ORIGINAL RESEARCH

Single-Center Experience on Growth in Infants Born With End-Stage Kidney Disease

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Objectives: Children with chronic kidney disease display poor growth that impacts health outcomes; data on infants with severe congenital anomalies of the kidney and urinary tract (CAKUT) are limited. We examined growth patterns in infants with CAKUT requiring dialysis in the first 30 days.

Methods: This study evaluated infants with severe CAKUT from 2014 to 2018 surviving past 30 days. Somatic growth parameters as per standard infant curves and nutritional information were recorded.

Results: Twenty four infants met inclusion criteria. Seventeen infants received dialysis, demonstrating somatic growth disruption most profound at a 1-2 months postnatal age. Growth trends were improved compared to infants with CAKUT who did not require dialysis. Linear growth failed to normalize by 1 year of age.

Conclusions: Infants with severe CAKUT are at high risk for early growth failure. Understanding of this deficit and impacts of early dialysis on growth and long-term outcomes are needed to identify targeted nutritional strategies.

Introduction

INFANTS WITH END-STAGE kidney disease (ESKD) offer a clinical challenge of competition between fluid balance and adequate nutritional provision to prevent catabolism and encourage somatic growth. Given infants with ESKD may have fluid overload, weight alone is often an unreliable measurement of nutritional status. For this reason, providers use z-scores of head circumference (HC) and linear growth to monitor nutritional status. As per data from the North American Pediatric Renal Trials and Collaborative Studies, the younger an individual is at the time of registration with chronic kidney disease (CKD), the worse the height deficit is during adulthood.[1] In addition to deficits in height, severe growth retardation with ESKD is linked to increased morbidity, mortality, and mental health problems in children and adults.[2–8] Children initiating dialysis with a height less than the first percentile for age-gender have a 2-fold increased mortality risk compared to those children initiating dialysis with a standard height.[6] Infants with ESKD are known to be at risk for neurodevelopmental impairments including cognitive delays.[9] There may be many causative factors leading to this risk; however, it is known that poor growth and nutritional deficits are a major risk for neurodevelopmental delays in preterm infants and childhood stunting is a serious risk factor for cognitive impairment.[10–12]

In infants with ESKD who require initiation of dialysis during the first 30 day as of life, severely impaired growth is highly plausible due to effects of caloric restriction from fluid limitation. Delays in establishing enteral feeds can occur due to medical issues such as hypotension and necessary surgical interventions to initiate kidney replacement therapy. Caloric delivery is suboptimal when an infant requires a restricted total fluid volume, yet medications such as inotropes and antibiotics comprise a significant fluid volume and so volume of parenteral nutrition delivery is limited. Further compounding this issue, the exchange of calories per milliliter from parenteral to enteral is not equivalent.

There is a paucity of literature that describes the specific feeding patterns of infants born with ESKD during the initiation of dialysis in the early (i.e., neonatal) hospital period. To better characterize growth in these infants for potential future-targeted interventions, we aimed to describe current practices and somatic growth patterns in a cohort of infants born with ESKD and required the initiation of dialysis.

Subjects and Methods

For this single-center pilot study, a retrospective review of our Fetal Care Center database was performed on infants

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diagnosed prenatally with fetal kidney dysfunction and evaluated during the pregnancy between January 1, 2014 and December 31, 2018. Fetal kidney dysfunction was defined as the presence of reduced maternal amniotic fluid volume (defined by an amniotic fluid index <6 or visualized deepest vertical pocket of amniotic fluid of being less than 2 cm) and kidney abnormalities as visualized on fetal imaging. Only infants admitted to the neonatal intensive care unit were included for analysis. Infants were excluded if they had bilateral renal agenesis or experienced death prior to 30 days of life. The primary cohort of interest was infants who were recipients of dialysis, characterized as any form of kidney replacement therapy. In 2015, our center began extracorporeal dialysis treatments of prolonged intermittent kidney replacement therapy by administering prefilter replacement fluids through the Aquadex FlexFlow System (CHF Solutions, Inc., Eden Prairie, Minnesota).[13] This modified continuous veno-venous hemofiltration system served as a bridge to peritoneal dialysis (PD). Additional information regarding dialysis and management standards is described in the supplemental appendix.

Somatic growth measurements of weight, length, and HC obtained throughout routine clinical care at Cincinnati Children's Hospital Medical Center were collected from the following time points: birth, 2-week, 1-month, 2-month, 3-month, 4-month, 6-month, 9-month, and 12-month chronological age (as available). During the initial hospital admission, anthropometric measurements are obtained weekly by a trained nursing staff using nude weights and length board to reduce variability. Subjects receiving chronic dialysis care at our center for ongoing dialysis needs have monthly outpatient measurements obtained similarly by a registered nephrology dietitian or by a trained nurse to reduce variability. To adjust for the influence of gender and gestational age (GA), both absolute measurements and associated z-scores as per the World Health Organization (WHO) and Fenton growth curves from the corresponding time points of interest were recorded. The WHO growth curves were used for any infant born ≥ 37 weeks GA or for growth time points at ≥ 50 weeks corrected GA. Fenton growth curves were used for infants <37 weeks birth GA to 50 weeks corrected GA. To better characterize growth of the dialysis cohort, somatic growth parameters from infants in the initial referral population who had severe kidney disease with adequate urine output that could be medically managed without dialysis in the first year of life were recorded from various subspecialty and pediatric visits.

To understand nutritional exposure, feeding patterns for recipients of dialysis at each time point were recorded. Specifically of interest were (1) the total prescribed daily fluid allowance (mL/kg/day), (2) percentage of infants receiving primarily enteral nutrition (defined as more than half the total fluid received), (3) the primary route of enteral feeds–oral, gastric, or postpyloric, and (4) type of enteral feeding (mother's own milk, pasteurized donor milk [DM], or commercial formula). There is no standardized feeding protocol for this complex subpopulation at our institution. Our institutional guidelines for severe congenital kidney anomalies following birth include fluid restriction to 40-80 mL/kg/day until adequate urine output is observed or dialysis is initiated. Maternal milk was used as the primary milk feed when available and the infant was stable enough for enteral feeds. The use of donor or infant formula was used when maternal milk supply was insufficient per the primary team and/or family choice.

Other variables of interest regarding demographics (gender, race, GA at birth, birth weight, and primary diagnosis), prenatal interventions (vesicoamniotic shunt placement or amnioinfusions, use of antenatal steroids), pregnancy complications (premature preterm rupture of membranes), delivery route, urine output characterization, and postnatal care were recorded. Urinary output during the first month of life was classified as anuria (<0.3 mL/kg/hour), oliguria (0.3-1 mL/kg/hour), and normal (>1 mL/kg/hour). Important neonatal outcomes included hospital length of stay, need for mechanical ventilation during the first month of life, need for any vasopressor support during the initial hospitalization, or diagnosis of a significant comorbidity during the initial hospitalization period such as pulmonary hypertension, sepsis, or necrotizing enterocolitis or other abdominal event. Data were manually extracted from the electronic medical record and managed using REDCap electronic data capture tools hosted at our center.[14,15] An institutional review board approval was obtained (#2017-0401) and a waiver of informed consent was granted.

Categorical data were described as n (%) and numeric data as median (interquartile range [IQR]) to adjust for any non-normal distribution. Data description and analyses were performed with R statistical software (version 3.4.3, The R Foundation for Statistical Computing).[16,17]

Results

Participants

This study examined 114 pregnancies referred for concerns of fetal kidney dysfunction over 4 years following when resuscitation began to be offered to this selected population. Of those, 68 received subsequent care elsewhere, 6 were excluded for a diagnosis of bilateral renal agenesis, 2 experienced an intrauterine fetal demise, and 34 were excluded for death before 30 days of age (Figure 1). Of the 26 remaining, 17 infants were recipients of dialysis.

These 17 infants were mainly White (64.7%) and male (58.8%). Fifteen (88.2%) had undergone fetal interventions, including vesicoamniotic shunt placement (4, 23.5%), fetal cystoscopy (1, 5.9%), or serial amnioinfusions (13, 76.5%). Median birth GA was 35 weeks (34, 37) with a median birth weight of 2,340 g (2,000; 2,471). All 17 infants received dialysis access in the first month of life (median 4 days, IQR: 3, 8) and began dialysis (of any form) at a median

Figure 1. Strobe diagram.

6 days of life (IQR: 4, 10). Ten infants were anuric and 4 were oliguric after delivery. Ten infants (64.7%) were born after practice changes and received extracorporal dialysis following birth by prolonged intermittent kidney replacement therapy for 23 days (IQR: 17, 31) prior to initiation of PD. The remaining 7 patients were able to be medically managed prior to initiation of PD for a minimum of 14 days following PD catheter placement. Three infants died during the study period prior to hospital discharge (18%) and 1 died after the study period prior to kidney transplant. Median corrected age at hospital discharge was 3 months (IQR: 2, 5). All infants who survived to discharge were discharged on chronic dialysis. Nine infants were followed at our institution for chronic dialysis care, with 6 infants transferring to an outside institution prior to neonatal intensive care unit discharge and one subsequently returning for chronic care prior to 1 year of age.

Morbidities during initial hospitalization were high: respiratory disease (100%), pulmonary hypertension (65%), and sepsis (47%). Eleven infants had hypotension that required vasopressors (65%). Descriptive characteristics are listed in Table 1.

Somatic Growth Trends

In infants requiring dialysis, growth trends demonstrated a profound lag in all parameters at 1-month and 2-month chronologic age, most notably in length and HC (Figure 2). Catch-up growth first appeared in weight, followed by HC and finally length, with length still failing to normalize by 1 year of life.

To better understand growth trends in this cohort, somatic z-score measurements of those infants who were not recipients of dialysis were plotted (Figures 2B-D). Of the 9 infants with severe kidney disease who had adequate urinary output which could be medically managed without dialysis, peak serum creatinine in the first 14 days of life was 2.06 mg/dL (IQR: 1.15, 2.65). Six of these infants were followed by nephrology after hospital discharge. Nearly

Table 1. Descriptive Characteristics of Infant Population Requiring Dialysis

Characteristics	n = 17
Male Gender	10 (59%)
Race	
White	11 (65%)
Black	5 (30%)
Other	1 (6%)
Gestational Age at Birth (weeks)	35 (34, 37)
Birth Weight (grams)	2,340 (2,000; 2471)
Primary Diagnosis	
Posterior Urethral Valves	9 (53%)
Bilateral Multicystic Kidney Disease	4 (24%)
Solitary Kidney with Multicystic Kidney Disease	3 (18%)
Ureteropelvic Junction Obstruction	1 (6%)
In-Utero Interventions	15 (88%)
# of Amnioinfusions	10 (8, 14)
Amnioinfusion Port	2 (12%)
Other Interventions	6 (35%)
Recipient of Antenatal Steroids	11 (65%)
Preterm Premature Rupture of Membranes	7 (41%)
PPROM Gestational Age	31 (27, 32)
Cesarean Delivery	10 (59%)
APGAR ≤ 5	
1 min	8 (47%)
5 min	1 (6%)
Mechanical Ventilation During First Month of Life	16 (94%)
Duration (days)	16.0 (10, 41)
Pulmonary Hypertension	11 (65%)
Vasopressor Dependency	11 (65%)
Duration (days)	14 (7.5, 21.5)
Hydrocortisone Exposure in the postnatal period	12 (71%)
Urine Output During First Month of Life	
Anuric (<0.3 mL/kg/hour)	10 (59%)
Oliguric (0.3 to <1 mL/kg/hour)	4 (24%)
Normal	3 (18%)
Received Peritoneal Dialysis	17 (100%)
Received PIKRT Using the Aquadex Smart Flow Ultrafiltration Device	10 (59%)
Duration of PIKRT (days)	23 (17, 31)
Sepsis During Hospitalization	8 (47%)
Necrotizing Enterocolitis/Other Abdominal Event	6 (35%)
Hospital Length of Stay (days)*	116 (93, 140)
Mortality Prior to Discharge	3 (18%)

*Six subjects transferred care prior to hospital discharge.

all 9 infants had weight and length recorded until 2 months of age, with 7 having growth parameters recorded to 4 months of age and 4 had complete growth records to 1 year. Growth trends in this cohort mimicked recipients of dialysis but with a lack of catch-up growth in all parameters (Figure 2B-D).

Nutritional Provision

Nutritional provision of infants receiving dialysis is described in Table 2. Median duration of parenteral nutrition dependency was 46 days (IQR 25, 60) with first enteral feed on day of life 7 (IQR 5, 13). All infants who survived to full enteral feeds received fortification (maximum fortification of 28 kcal, IQR 27, 28); initiation of the first fortification occurred at a median of 21 days (IQR 15, 40). In our cohort, only 2 infants received primarily DM in the first 2 months of life. One infant was initiated on DM by day of life 7 but then transitioned to primarily maternal milk by 1 month of life, whereas the other infant remained on parenteral nutrition for the first month of life and then was subsequently initiated on DM and transitioned to formula by 4 months of life.

Enteral nutrition in the nondialysis cohort was initially similar to recipients of dialysis with only 1 subject receiving an enteral intake on day of life 1. At 2 months of life, all infants who avoided dialysis were on enteral feeds of >150 mL/kg/day of breast milk (100%). Three infants at 2 months were primarily gavage-fed and all 3 had a gastrostomy tube placed by 1 year of life. The remaining infants had unquantified ad lib oral intake volumes after 2 months of age. Eight (89%) infants in the no dialysis cohort received fortified feeds with a median maximum fortification of 28 kcal (IQR: 26, 28).

Growth Hormone Supplementation

Of those followed at our institution for chronic dialysis care, 4 infants in the dialysis cohort received growth hormone therapy between 6 and 10 months of age for growth failure (defined as a height Standard Deviation Score (SDS) <−1.88 or a height velocity SDS <−2) once metabolic and nutritional factors affecting growth (such as malnutrition, sodium wasting, secondary hyperparathyroidism, and hypothyroidism) were addressed.[17] Of those who qualified from z-score alone but did not receive treatment, parathyroid hormone concentrations were often elevated (1355 pg/mL IQR: 531, 1,965). One infant in the nondialysis cohort received growth hormone therapy at 8 months of life.

Discussion

This retrospective analysis of a cohort of infants with ESKD following birth requiring dialysis in the first 30 days of life demonstrates impaired growth with linear growth velocity being most affected. As severe growth retardation is linked to increased mortality, morbidity, and mental health problems in children and adults, this emphasizes the need for future large cohort studies in this patient population, especially as survival following birth continues to improve.

Growth represents a state of wellbeing, and growth impairment can occur due to insufficient nutrient provision or due to increased demands. We found that infants with significant CKD due to congenital kidney anomalies have severe growth impairment in all parameters, even falling behind those requiring dialysis in the neonatal period.

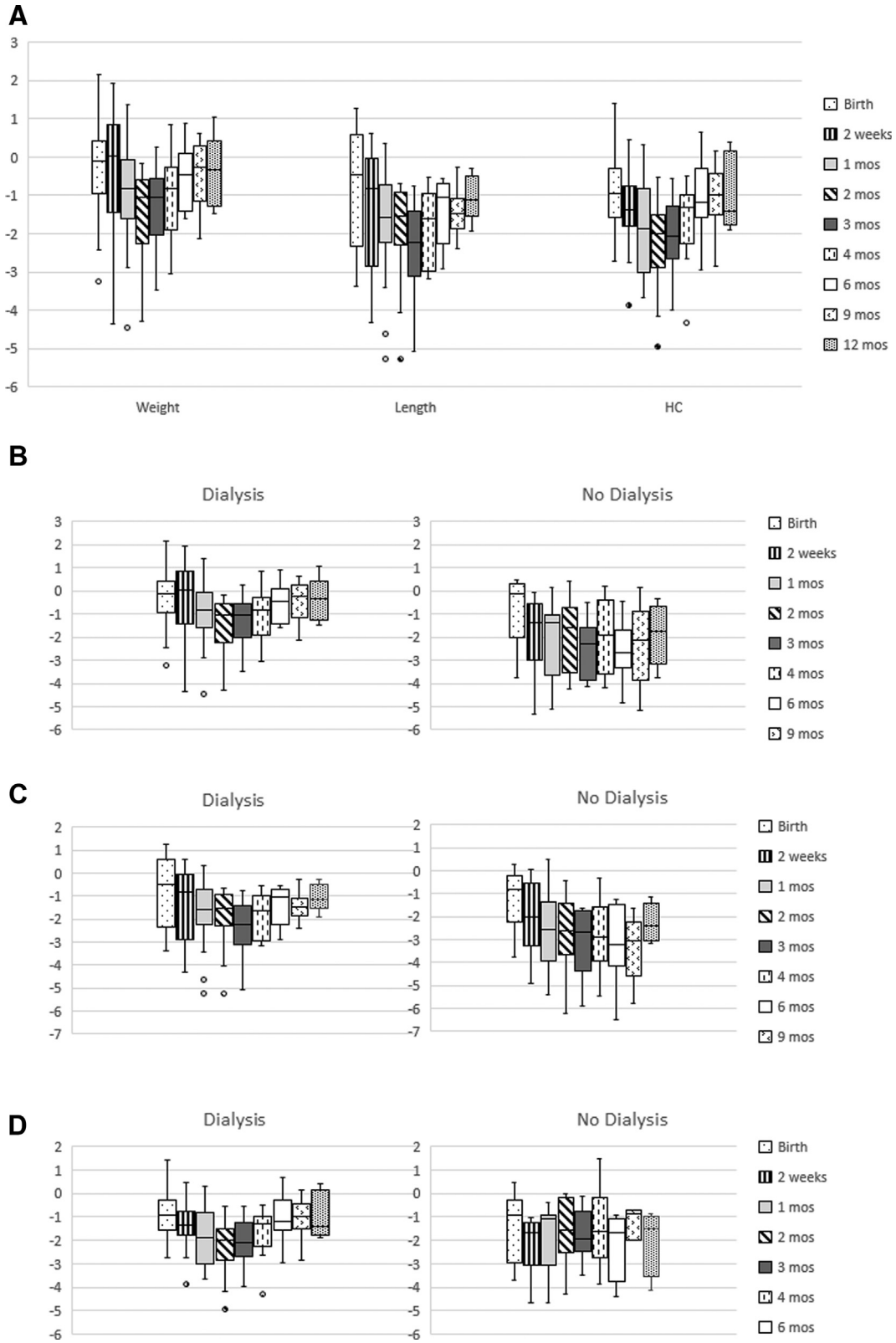

Figure 2. Somatic growth in infants. (A) Graph of weight, length, and head circumference z-scores for infants with kidney anomalies requiring dialysis across time from birth to 12 months of chronological age. (B) Weight comparison of z-scores overtime between infants with kidney disease who required dialysis versus those who were able to avoid dialysis. (C) Length comparison of z-scores overtime between infants with kidney disease who required dialysis versus those who were able to avoid dialysis. (D) Head circumference comparison of z-scores overtime between infants with kidney disease who required dialysis versus those who were able to avoid dialysis.

Table 2. Descriptive Characteristics of Nutrition in Infants Requiring Dialysis

	Birth	2 weeks	1 mo	2 mo	4 mo	6 mo	9 mo	12 mo
Age	n = 16	n = 16	n = 17	n = 17	n = 12	n = 8	n = 9*	n = 8
Daily Fluid Allowance (mL/kg/day)	50 (40, 60)	95 (78, 133)	135 (90, 150)	140 (120, 150)	115 (99, 123)	100 (85, 100)	90 (80, 100)	80 (80, 85)
Recipient of Primarily Enteral Nutrition	0 (0%)	4 (25%)	11 (65%)	14 (82%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)
Enteral Nutrition Recipient	n = 0	n = 12	n = 14	n = 15	n = 12	n = 8	n = 10	n = 9
Main Enteral Route								
Oral		1 (8%)	1 (7%)	3 (20%)	2 (17%)	2 (25%)	4 (40%)	3 (33%)
Gastric		9 (75%)	11 (79%)	10 (67%)	9 (75%)	6 (75%)	5 (50%)	4 (44%)
Post-pyloric		2 (17%)	2 (14%)	2 (13%)	1 (8%)	0 (0%)	1 (10%)	2 (22%)
Main Enteral Type								
Human Milk†		4 (100%)	13 (93%)	10 (67%)	9 (75%)	5 (62%)	2 (20%)	1 (11%)
Formula		0 (0%)	1 (7%)	5 (33%)	3 (25%)	3 (38%)	8 (80%)	8 (89%)

*Return of prior infant for readmission.
†Maternal or donor milk includes fortified and unfortified.

Hypothesis for this witnessed observation include the restricted nutrient delivery due to fluid restriction, metabolic acidosis, minor electrolyte disturbances, and anemia, among others and warrant closer evaluation and further research. In addition, there may be differences in nutritional follow-up in those infants on dialysis versus those infants with severe CKD who are medically managed. Although this study only demonstrated association, there is plausibility that fluid restriction is the main contributor to growth failure. The maximum fluid provision to 140 mL/kg/day occurred at 2 months (Table 2), but at the majority of time points, infants were provided with 115 mL/kg/day or significantly lower fluid volumes given that this number accounts for additional fluids from medications. Even if an infant is provided a highly nutrient dense milk of 30 kcal/oz at a fluid volume of 80 mL/kg/day, the caloric provision is only 80 kcal/kg/day. This falls short of the recommended daily allowance of 100-120 kcal/kg/day for a healthy term infant, let alone for an infant with increased metabolic demands from medical complexity. With 7 consecutive days of energy intake at 75% of the recommended intake, these patients qualify as having severe malnutrition.[1,18]

Volume of nutrition provision is not the only issue. The content of enteral feeding is also critical. As in many other high-risk populations, breast milk is the preferred milk choice. Intestinal perforation, necrotizing enterocolitis, or any sudden intra-abdominal event that compromises the peritoneum can impact the future potential for PD which is necessary for survival in this population. Breast milk is one protective strategy against these catastrophes.[19,20] Breast milk has varied macronutrient content, so milk analysis and targeted fortification could be used to optimize nutrient delivery.[31]

Aside from nutritional support, current modifications to impact growth in patients with severe ESKD remain unexplored. Currently, treatment options to improve linear growth velocity during infancy and childhood only contribute to stabilizing growth velocity, thus failing to achieve adequate catch-up growth when compared to peers.[5,21-24] Recombinant human growth hormone in children with CKD-associated growth failure also continues to be underused despite repeated demonstrated safety and efficacy.[25,26]

Degree of clinical illness cannot be ignored as an important contributor to early delays in initiation of enteral nutrition, further fluid restriction, increased macronutrient need, and growth failure. Of great interest, those patients who required early neonatal dialysis were compared to those who did not receive dialysis. Despite high levels of clinical illness, as demonstrated by need for mechanical ventilation, pulmonary hypertension, hypotension, and sepsis, those receiving dialysis early in life ultimately appears to have better catch-up growth by 1 year of life, although true difference and statistical analysis were severely limited by overall number in each cohort. This should be further explored.

Despite these interesting findings, the retrospective observational nature of this study severely restricts ability to determine a causal relationship between growth, nutrition, and dialysis. Nutrition of the nondialysis cohort and volume of daily intake after discharge were severely limited to understand nutritional comparisons. In addition, analysis is largely limited by cohort size and what appears to be a witnessed difference, may not be significant at a larger n. Irrespective of these limitations, these findings are suggestive of an improvement in growth in congenital anomalies of the kidney and urinary tract infants receiving dialysis and warrant additional prospective evaluation.

Practical Application

Infants with ESKD are at high risk for growth failure, most profound in the first 2 months of life. This may be

due to the high degree of systemic illness in this population during the neonatal period but delays in initiation of enteral nutrition are likely contributory. Implications and associations related to this deficit on long-term outcomes are greatly needed as overall survival continues to improve. Interventions to improve growth and early nutrition with greater human milk provision, aggressive parenteral nutrition, and optimized fluid status with early dialysis are all attractive targets for further study and may improve outcomes of neurodevelopment and mortality.

Credit Authorship Contribution Statement

Cara L. Slagle: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Stefanie L. Riddle:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation. **Kera McNelis:** Methodology, Data display, Writing – review & editing. **Donna Claes:** Methodology, Data display, Writing – review & editing.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2022.09.007.

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