.27	0.67	0.6, 1.94	0.06
initial height SDS	−0.58	0.1	−0.68, −0.48	0.001
treatment				
USRDS control (treatment group ref)	−1.37	0.56	−1.93, −0.81	0.012
RRT				
dialysis	−1.47	0.5	−1.97, −0.97	0.004
no RRT (transplant ref)	−2.15	0.7	−2.85, −1.45	0.004
cause of ESRD				
polycystic kidney	0.35	0.5	−0.15, 0.85	0.48
other (urological ref)	−0.04	0.4	−0.44, 0.36	0.93
Dependent variable				
1-yr height ΔSDS				
Independent variables				
intercept	1.26	1.31	−0.05, 2.57	0.35
initial height SDS	−0.67	0.14	−0.81, −0.53	0.001
treatment				
USRDS control (urological subjects only) (treatment group ref)	−1.74	0.67	−2.41, −1.07	0.015
RRT				
dialysis	−2.24	1.3	−3.54, 0.94	0.11
no RRT (transplant ref)	−1.5	1.23	−2.73, −0.27	0.23
Dependent variable				
2-yr height ΔSDS				
Independent variables				
intercept	−0.52	0.82	−1.34, 0.3	0.53
treatment				
literature control (treatment ref)	−1.83	0.57	−2.4, −1.26	0.003
creatinine clearance				
<10 ml/min per 1.73 m^2	0.22	0.9	−0.68, 1.12	0.8
10–50 ml/min per 1.73 m^2	1.11	0.8	0.31, 1.91	0.17
>50 ml/min per 1.73 m^2 (ref)				

[a] CI, confidence interval; SDS, standard deviation score; ΔSDS, change in SDS; USRDS, US Renal Data System; ref, referent group; RRT, renal replacement therapy.

children with chronic renal failure rigorously treated with sodium and water supplementation and the most comprehensive comparison available of the potential benefits of sodium and water supplementation on growth. Our method of nutritional intervention with a dilute, high-volume sodium supplemented feeding regimen was more successful in improving growth than were previously reported series of nutritional intervention in children with severe CRI (11,12). The stabilization of growth in the treatment compared with the control groups of patients demonstrates the ability of sodium and water supplementation to overcome typical growth retardation seen in infants and children with chronic renal failure. The specified nutritional prescription provided to these patients is a simple recipe that can be easily generalized to all polyuric congenital causes of CRI.

The importance of nutritional supplementation in children with chronic renal failure was recently highlighted in publications from the group at Great Ormond Street (22,23), which demonstrated catch-up growth in children with chronic renal failure after provision of supplemental enteral nutrition. Their results are difficult to compare with ours because enteral nutrition in their study was not initiated until growth failure had already occurred, and because they did not report detailed information regarding the composition, especially caloric density and sodium supplementation, which was commonly provided (S. Ledermann, personal communication), of the feedings their patients received. Their results, however, do demonstrate that meticulous nutritional support is a key component of the successful management of the child with chronic renal failure, and such support can often improve growth in growth-retarded children without the addition of growth hormone.

The estimated C_{cr} seen after the initiation of feeds was improved in the 13 patients who received sodium supplemented feedings only. In addition, four patients experienced worsening of renal function in their second year or were preemptively transplanted. Analysis of these data suggests that the use of sodium-supplemented feedings may be also a therapeutic intervention to transiently improve the GFR, allowing deferment of RRT and facilitating planning for a preemptive renal transplant.

The overall cost of sodium and water supplementation added to the usual cost of dietary supplements is only cents per day, or an estimated $50 per year. The use of table salt and baking soda makes it possible for families to inexpensively prepare these supplements at home (Appendix). The current average wholesale cost of growth hormone is $420 for a 5-mg/ml vial (24), and the annual cost of growth hormone can be as high as $15,000. Clearly, sodium and water supplementation is inexpensive compared with growth hormone therapy or dialysis.

We conclude that specified nutritional therapy consisting of sodium and water supplementation can maintain or improve the growth of children with polyuric causes of CRI. This approach not only promotes improved growth rates in this patient population, but also likely delays the need for dialysis until preemptive renal transplantation can be accomplished. This cost-effective form of nutritional intervention to improve growth can be administered in any clinical setting and may be particularly suited to regions of the world where dialysis is either technologically or financially impossible.

Acknowledgments

This work was supported by the American Kidney Fund/Amgen Clinical Scientist in Nephrology Fellowship Award. We thank Dr. R.A. Wolfe for his advice on the statistical analyses and Dr. F.K. Port for his review of the article in manuscript. Some of the data reported here were supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. Presented in abstract form at the ASN meeting in New Orleans, Louisiana, October 1996.

Appendix: Instructions for Sodium Chloride and Sodium Bicarbonate Solutions

Salt solutions can be made inexpensively at home and then can be measured out in small amounts to be added to formulas. However, you must be extremely careful with these solutions: if given to a child undiluted, the concentration of the solution could make them very sick. Please make the recipes carefully—mark the bottles carefully and only have one person responsible for making them. Never give these solutions to a child without diluting them in some other fluid.

NaCl Solution (Salt Solution)

Take 1/3 cup table salt (without iodine) and mix with 1 quart water. Store in refrigerator. Discard after 2 wk and make a new batch.

1 ml = 1 mEq

The prescription for your child is to add _____ ml of NaCl solution to _____ ml of _____ times daily.

$NaHCO_3$ Solution (Sodium Bicarbonate Solution)

Add one 8-ounce box of Arm and Hammer baking soda to 3 quarts of water. Store in refrigerator. Keep tightly capped. Discard after 2 wk and make a new batch.

1 ml = 1 mEq

If you can find a 4-ounce box of baking soda or you have a scale, you can measure out 4 ounces and add to 11/2 quarts of water to save room.

The recipe for your child is to add _____ ml $NaHCO_3$ solution to each _____ ml of _____ (must be in water or a nonacid drink) _____ times a day.

References

1. Abitbol C, Chan JC, Trachtman H, Strauss J, Greifer I: Growth in children with moderate renal insufficiency: Measurement, evaluation, and treatment [Review]. *J Pediatr* 129: S3–S8, 1996
2. Karlberg JSF, Hennicke M, Wingen A, Rigden S, Mehls O, European Study Group: Nutritional treatment of chronic renal failure in childhood. *Pediatr Nephrol* 10: 283–287, 1996
3. Hellerstein SHM, Grupe WE, Fine RN, Fennell RS, Chesney RW, and Chan JCM: Nutritional management of children with chronic renal failure. Summary of the task force on nutritional management of children with chronic renal failure. *J Pediatr* 1: 195–211, 1987
4. Sedman AS, Friedman A, Boineau F, Strife CF, Fine R: Nutritional management of the child with mild to moderate chronic renal failure [Review]. *J Pediatr* 129: S13–S38, 1996
5. Rigden SP, Start KM, Rees L: Nutritional management of infants and toddlers with chronic renal failure. *Nutr Health* 5: 163–174, 1987
6. Holliday MA, ET, Morris CR, Jarrah AS, Harrah JL: Pitressin-resistant hyposthenuria in chronic renal disease. *Am J Med* 42: 378–387, 1967
7. Tejani ACL, Sullivan EK: A longitudinal study of the natural history of growth post-transplantation. *Kidney Int* 49[Suppl]: 103–108, 1996
8. Kaiser BA, Polinsky MS, Stover J, Morgenstern BZ, Baluarte JH: Growth of children following the initiation of dialysis: A comparison of three dialysis modalities. *Pediatr Nephrol* 8: 733–738, 1994
9. Hokken-Koelga ACS, Van Zaal AE, De Ridder MA, Wolff ED, De Jong MCJW, Donckerwolke RA, De Muinck Keizer-Schrama SMPF, Drop SLS: Growth after renal transplantation in prepubertal children: Impact of various treatment modalities. *Pediatr Res* 35: 367–371, 1994
10. Wolfe RA, Port FK, Webb RL, Bloembergen WE, Hirth R, Young EW, Ojo AO, Stawderman RL, Gillespie B, Held PJ, Parekh R, Stack A, Tedeschi PJ, Loos E, Hulbert-Shearon T, Ashby VB, Callaard S, Orzol SM, Carrol CC, Wheeler JR, Jones CA, Frederick PR, Greer JW, Agodoa LYC: Excerpts from the United States Renal Data System 1998 Annual Data Report. *Am J Kidney Dis* 32[Suppl 1]: S1–S162, 1998
11. Brewer E: Growth of small children managed with chronic

peritoneal dialysis and nasogastric tube feedings: 203-month experience in 14 patients. *Adv Perit Dial* 6: 269–272, 1990
12. Abitbol CL, Zilleruelo G, Montane B, Strauss J: Growth of uremic infants on forced feeding regimens. *Pediatr Nephrol* 7: 173–177, 1993
13. Turenne MN, Port FK, Strawderman RL, Ettenger RB, Alexander SR, Lewy JE, Jones CA, Agodoa LYC, Held PJ: Growth rates in pediatric dialysis patients and renal transplant recipients. *Am J Kidney Dis* 30: 193–203, 1997
14. National Research Council. Subcommittee on the Tenth Edition of the RDAs. *Recommended Dietary Allowances*, 10th Ed., Washington, DC, National Academy Press, 1989
15. National Institutes for Health. *US Renal Data System 1998 Annual Data Report*, Bethesda, National Institute of Diabetes and Digestive and Kidney Disease, 1998
16. Rizzoni G, Basso T, Setari M: Growth in children with chronic renal failure on conservative treatment. *Kidney Int* 26: 52–58, 1984
17. Wassner S, Kulin HE: Diminished linear growth associated with chronic salt depletion. *Clin Pediatr (Phila)* 29: 719–721, 1990
18. Ray PE, Lyon RC, Ruley EJ, Holliday MA: Sodium or chloride deficiency lowers muscle intracellular pH in growing rats. *Pediatr Nephrol* 10: 33–37, 1996
19. Fine BP, Ty A, Lestrange N, Maher E, Levine OR: Diuretic-induced growth failure in rats and its reversal by sodium repletion. *J Pharmacol Exp Ther* 242: 85–89, 1987
20. Wassner S: Altered growth and protein turnover in rats fed sodium-deficient diets. *Pediatr Res* 26: 608–613, 1989
21. Fine BP, Ty A, Lestrange N, Levine R: Sodium deprivation growth failure in the rat: Alterations in tissue composition and fluid spaces. *J Nutr* 117: 1623–1628, 1987
22. Ledermann SE, Shaw V, Trompeter RS: Long-term enteral nutrition in infants and young children with chronic renal failure. *Pediatr Nephrol* 13: 870–875, 1999
23. Kari JA, Gonzales C, Ledermann SE, Shaw V, Rees L: Outcome and growth of infants with severe chronic renal failure. *Kidney Int* 57: 1681–1687, 2000
24. *2000 Drug Topics Red Book*, 465th Ed., Oxford, Blackwell Science, 2000.

J Am Soc Nephrol 13: 1419–1422, 2002

Six figures were printed with improper labeling in the article by Mortier *et al.*, "Hemodynamic Effects of Peritoneal Dialysis Solutions on the Rat Peritoneal Membrane: Role of Acidity, Buffer Choice, Glucose Concentration, and Glucose Degradation Products," which appeared on pages 480–489 in the February 2002 issue of *JASN*. Corrected versions of Figures 2 through 7 appear below. The online version has already been corrected.

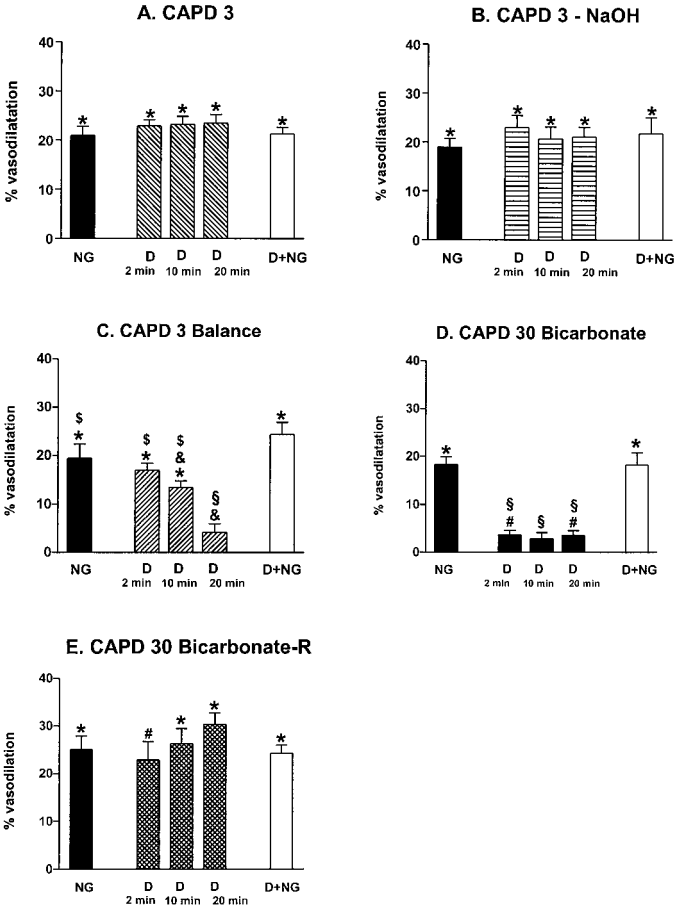

Figure 2. Percentage change of luminal diameters of mesenteric arteries after local application of continuous ambulatory peritoneal dialysis (CAPD) 3 (A, $n = 6$), CAPD 3 neutralized with NaOH (B, $n = 6$), CAPD 3 balance (C, $n = 6$), CAPD 30 bicarbonate (D, $n = 6$), and resterilized CAPD 30 bicarbonate to increase the glucose degradation product levels (E, $n = 6$). The vasodilatory capacities of nitroglycerin 10^{-4} M dissolved in Earle's balanced salt solution (EBSS) (NG), dialysate (D), and nitroglycerin 10^{-4} M dissolved in dialysate (D + NG) were compared. The three interventions were applied in random order. *$P < 0.001$ *versus* EBSS, #$P < 0.05$ *versus* EBSS, §$P < 0.01$ *versus* NG and D + NG, \$$P < 0.01$ *versus* D + NG, &$P < 0.01$ *versus* D 2 min.

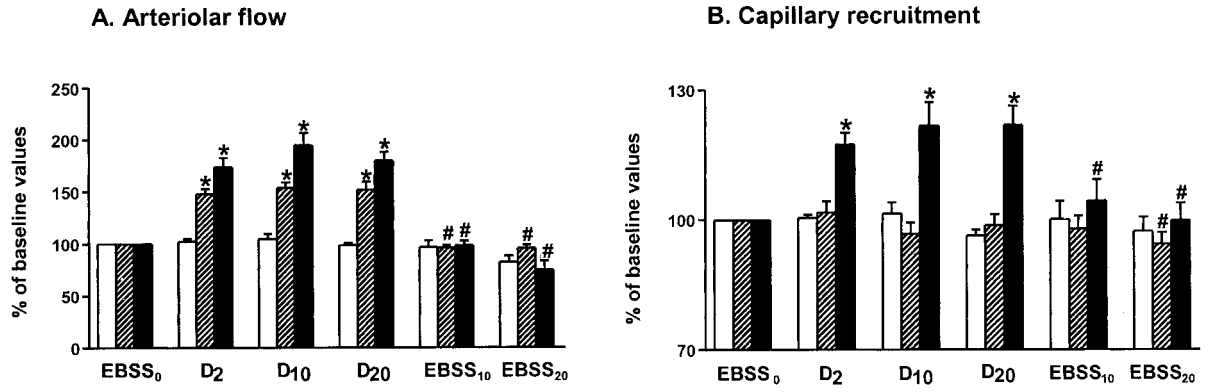

Figure 3. (A) Percentage change of arteriolar flow or (B) perfused capillary length per area after superfusion with Earle's balanced salt solution (EBSS) (open bars, $n = 6$), continuous ambulatory peritoneal dialysis (CAPD) 2 (hatched bars, $n = 6$), or CAPD 3 (solid bars, $n = 6$). Measurements were made before exposure to dialysate ($EBSS_0$), 2 min after dialysate (D_2), 10 min after dialysate (D_{10}), 20 min after dialysate (D_{20}), 10 min after withdrawal of dialysate ($EBSS_{10}$), and 20 min after withdrawal of dialysate ($EBSS_{20}$). (A) $*P < 0.0001$ *versus* $EBSS_0$, $\#P < 0.0001$ *versus* D_{20}. (B) $*P < 0.05$ *versus* $EBSS_0$, $\#P < 0.05$ *versus* D_{20}.

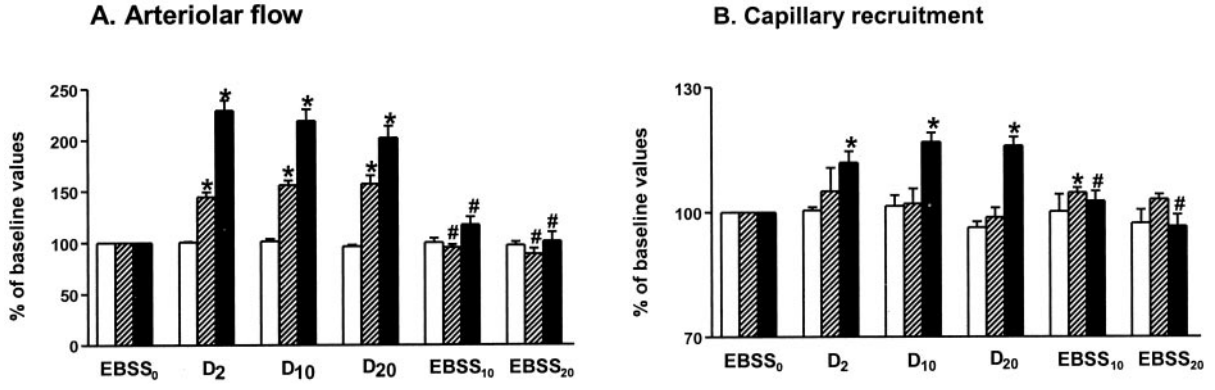

Figure 4. Percentage change of (A) arteriolar flow or (B) perfused capillary length per area after superfusion with Earle's balanced salt solution (EBSS) (open bars, $n = 6$), continuous ambulatory peritoneal dialysis (CAPD) 2 neutralized with NaOH (hatched bars, $n = 6$), or CAPD 3 neutralized with NaOH (solid bars, $n = 6$). Measurements were made before exposure to dialysate ($EBSS_0$), 2 min after dialysate (D_2), 10 min after dialysate (D_{10}), 20 min after dialysate (D_{20}), 10 min after withdrawal of dialysate ($EBSS_{10}$), and 20 min after withdrawal of dialysate ($EBSS_{20}$). (A) $*P < 0.0001$ *versus* $EBSS_0$, $\#P < 0.0001$ *versus* D_{20}. (B) $*P < 0.05$ *versus* $EBSS_0$, $\#P < 0.05$ *versus* D_{20}.

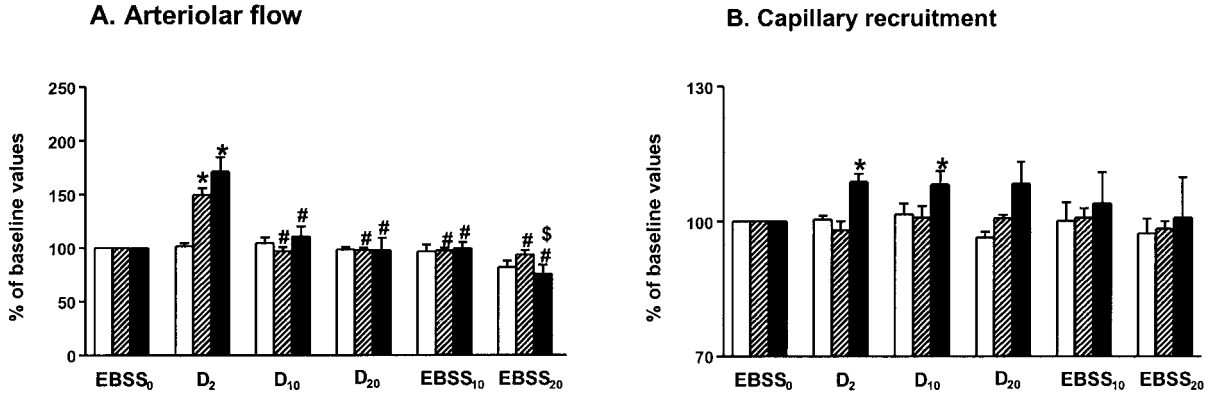

Figure 5. Percentage change of (A) arteriolar flow or (B) perfused capillary length per area after superfusion with Earle's balanced salt solution (EBSS) (open bars, $n = 6$), continuous ambulatory peritoneal dialysis (CAPD) 2 balance (hatched bars, $n = 6$), or CAPD 3 balance (solid bars, $n = 6$). Measurements were made before exposure to dialysate ($EBSS_0$), 2 min after dialysate (D_2), 10 min after dialysate (D_{10}), 20 min after dialysate (D_{20}), 10 min after withdrawal of dialysate ($EBSS_{10}$), and 20 min after withdrawal of dialysate ($EBSS_{20}$). (A) $*P < 0.001$ *versus* $EBSS_0$, $\#P < 0.01$ *versus* D_2. (B) $*P < 0.05$ *versus* $EBSS_0$.

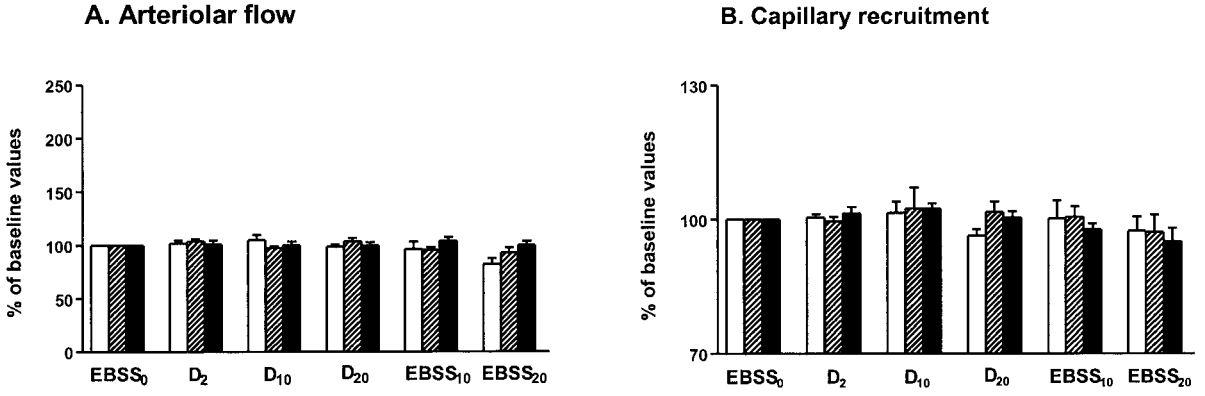

Figure 6. Percentage change of (A) arteriolar flow or (B) perfused capillary length per area after superfusion with Earle's balanced salt solution (EBSS) (open bars, $n = 6$), continuous ambulatory peritoneal dialysis (CAPD) 20 bicarbonate (hatched bars, $n = 6$), or CAPD 30 bicarbonate (solid bars, $n = 6$). Measurements were made before exposure to dialysate ($EBSS_0$), 2 min after dialysate (D_2), 10 min after dialysate (D_{10}), 20 min after dialysate (D_{20}), 10 min after withdrawal of dialysate ($EBSS_{10}$), and 20 min after withdrawal of dialysate ($EBSS_{20}$).

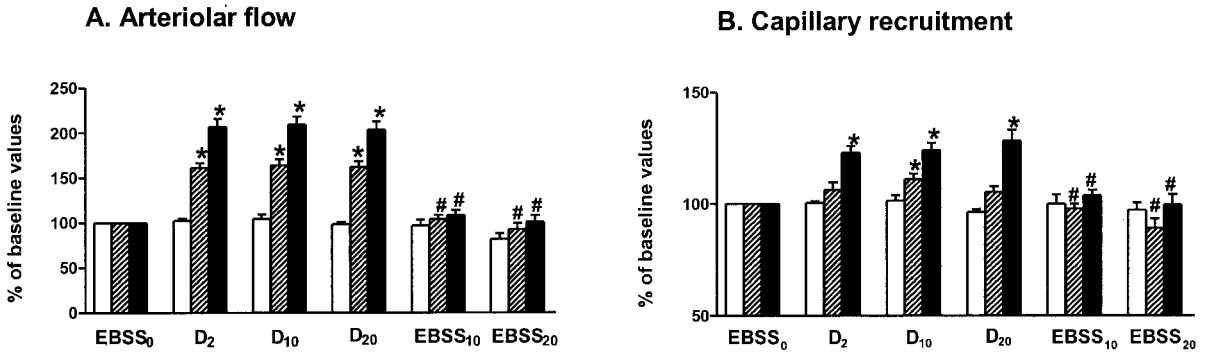

Figure 7. Percentage change of (A) arteriolar flow or (B) perfused capillary length per area after superfusion with Earle's balanced salt solution (EBSS) (open bars, $n = 6$), resterilized continuous ambulatory peritoneal dialysis (CAPD) 20 bicarbonate (hatched bars, $n = 6$), or resterilized CAPD 30 bicarbonate (solid bars, $n = 6$). Measurements were performed before exposure to dialysate ($EBSS_0$), 2 min after dialysate (D_2), 10 min after dialysate (D_{10}), 20 min after dialysate (D_{20}), 10 min after withdrawal of dialysate ($EBSS_{10}$), and 20 min after withdrawal of dialysate ($EBSS_{20}$). (A) $*P < 0.00001$ *versus* $EBSS_0$, $\#P < 0.0001$ *versus* D_{20}. (B) $*P < 0.01$ *versus* $EBSS_0$, $\#P < 0.05$ *versus* D_{20}.

Letter from the authors of "Improved Growth in Young Children with Severe Chronic Renal Insufficiency Who Use Specified Nutritional Therapy," which appeared on pages 2418–2426 of the November 2001 issue of *JASN*.

Regarding the homemade sodium solutions that we provided in the appendix to our article (1), use of these solutions began at our institution over 10 y ago after a pharmacy error resulted in an adverse event in a young child. It is estimated that medication errors occur in 6 of 100 orders in a pediatric inpatient pharmacy, and errors in dosing are frequent by parents (2,3). Potential errors can occur by the physician, pharmacy, and patient.

The controversy of homemade *versus* pharmacy-made solutions has also been under debate in the pediatric population with respect to the use of oral rehydration solutions. The error rate of homemade cereal-based rehydration solution was 3% when all ingredients were added and 1% in a premixed packet in a randomized clinical trial based in Boston (4). None of the mixing errors resulted in an adverse event.

Nevertheless, it is important to have personal, written instruction to the family and regular review and education of medication dosing. We carefully screen families to make sure that they are capable of mixing both their child's formula and the sodium solutions correctly. If not, we have a pharmacy make up the sodium chloride or bicarbonate solutions. Since minimizing the risk to the patient is of utmost importance, we would recommend that a pharmacy-based solution be used in an industrialized nation. We would also suggest that the solution be kept at a standard concentration of 1 mEq of sodium chloride/1 cc so that frequent adjustments by dietician and physician can be made without the risk of further errors.

We previously made and tested our homemade salt solutions. However, in following these same instructions in 2001, we realize that the packaging of Arm and Hammer has changed, which would lead to errors in preparation of these home-based solutions if our original instructions were followed. Although our recent laboratory testing of the solution did not produce solutions of 1.7 mEq/cc sodium concentration as suggested, the inaccuracies with new packaging make it imperative that we revise our home-based solutions. In formulating a home-based regimen, local supplies, *i.e.*, salt and bicarbonate sources and water constituents, all need to be considered. Our written outline is just an example and should not be used as a universal formula for a salt solution in any region or non-industrialized country.

Sincerely,

Rulan Parekh, Johns Hopkins Medicine, Baltimore, Maryland; William E. Smoyer, Joan L. Milne, David B. Kershaw, and Aileen B. Sedman, University of Michigan, Ann Arbor, Michigan; Joseph T. Flynn, Montefiore Medical Center, Bronx, New York; Timothy E. Bunchman, University of Alabama, Birmingham, Alabama

References

1. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, Sedman AB: Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. *J Am Soc Nephrol* 12: 2418–2426, 2001
2. Kaushal R, Barker KN, Bates DW: How can information technology improve patient safety and reduce medication errors in children's health care? *Arch Pediatr Adolesc Med* 155: 1002–1007, 2001.
3. McMahon SR, Rimsza ME, Bay RC: Parent can dose liquid medication accurately. *Pediatrics* 100: 330–333, 1997
4. Meyers A, Sampson A, Saladino R, Dixit S, Adams W, Mondolfi A: Safety and effectiveness of homemade and reconstituted packet cereal-based oral rehydration solutions: a randomized clinical trial. *Pediatrics* 100: 1997. Available at: http://www.pediatrics.org/cgi/content/full/100/5/e3.