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Early nephrectomy in neonates with symptomatic autosomal recessive polycystic kidney disease☆

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ABSTRACT

Introduction: Autosomal recessive polycystic kidney disease (ARPKD) is a rare cause of renal failure with a highly variable clinical course. Patients who are symptomatic early in life frequently require early nephrectomy and peritoneal dialysis. In these patients there are little data to guide clinicians on whether to select unilateral nephrectomy or bilateral nephrectomy at the initial operative intervention. We review our experience with this disease process.

Methods: A retrospective review was performed of 11 patients at our institution with ARPKD symptomatic within the first month of life. Charts were reviewed for relevant clinical data, and patients were divided into groups based on undergoing either unilateral or bilateral nephrectomy at their initial intervention. The decision for unilateral versus bilateral nephrectomy was decided by the clinical team without any available guidelines.

Results: Of the 11 patients reviewed, two patients died within the first two weeks from other complications. The remaining 9 all required nephrectomy, with 5 undergoing synchronous bilateral nephrectomy, and 4 undergoing initial unilateral nephrectomy. All four patients required removal of their contralateral kidney, a median of 25.5 days later. There was no difference in mortality, ventilator free days, or time to full feeds between the two groups, although the group undergoing initial unilateral nephrectomy had more TPN days than their counterparts (28 vs 17 days, $p = 0.014$).

Conclusions: In our cohort, there were few significant differences between the groups based on choice of initial unilateral or bilateral nephrectomy, and all children ultimately required removal of both kidneys. These data suggest that anesthetic exposures and other clinical outcomes might be optimized by initial bilateral nephrectomy.

Level of evidence: III.

Autosomal recessive polycystic kidney disease (ARPKD) is a rare inherited cause of renal failure affecting between 1:20,000 and 1:40,000 live births [1–17]. While the clinical course of the disease is highly variable, diagnosis is typically made prenatally or shortly after birth. In neonates who present early, mortality rates can approach 30%–50% [4,5]. Surgical interventions may be warranted early owing to massive nephromegaly resulting in respiratory distress or fulminant renal failure requiring peritoneal dialysis [2,6–9]. The most severe cases require abdominal decompression early, and undergo unilateral or bilateral nephrectomy with peritoneal dialysis catheter placement for renal replacement therapy.

Very little data exist on the optimal strategy regarding nephrectomy in these individuals and most of the published data are case reports. Some surgeons prefer synchronous bilateral nephrectomy in the case of symptomatic massive nephromegaly to improve abdominal domain for peritoneal dialysis, and to avoid need for reoperation at a later date [7,8,10]. Others advocate for the least invasive approach that addresses the patients issues at the initial operation, preferring unilateral nephrectomy and peritoneal dialysis catheter placement early with staged contralateral nephrectomy at a later date, if required [6,9,11–13].

To better inform clinicians about proper approach to be taken in the correct clinical scenario, we performed a retrospective review of our center's experience with neonatal ARPKD. We aimed to evaluate outcomes relative to the type of initial operation performed. We hypothesized that bilateral nephrectomy would improve survival rate through the neonatal period.

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; TPN, total parenteral nutrition; PD, peritoneal dialysis; IQR, interquartile range.

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1. Methods

With the approval of the University of Michigan Institutional Review Board (HUM 00123686), we performed a retrospective review of the medical records of all neonatal patients diagnosed with ARPKD within the first 30 days of life at our institution born between 1/1/2006 and 6/31/2018. We excluded patients with a delayed diagnosis since they have a less severe clinical course, and therefore do not require early nephrectomy. Demographic and clinical data were gathered including family history, prenatal evaluations and findings, comorbidities, critical care support required, operative data, complications, and outcomes.

From this initial cohort, patients undergoing nephrectomy were identified and were divided into two groups based on whether they underwent unilateral nephrectomy or bilateral nephrectomy at their initial operative intervention. The primary outcome evaluated was 1-year survival. Since it has been hypothesized that early bilateral nephrectomy may improve respiratory and/or cardiovascular parameters, we also evaluated ventilator requirement and hypertension requiring antihypertensive medications for management [14–17]. Data were also gathered regarding feeding intolerance, and need for dialysis, timing, and route.

Sample characteristics are reported as number of observations and percentage for categorical variables, and median and range for continuous variables. Chi-squared and Fisher's exact tests were used as appropriate for categorical outcomes. Wilcoxon rank sum test and Student's *t*-test were used to compare continuous variables. Data were aggregated in a secure Microsoft Excel file. All analyses were conducted in STATA v15.1 (STATACorp, College Station, TX), with a p-value less than 0.05 being considered significant.

2. Results

Eleven patients were identified. Two patients died prior to undergoing nephrectomy — one at 11 days of age from neonatal encephalopathy, and one at 2 days of age from lethal pulmonary hypoplasia. Of the nine patients undergoing nephrectomy, five underwent synchronous bilateral nephrectomy at their initial operative intervention, while four underwent a unilateral nephrectomy first. Eight different surgeons performed the total of 13 surgeries in the study's groups (5 bilateral nephrectomies, 4 initial unilateral nephrectomies, and 4 subsequent contralateral nephrectomies). Five surgeons performed two of the procedures each with the remainder performing one each. The surgeons were all Pediatric Surgery Board Certified. The cohort was predominantly female (8 females, 1 male), and most had prenatal imaging consistent with polycystic kidney disease (88.9%), all with evidence of oligohydramnios or anhydramnios. One-third of patients had a family history of ARPKD. The most common associated comorbidity was pulmonary hypoplasia, present in seven patients (77.8%), followed by pulmonary hypertension, congenital hepatic fibrosis, and hypertension. See Table 1.

Table 1
Demographics.

	Bilateral Nephrectomy ($n = 5$)	Unilateral Nephrectomy ($n = 4$)
Gender		
Male, *n (%)*	0 (0%)	1 (25%)
Female, *n (%)*	5 (100%)	3 (75%)
Birth Weight (kg), *median (IQR)*	2.90 (2.63–3.05)	3.01 (2.17–3.20)
Prenatal Diagnosis, *n (%)*	5 (100%)	3 (75%)
Family History of ARPKD, *n (%)*	2 (40%)	1 (25%)
Associated Prenatal Conditions, *n (%)*		
Oligohydramnios	2 (40%)	3 (75%)
Anhydramnios	3 (60%)	1 (25%)
Maternal hypothyroidism	0 (0%)	1 (25%)
Maternal Gestational Diabetes	0 (0%)	1 (25%)
Comorbidities, *n (%)*		
Pulmonary Hypoplasia	5 (100%)	2 (50%)
Pulmonary Hypertension	2 (40%)	1 (25%)
Congenital Hepatic Fibrosis	0 (0%)	1 (25%)
Hypertension	0 (0%)	1 (25%)

IQR = Interquartile range.

All patients required mechanical ventilation shortly after birth for respiratory failure. Two patients (22.2%) required high frequency ventilation for management of their respiratory failure, while the remainder were managed on conventional ventilators. Urine output in the preoperative time period was variable — ranging from very minimal output despite diuretic therapy to as high as 1–2 ml/kg/h with diuretics (typically furosemide and chlorothiazide). All patients in our cohort ultimately required peritoneal dialysis (PD), with one patient requiring hemodialysis (HD) before PD could be initiated. There was no difference in time to tolerance of full feeds (median 20 days of life for synchronous bilateral nephrectomy vs 29 days of life for unilateral nephrectomy, $p = 0.309$); however, it is noteworthy that of the nine patients in our series only two patients were able to achieve full feeds prior to having both kidneys removed. Additionally, the group undergoing unilateral nephrectomy first had a significantly higher number of TPN days (median 28 vs 17, $p = 0.014$). (See Table 2.)

The most common indication for nephrectomy in this population was a combination of respiratory failure and oligoanuria. Of the nine patients who underwent nephrectomy, six were oliguric at the time of their nephrectomy, and there was a trend toward earlier initial nephrectomy in this group, though the difference was not statistically significant (median 5.5 days of life vs 16 days of life, $p = 0.091$). Indications for nephrectomy were generally related to respiratory status frequently compounded by varying degrees of oligoanuria. Finally, two patients had severe hypertension that was refractory to medical management and nephrectomy was elected as intervention to improve blood pressure control.

There was no difference in mortality within 1 year between the two groups (bilateral nephrectomy 40% vs unilateral nephrectomy 25%, $p = 1.00$). Most patients underwent their first nephrectomy within the first two weeks of life, with one patient not requiring a nephrectomy until approximately 7 months old. In the group that underwent an initial unilateral nephrectomy, all patients required a subsequent contralateral nephrectomy, with a median of 25.5 days (IQR 13–57) between their first and second nephrectomies. The indications for the second nephrectomy cited were enlarging kidney size in three patients, continued respiratory compromise in two patients, and persistent hypertension in two patients (multiple indications listed for some patients). There was a trend toward increased 30-day ventilator free days in the bilateral nephrectomy group, though this was not statistically significant (14 days vs 7 days, $p = 0.372$). Length of stay was significantly shorter in the bilateral nephrectomy group (102 days vs 154 days, $p = 0.021$).

All 5 patients undergoing bilateral nephrectomy underwent bilateral retroperitoneal nephrectomy via bilateral separate flank incisions. Of the 8 total nephrectomies performed in unilateral nephrectomy group (initial unilateral nephrectomy, followed by contralateral nephrectomy in each of 4 patients), 3 were performed via subcostal incision, and the remaining 5 via a retroperitoneal approach through a flank incision. All patients in our cohort received a peritoneal dialysis catheter at the time of their initial nephrectomy, with five patients receiving a tunneled central venous catheter, and two patients receiving a gastrostomy tube simultaneously. Of note, all 9 patients in our cohort required a tunneled central venous catheter at some point in their care and 7 of the 9 (77.8%) underwent gastrostomy tube placement during admission. The most common postoperative complications centered around PD catheter dysfunction or infection (44.4%), central line infection (22.2%), and postoperative ileus (11.1%). One patient with PD catheter dysfunction required revision of their PD catheter. There was not a statistically significant difference in time to utilization of peritoneal dialysis catheter, though the group undergoing unilateral nephrectomy utilized

Table 2
Outcomes.

	Bilateral Nephrectomy ($n = 5$)	Unilateral Nephrectomy ($n = 4$)	p-values
Death within 1 year of life, *n (%)*	2 (40%)	1 (25%)	1.00[a]
Age at First Nephrectomy, *median (IQR)*	6 (5–8)	6.5 (5.5–119)	0.621[b]
Days to second nephrectomy, *median (IQR)*		25.5 (13–57)	
Hemodialysis required, *n (%)*	0 (0%)	1 (25%)	0.444[a]
Peritoneal dialysis required, *n (%)*	5 (100%)	4 (100%)	
Days to Peritoneal Dialysis Catheter Use, *median (IQR)*	3 (2–5)	9 (3–26.5)	0.213[b]
Mechanical Ventilation required, *n (%)*	5 (100%)	4 (100%)	
30 day vent free days, *median (IQR)*	14 (12–21)	7 (2.5–20.5)	0.327[b]
Age at Full Feeds (days), *median (IQR)*	20 (16.5–29)	29 (22–35)	0.309[b]
TPN days, *median (IQR)*	17 (16–20)	28 (25–31)	0.014[b]
Length of stay (days), *median (IQR)*	102 (88.5–114.5)	154 (137–277.5)	0.021[b]

[a] Fisher's Exact Test.
[b] Wilcoxon Rank Sum Test.

the catheter a median of 9 days after insertion as compared to 3 days in the bilateral nephrectomy group ($p = 0.213$).

3. Discussion

ARPKD is a disease process with a highly variable clinical course, ranging from initial normal renal function and progressive renal dysfunction to early respiratory and renal failure. For patients who fall into the latter category, early surgical intervention for nephrectomy, dialysis catheter placement, and feeding access are often required. To this point, the literature surrounding the optimal surgical management of these patients has been limited to case reports, which have reported success with unilateral [6,9,13] and bilateral [7,8,10] nephrectomies. Recent recommendations from an international multidisciplinary conference state that there is insufficient evidence to demonstrate the benefit of nephrectomy for respiratory compromise or severe hypertension [11]. This series is the first to our knowledge to compare outcomes between patients undergoing unilateral and bilateral nephrectomy in ARPKD.

Our data are in a cohort of children diagnosed at birth or prenatally with symptomatic disease requiring significant critical care and surgical intervention — all patients required mechanical ventilation, nephrectomy and peritoneal dialysis, most within the first month of life. While a large variety of phenotypes present on the spectrum of ARPKD, this cohort represents more early and severe disease than other reviews have discussed. In this setting, there were no differences in mortality rate within the first year of life, duration of mechanical ventilation, or 30-day ventilator free days between the operative approaches around nephrectomy.

Other authors have suggested a difference in nutritional measures in patients undergoing unilateral nephrectomy [11]. In our series, there was no difference in age full feeds were attained between the two groups, but there were a lower number of TPN days in those undergoing a bilateral nephrectomy first. Importantly, all patients in our group ultimately required removal of both kidneys, for continued respiratory compromise, enlarging size of the remaining kidney, or persistent hypertension. There was a significantly shorter length of stay in the group undergoing the initial bilateral nephrectomy, which is likely impacted in part by the time between initial and second nephrectomies.

This study has several limitations. Despite demographically similar groups, the retrospective nature of the study design exposes the data to biases inherent in chart review. The choice of unilateral or bilateral nephrectomy was left up to the clinical team, and the rationale for this decision is not easily captured by retrospective review. Owing to the relative rarity of the disease process, the cohort being studied is small which increases the risk of type II error. Further, all patients in this cohort had relatively severe disease, requiring early respiratory support, nephrectomy and initiation of renal replacement therapy, and the findings of this study may not be more broadly applicable to all infants with ARPKD. Finally, the choice of surgical approach (i.e. subcostal versus flank incision, transperitoneal versus retroperitoneal approach) must be individualized to the patient's needs, and the relative risks of complications with each approach discussed among the care team and with the patient's parents.

Despite these limitations, this study describes an important subset of infants with ARPKD — those with early diagnosis and symptomatic disease. Within this group, there were few meaningful differences in outcomes between those who underwent bilateral nephrectomy at their initial operation compared to initial unilateral nephrectomy, and all patients ultimately required removal of both kidneys. We suggest that bilateral nephrectomy is a safe option in these patients, if the operative intervention is technically feasible and the patients tolerate the initial portion of the procedure well. Given the rarity of this disease process, our data suggest that patient care as well as further research and quality improvement efforts would be improved by standardization of care to a single pathway that minimizes the number of anesthetic exposures each patient requires. Further study, likely in a prospective, multicenter, observational study, is needed to better define risks within these groups and bring more clarity to the optimal management of this condition.

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