Received: 8 October 2020 | Revised: 14 December 2020 | Accepted: 19 December 2020

DOI: 10.1111/petr.13974

ORIGINAL ARTICLE

WILEY

Practice patterns and influence of allograft nephrectomy in pediatric kidney re-transplantation: A pediatric nephrology research consortium study

Priya S. Verghese[1] | Kera E. Luckritz[2] | Asha Moudgil[3] | Jayanthi Chandar[4] | Daniel Ranch[5] | John Barcia[6] | Jen-Jar Lin[7] | Matthew Grinsell[8] | Rima Zahr[9] | Rachel Engen[1] | Katherine Twombley[10] | Paul K. Fadakar[11] | Amrish Jain[12] | Samhar Al-Akash[13] | Sharon Bartosh[14]

[1]Division of Pediatric Nephrology, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[2]Department of Pediatrics, C.S. Mott Children's Hospital Michigan Medicine, Ann Arbor, MI, USA

[3]Division of Pediatric Nephrology, Children National Hospital, Washington, DC, USA

[4]Division of Pediatric Nephrology, Department of Pediatrics, University of Miami Miller School of Medicine and Miami Transplant Institute, Miami, FL, USA

[5]Department of Pediatrics, Division of Pediatric Nephrology, Joe R. and Teresa Lozano Long School of Medicine, University of Texas Health at San Antonio, San Antonio, TX, USA

[6]Division of Pediatric Nephrology, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, USA

[7]Department of Pediatrics Nephrology, Wake Forest University Baptist Health, Winston-Salem, NC, USA

[8]Division of Nephrology and Hypertension, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA

[9]Division of Pediatric Nephrology, Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

[10]Acute Dialysis Units, Pediatric Kidney Transplant, Medical University of South Carolina, Charleston, SC, USA

[11]Pediatric Nephrology, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

[12]Division of Pediatric Nephrology, Department of Pediatrics, Central Michigan University College of Medicine and Children's Hospital of Michigan, Detroit, MI, USA

[13]Division of Pediatric Nephrology, Department of Pediatrics, Driscoll Children's Hospital, Corpus Christi, TX, USA

[14]Division of Pediatric Nephrology, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Correspondence
Priya S. Verghese, Division of Pediatric Nephrology, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 37, Chicago, Illinois 60611-2605.
Email: pverghese@luriechildrens.org

Abstract

Introduction: There are no guidelines regarding management of failed pediatric renal transplants.

Materials & Methods: We performed a first of its kind multicenter study assessing prevalence of transplant nephrectomy, patient characteristics, and outcomes in pediatric renal transplant recipients with graft failure from January 1, 2006, to December 31, 2016.

Results: Fourteen centers contributed data on 186 pediatric recipients with failed transplants. The 76 recipients that underwent transplant nephrectomy were not significantly different from the 110 without nephrectomy in donor or recipient

Abbreviations: DSA, Donor-specific antibody; ELISA, Enzyme-Linked Immunosorbent Assay; HLA, Human Luekocyte Antigen; KTx, Kidney transplant; PNRC, Pediatric Nephrology Research Consortium; PRA, Panel Reactive Antibody.

demographics. Fifty-three percent of graft nephrectomies were within a year of transplant. Graft tenderness prompted transplant nephrectomy in 91% ($P < .001$). Patients that underwent nephrectomy were more likely to have a prior diagnosis of rejection within 3 months (43% vs 29%; $P = .04$). Nephrectomy of allografts did not affect time to re-listing, donor source at re-transplant but significantly decreased time to ($P = .009$) and incidence ($P = .0002$) of complete cessation of immunosuppression post-graft failure. Following transplant nephrectomy, recipients were significantly more likely to have rejection after re-transplant (18% vs 7%; $P = .03$) and multiple rejections in first year after re-transplant (7% vs 1%; $P = .03$).

Conclusions: Practices pertaining to failed renal allografts are inconsistent—40% of failed pediatric renal allografts underwent nephrectomy. Graft tenderness frequently prompted transplant nephrectomy. There is no apparent benefit to graft nephrectomy related to sensitization; but timing / frequency of immunosuppression withdrawal is significantly different with slightly increased risk for rejection following re-transplant.

KEYWORDS

pediatric re-transplant, transplant nephrectomy

1 | INTRODUCTION

Despite dramatic improvements in the past few decades, survival of a pediatric kidney transplant is suboptimal and allograft failure remains a burdensome reality. How to manage a failed or failing allograft remains controversial, and there are still no clear guidelines on the role of allograft nephrectomy. While nephrectomies were initially attempted due to the perceived benefits of removing the source of chronic inflammatory response syndrome,[1] these benefits are now less clear. In 2013, 34 pediatric renal transplant recipients from a single center in London were studied. The 53% that underwent graft nephrectomy were more likely to have had severe rejection, early graft loss or evidence of inflammation, and the nephrectomies were associated with higher levels of circulating donor specific antibody.[2] Subsequent studies published suggest an immune response following allograft nephrectomy with increased panel reactive antibody may lead to greater difficulty in re-transplantation and poorer outcomes following re-transplantation.[3-5] As with many pediatric transplant related questions, due to the smaller numbers, center-specific immunosuppression practices, and heterogenous patient populations, no single-center study has provided sufficient data to guide pediatric practice.

The Pediatric Nephrology Research Consortium (PNRC) is an international research consortium of pediatric nephrology sites. We invited the PNRC sites that perform kidney transplantation to participate in our study to do a descriptive analysis of practice patterns in failed allograft management. We hypothesized that there would be diversity in the management of failed kidney transplants based on recipient and center demographics. In addition, we aimed to test the secondary hypotheses that pediatric kidney transplant recipients would have reduced or delayed re-transplantation possibly due to increased sensitization following nephrectomies; the rationale for this being adult studies that have demonstrated increased sensitization following nephrectomies.[6,7] In addition, we thought it plausible that pediatric kidney recipients who underwent failed allograft nephrectomy would potentially undergo rapid immunosuppression withdrawal due to pediatric-specific immunosuppression side effects including but not limited to infections, impact on growth etc[8,9] contributing to the sensitization. Our objectives were to assess prevalence of transplant nephrectomy following graft failure in pediatric kidney transplant recipients from January 1, 2006, to December 31, 2016; to assess the influence of transplant and recipient characteristics on the decision to perform transplant nephrectomy following graft failure; and to assess the influence of transplant nephrectomy on re-transplant access and outcomes.

2 | METHODS

2.1 | Study population and centers

Pediatric kidney recipients less than 18 years old at time of transplantation were considered eligible for inclusion if they had failure of their primary kidney transplant between January 1, 2006, and December 31, 2016. Graft failure was defined as return to chronic dialysis or activation on the deceased donor list / setting a date for a living donor transplant. Patient follow-up continued until end of study period. Multi-organ transplant recipients were excluded.

Center participation was approved by the respective individual site Institutional Review Boards.

2.2 | Data/specimen analysis

Data were collected on 186 pediatric kidney recipients, from 14 participating institutions in a de-identified format via a RedCap database by each site. Donor-recipient demographics, presence and indications of graft nephrectomy, recipient re-transplantation rates, and outcomes were collected. In addition, graft tenderness, diagnoses such as hypertension, immunosuppression changes, and biopsy-proven rejection were obtained by chart review to assess for an association with transplant nephrectomy. Donor-specific antibody (DSA) data were collected for patients only at the time of renal replacement therapy initiation since the majority of centers did not test for DSA following return to dialysis. DSA testing technique was single antigen beads in all but one patient who underwent ELISA technique.

Continuous data are presented as means and compared by t test. Nominal variables are reported as percentages and compared with chi-square test. Actuarial graft survival was computed by cox regression and hazard ratios calculated to model the effects of pre-transplant nephrectomy on KTx outcomes in univariate analysis. *P* values < .05 were considered statistically significant. All statistical analysis was performed with STATA/IC 11.0, College Station, Texas, USA.

3 | RESULTS

Between January 1, 2006, and December 31, 2016, there were 186 pediatric transplant recipients who had graft failure from a total of 14 centers. Recipient characteristics are found in Table 1.

Seventy-six patients underwent transplant nephrectomy at varying times following graft failure. Allograft nephrectomy was performed within the first week after transplantation in 10 (13%), in at 7-30 days in 8 (11%), at 31-365 days post-transplant in 22 (29%), and after 1-year post-transplant in 36 (47%) [4 within 1-2 years post-transplant; 25 within 2-5 years post-transplant; and 7 more than 5 years post-transplant]. In the majority of patients, dialysis was initiated only after nephrectomy, but in 24 (32%) and 6 (8%), respectively, the failed allograft nephrectomy was 30-365 days and >365 days after the initiation of dialysis.

Patients that underwent nephrectomy after graft failure were not significantly different from the 110 patients without nephrectomy in gender, race, age at transplant, etiology of end stage renal disease, donor type, degree of sensitization [Table 1], or prevalence of donor-specific antibody [Figure 1]. Of the 104 recipients

TABLE 1 Comparative analysis of recipients with failed allografts that did and did not undergo transplant nephrectomy

	Failed Allograft Nephrectomy+ N=76	Failed Allograft Nephrectomy – N = 110	*P* value
Female	31 (41%)	48 (44%)	.69
Race:			
Caucasian	33 (43%)	53 (48%)	.06
African American	25 (33%)	23 (21%)	
Asian	2 (3%)	5 (5%)	
Hispanic	16 (21%)	19 (17%)	
Unknown	0 (0%)	10 (9%)	
ESRD Etiology:			
CAKUT	31 (41%)	48 (44%)	.79
FSGS	19 (25%)	18 (16%)	
Glomerular disease	15 (20%)	23 (21%)	
Tubulo-interstitial disease	7 (9%)	12 (11%)	
Unknown/Other	4 (5%)	9 (8%)	
Donor type:			
Deceased Donor	54 (71%)	63 (57%)	.16
Living Related Donor	19 (25%)	40 (36.5%)	
Living Unrelated Donor	3 (4%)	7 (6.5%)	
Primary renal transplant	71 (93%)	103 (94%)	.95
0% PRA at transplant for Class 1 and 2	43 (57%)	63 (57%)	1
Age at transplant (years)	10.4 ± 5.9	9.7 ± 5.6	.43

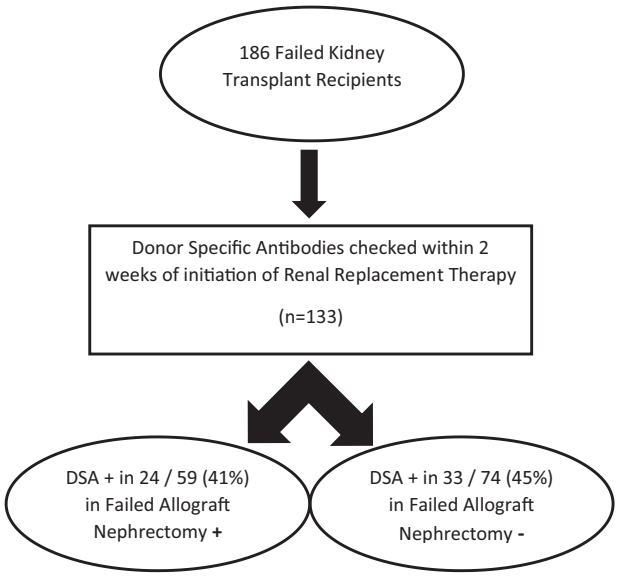
that underwent DSA testing within 2 weeks of renal replacement therapy initiation, patients that underwent nephrectomy were less likely to have had DSA than those that did not undergo nephrectomy (DSA + in 9/29 [31%] vs 33/75 [44%] $P = .03$).

Indications for transplant nephrectomies varied [Table 2]. In transplant recipients that developed graft tenderness, they were significantly more likely to undergo a nephrectomy: 33 patients had graft tenderness preceding or coinciding with their graft failure, of whom 30 (91%) went on to have a transplant nephrectomy [$P < .001$].

Transplant nephrectomies performed in the first week and month post-transplant were most commonly for graft thrombosis (80% and 63%, respectively). Indications for transplant nephrectomy after the first year post-transplant were almost always for the development of symptoms including graft tenderness (17 patients = 22%); poorly controlled hypertension (7 patients = 9.2%), and gross hematuria with fever (1 patient = 1.3%). Of note, 3 patients underwent late nephrectomy for elective reasons that is with the intention of reducing immunosuppression or addressing rising panel reactive antibody. All 3 patients were non-Hispanic Caucasian males from different transplant centers, with varying end-stage renal disease etiology. Two were recipients of living related transplant. All 3 patients underwent a kidney biopsy prior to the transplant nephrectomy which demonstrated acute cellular rejection and one also had concurrent antibody-mediated rejection. All 3 had moderate to severe interstitial fibrosis and tubular atrophy on biopsy as was expected. Although all 3 were re-listed, only 2 underwent a subsequent transplant with living unrelated donors, one of whom went on to develop acute cellular rejection and delayed graft function. Interestingly, both recipients were still on immunosuppression at the time of re-transplant (one with prednisone and one with tacrolimus and mycophenolate mofetil). Only 1 patient that underwent elective nephrectomy was weaned off immunosuppression completely and he remained on the transplant list awaiting an organ offer at the time of manuscript preparation.

Recipients that underwent transplant nephrectomy were significantly more likely to have had a kidney biopsy with a confirmed diagnosis of rejection within 3 months of graft failure (43% vs 29%; $P = .04$) [Table 1]. Patients that underwent late nephrectomies more than 1 year after graft failure were also significantly more likely to have had multiple episodes of biopsy-proven rejection (7% vs 1%; $P = .03$).

Analysis of individual center practices demonstrated significant variation. Although 47% of the patients in the study underwent nephrectomy following graft failure, two centers reported that they had not performed a single transplant nephrectomy during the study



Human Leucocyte Antibody Type*		
Class I: incidence (%) MFI range	4 (17%) 3604 - 8871	3 (9%) 634-4000
Class II incidence (%) MFI range	4 (17%) 3273-4814	12 (36%) 2078-42,555
Both Class I and II	13 (54%)	18 (55%)

*Summary statistics limited by missing data

FIGURE 1 Incidence of donor-specific antibodies assessed at time of initiation of renal replacement therapy and association with transplant nephrectomy

TABLE 2 Comparison of symptoms preceding and indications for transplant nephrectomy

	Timing of Transplant Nephrectomy			
	<7 days (n = 10)	7-30 days (n = 8)	31-365 days (n = 22)	>365 days (n = 36)
Graft thrombosis	8 (80%)	5 (63%)	8 (36%)	1 (3%)
Graft tenderness	2 (20%)	5 (63%)	6 (27%)	17 (47%)
Poorly controlled hypertension	0	1 (13%)	3 (14%)	7 (19%)
Gross hematuria with or without fever	0	1 (13%)	1 (5%)	1 (3%)
Elective with physician goal to reduce immunosuppression	0	0	0	3 (8%)
Recurrent disease	0	2 (26%)	7 (32%)	4 (11%)
Severe rejection	0	1 (13%)	1 (5%)	0
Other causes	0	0	0	2 (5%) -to create surgical space -chronic pyelonephritis

TABLE 3 Comparative analysis of immunosuppression in recipients with failed allografts that did and did not undergo transplant nephrectomy

	Failed Allograft Nephrectomy+ N=76	Failed Allograft Nephrectomy – N = 110	*P* value
Induction:			
Thymoglobulin	35 (46%)	46 (42%)	.12
IL-2 Receptor Inhibitor	24 (32%)	42 (38%)	
Alemtuzumab	13 (17%)	21 (19%)	
Other/Unknown	4 (5%)	1 (1%)	
Maintenance:			
Steroid inclusive	43 (57%)	62 (56%)	.44
Tacrolimus	60 (79%)	63 (57%)	
Cyclosporine	10 (13%)	30 (27%)	
Mycophenolate Mofetil	61 (80%)	71 (65%)	
Azathioprine	5 (5%)	15 (13%)	
Sirolimus	4 (5.2%)	15 (13%)	

period (centers reported on 6 and 1 patients, respectively) and 3 centers reported all recipients with graft failures underwent transplant nephrectomy (centers reported on 5, 6, and 7 patients, respectively). The nephrectomy rate in the remaining centers ranged from 28% to 67%.

In univariate analysis, neither induction immunosuppression ($P = .12$) nor maintenance immunosuppression ($P = .44$) were associated with the decision to perform a transplant nephrectomy [Table 3]. Steroid inclusive vs steroid avoidance protocols were specifically analyzed and did not have a significant impact on decision to perform allograft nephrectomy. Patients that underwent transplant nephrectomy were significantly more likely to have their immunosuppression completely stopped than not (56% vs 26.5%; $P < .0002$) and the timing of cessation varied significantly (p 0.009) [Figure 2].

Outcomes in recipients with failed allografts that underwent nephrectomies are found in Table 4. Most patients in the study cohort were treated with chronic hemodialysis regardless of whether they had undergone transplant nephrectomy or not (66% vs 55%, respectively; $P = .6$). Comparison of the incidence of de novo DSA was not possible due to missing data. Allograft nephrectomy did not affect re-listing rate (64% and 55% in patients that did and did not undergo transplant nephrectomy, respectively; $P = .35$) or re-transplant rate (47% and 42% in patients that did and did not undergo transplant nephrectomy, respectively; $P = .46$). Peak PRA prior to and PRA at re-transplant was not significantly different between patients that had undergone previous transplant nephrectomy and not. Of the 82 patients that were re-transplanted, 12 patients underwent de-sensitization: 7 had undergone previous transplant nephrectomy and 5 had not ($P = .24$). Donor source, living or deceased, was not significantly different ($P = .46$) nor was time to re-transplant ($P = .67$).

Re-transplantation outcomes were assessed in patients stratified by whether they had undergone previous transplant nephrectomy. Significantly more patients in the nephrectomy cohort had biopsy-proven transplant rejection in their subsequent transplant (14 vs 8; $P = .03$). There were a total of 9 graft failures: 5 were in the nephrectomy cohort with numbers being too small to be significant ($P = .5$). Tragically, one patient in the transplant nephrectomy group died of uncontrolled uremia-related complications. The patient had exhausted all potential vascular access sites and was consequently deemed to not be a suitable candidate for transplant or dialysis.

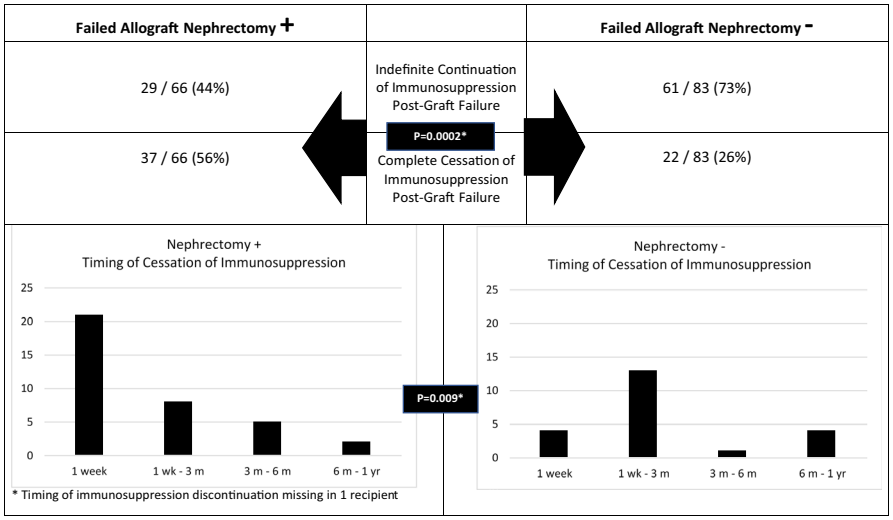


FIGURE 2 Impact of transplant nephrectomy on immunosuppression management following failed pediatric kidney transplant

4 | DISCUSSION

Pediatric transplant literature on the role of transplant nephrectomy following allograft failure is scarce. Even in adults, there are no consensus guidelines on immunosuppression withdrawal or allograft nephrectomy following the failure of a renal transplant. While allograft nephrectomy has been associated with lower adjusted relative risk for all-cause mortality (adjusted HR 0.68) in adults,[1] the development of DSA and non-DSA anti-HLA antibodies are increased following allograft nephrectomy and may develop in more than 50% of patients whose immunosuppression has been stopped after an allograft nephrectomy.[6,7] A recent metanalysis in 2018 in adults, based on 13 studies including 1923 patients, suggested that there is no advantage of graft nephrectomy in the absence of clinical symptoms.[10] The PNRC provided us the platform to perform a multicenter retrospective study to assess current practice regarding transplant nephrectomy and the influence of transplant nephrectomy on re-transplant access and outcomes. In children this is the largest study of its kind addressing this question, and to our knowledge, a similar study has not been attempted.

In this study, we demonstrate that failed allograft nephrectomy did not impact the re-transplant listing rate, the re-transplant rate, or the timing to re-transplant. We were unable to prove or disprove our hypothesis that sensitization would be a risk factor of allograft nephrectomy in pediatrics due to most centers not checking DSA following graft failure. But the peak PRA prior to and at re-transplant was not significantly different between patients that had undergone failed allograft nephrectomy and not, as has been demonstrated in adult studies.[5] Tittlebach-Helmrich et al did demonstrate a transient increase in PRA which normalized by re-transplant[11] and others have demonstrated a higher PRA associated with graft nephrectomy with older immunosuppression techniques than utilized in our study.[12,13] Of the 12 patients that underwent de-sensitization prior to re-transplant, 7 had undergone previous transplant nephrectomy. Immunosuppression was completely stopped in significantly more patients that had undergone nephrectomy despite studies demonstrating that the removal of failed allografts may be associated with increased allosensitization. This is potentially explained by the removal of the failed allograft being the removal of the "sink" for absorption of alloantibodies and the persistence of antigen-presenting cells after allograft nephrectomy. Even in children, it has been hypothesized that removal of the failed transplant is associated with higher circulating HLA antibody levels.[2] The timing of immunosuppression cessation was also significantly different in patients following transplant nephrectomy although the infectious and sensitization implications of this are unclear and worth exploring in pediatric patients in whom prolonged immunosuppression could potentially exacerbate susceptibility to infections related to pediatric factors and indwelling catheters (most children are too small for fistula/grafts).

Outcomes in the 82 patients that were re-transplanted demonstrated that failed allograft nephrectomy was associated with a significantly higher incidence of biopsy-proven rejection after re-transplantation as has been demonstrated in adults.[14] Some older studies do not show the increased rejection rate that we demonstrated[15] but modern immunosuppression was not used, and the overall rejection rate was much higher in those cohorts. Graft survival was not significantly different although numbers are small. This is consistent with adult studies[3,5,7,16-19] although there are contradicting adult studies that have demonstrated inferior graft survival.[20,21] Patient survival was not significantly different which is consistent with adult data.[20] The lack of complete donor-specific antibody data and HLA matching data makes these findings difficult to interpret.

In this study, 41% of the 186 pediatric kidney recipients included underwent transplant nephrectomy at varying times following graft failure. We did not find an association with any transplant or demographic characteristics and the physician decision to proceed with allograft nephrectomy. There was center-specific practice variation suggesting that patient-specific factors did not always drive decision to remove failed allograft.

TABLE 4 Comparative analysis of outcomes in recipients with failed allografts that did and did not undergo transplant nephrectomy

	Failed Allograft Nephrectomy+ N=76	Failed Allograft Nephrectomy – N = 110	*P* value
Re-listed for transplant	49 (64%)	61 (55%)	.35
Time to re-listing (mean in days)	495	436	.67
PRA = 0% at time of re-transplant	5 (7%)	14 (13%)	.22
Peak PRA prior to re-transplant			
0%	3 (4%)	9 (8%)	.8*
1%-49%	10 (13%)	7 (6%)	
50-97%	8 (11%)	8 (7%)	
>=98%	13 (17%)	12 (11%)	
De-sensitization prior to re-transplant	7 (9%)	5 (5%)	.24
Re-Transplanted	36 (47%)	46 (42%)	.46
DD	24 (32%)	31 (28%)	
LRD	6 (8%)	7 (6%)	
LURD	6 (8%)	8 (7%)	
Rejection in re-transplanted kidney	14 (18%)	8 (7%)	.03
Multiple rejection episodes (≥2) in first year after re-transplant	5 (7%)	1 (1%)	0.03
Antibody-mediated rejection	5 (7%)	3 (3%)	.5
Indication biopsy after re-transplant	21 (28%)	21 (19%)	.36
Re-transplant graft failure	5 (7%)	4 (4%)	.48
Reasons:			
Recurrence of original disease	3 (4%)	1 (1%)	
Acute rejection	0 (0%)	3 (1 non-adherent)	
Chronic rejection	1 (1%)	0 (0%)	
Death	1 (1%)	0 (0%)	

*Please note there was large missing data for this variable.

Interestingly, DSA was detected in significantly more recipients at dialysis initiation that went on to retain their grafts as compared to those that underwent transplant nephrectomy. Our data do not allow the evaluation of whether prevention of sensitization was a factor for whether recipients would subsequently undergo transplant nephrectomy.

The most common indication for transplant nephrectomy in the first month post-transplant was graft thrombosis which was intuitive but documented indications for transplant nephrectomy after the first year post-transplant were most often for the development of symptoms such as graft tenderness, which accounted for 47% of the nephrectomized transplant recipients. Recipients with painful grafts / graft intolerance syndrome are likely to have ongoing resistant rejection which could lead to sensitization. Graft nephrectomy has been proposed to be potentially beneficial in patients with graft intolerance syndrome[22,23] although this is yet to be proven.[24] In 2 patients, the indication for nephrectomy was severe antibody-mediated rejection. Minson et al demonstrated a higher incidence of transplant nephrectomy in patients that had severe rejection[2] Withdrawal of immunosuppression with an in situ allograft is associated with enhanced risk of allosensitization and may enhance the ability of the allograft to act as a source of inflammation contributing to morbidity and mortality. While the retention of some level of immunosuppression may mitigate this risk, it could also increase the risk of immunosuppression-related complications: infection, malignancy, and those associated with long-term corticosteroid exposure. Three patients underwent elective late nephrectomy with the intention of reducing immunosuppression or addressing rising panel reactive antibody, but only 1 of those patients was weaned completely off immunosuppression and was placed on the transplant waiting list. The other 2 were never weaned off immunosuppression, but underwent a subsequent transplant with living unrelated

transplants, one of whom went on to develop acute cellular rejection and delayed graft function. The small sample size does not allow recommendations on the role of elective transplant nephrectomy for immunosuppression withdrawal.

Our study had the expected limitations of being a retrospective data collection study. In addition, our numbers are small, and our study was inadequately powered to truly answer any clinical question on the effectiveness vs risk of transplant nephrectomy. The 14 centers that participated were varied in size, immunosuppression protocols, and geography. Analysis of individual center practices demonstrated significant variation in practices by center, independent of patient, and transplant demographics, which limit the generalizability of this study. Fortunately, the patients included were fairly heterogenous potentially alleviating some of the inherent issues regarding the applicability and generalizability of the study to other pediatric transplant recipients. A final limitation is the lack of markers and measures of inflammation, lack of more robust rejection data, and lack of re-hospitalizations and quality of life data which would require a prospective study.

In conclusion, our study does not allow for clear consensus regarding timing, benefits, and harms of allograft nephrectomy vs leaving the allograft in situ. For a definitive study, a prospective, multicenter, randomized controlled trial is needed. The logistics and feasibility of such a study are complicated; therefore, our recommendations based on the retrospective multicenter study presented here is that failed allograft nephrectomy does not offer an obvious benefit and may play a causal role in the observed increased rejections following re-transplant. If allograft nephrectomy is indicated for symptomatic (graft tenderness resistant to steroids) or surgical reasons (graft thrombosis), maintaining immunosuppression should be considered to reduce immunologic anti-graft activity although duration and specific guidelines cannot be formulated based on our study. Diversity of center-specific practice patterns continue to highlight the need for a unified approach to pediatric transplant medicine and the need for more evidence-based pediatric consensus guidelines.

AUTHORS' CONTRIBUTIONS

Verghese PS: Contributed to conception or design of the work; analysis of data for the work, acquisition of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Luckritz KE, Moudgil, Chandar J, Ranch D, Barcia J, Lin JJ, Grinsell M, Zahr R, Engen R, Twombley K, Fadakar, Jain A, Al-Akash S: Contributed to analysis of data for the work, acquisition of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Bartosh S: Contributed to analysis of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ORCID

Priya S. Verghese https://orcid.org/0000-0002-8836-0881
Asha Moudgil https://orcid.org/0000-0002-9376-6659
Katherine Twombley https://orcid.org/0000-0003-2073-2834

REFERENCES

1. Ayus JC, Achinger SG, Lee S, Sayegh MH, Go AS. Transplant nephrectomy improves survival following a failed renal allograft. *J Am Soc Nephrol*. 2010;21(2):374-380.
2. Minson S, Munoz M, Vergara I, et al. Nephrectomy for the failed renal allograft in children: predictors and outcomes. *Pediatr Nephrol*. 2013;28(8):1299-1305.
3. Lucarelli G, Vavallo A, Bettocchi C, et al. Impact of transplant nephrectomy on retransplantation: a single-center retrospective study. *World J Urol*. 2013;31(4):959-963.
4. Knight MG, Tiong HY, Li J, Pidwell D, Goldfarb D. Transplant nephrectomy after allograft failure is associated with allosensitization. *Urology*. 2011;78(2):314-318.
5. Dinis P, Nunes P, Marconi L, et al. Kidney retransplantation: removal or persistence of the previous failed allograft? *Transplant Proc*. 2014;46(6):1730-1734.
6. Del Bello A, Congy-Jolivet N, Sallusto F, et al. Donor-specific antibodies after ceasing immunosuppressive therapy, with or without an allograft nephrectomy. *Clin J Am Soc Nephrol*. 2012;7(8):1310-1319.
7. Sanchez-Gonzalez A, Carrasco-Valiente J, Arenas-Bonilla AJ, et al. Graft Survival in Patients Who Received Second Allograft, Comparing Those With or Without Previous Failed Allograft Nephrectomy. *Transplant Proc*. 2016;48(9):2895-2898.
8. Delucchi A, Toro L, Alzamora R, et al. Glucocorticoids Decrease Longitudinal Bone Growth in Pediatric Kidney Transplant Recipients by Stimulating the FGF23/FGFR3 Signaling Pathway. *J Bone Miner Res*. 2019;34(10):1851-1861.
9. Dharnidharka VR, Sullivan EK, Stablein DM, Tejani AH, Harmon WE. North American Pediatric Renal Transplant Cooperative S. Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation*. 2001;71(8):1065-1068.
10. Lin J, Wang R, Xu Y, Chen J. Impact of renal allograft nephrectomy on graft and patient survival following retransplantation: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2018;33(4):700-708.
11. Tittelbach-Helmrich D, Pisarski P, Offermann G, et al. Impact of transplant nephrectomy on peak PRA levels and outcome after kidney re-transplantation. *World J Transplant*. 2014;4(2):141-147.
12. Lair D, Coupel S, Giral M, et al. The effect of a first kidney transplant on a subsequent transplant outcome: an experimental and clinical study. *Kidney Int*. 2005;67(6):2368-2375.
13. Douzdjian V, Rice JC, Carson RW, Gugliuzza KK, Fish JC. Renal retransplants: effect of primary allograft nephrectomy on early function, acute rejection and outcome. *Clin Transplant*. 1996;10(2):203-208.
14. Schleicher C, Wolters H, Kebschull L, et al. Impact of failed allograft nephrectomy on initial function and graft survival after kidney retransplantation. *Transpl Int*. 2011;24(3):284-291.

15. Sumrani N, Delaney V, Hong JH, Daskalakis P, Sommer BG. The influence of nephrectomy of the primary allograft on retransplant graft outcome in the cyclosporine era. *Transplantation*. 1992;53(1):52-55.
16. Fadli SE, Pernin V, Nogue E, et al. Impact of graft nephrectomy on outcomes of second kidney transplantation. *Int J Urol*. 2014;21(8):797-802.
17. Surga N, Viart L, Wetzstein M, Mazouz H, Collon S, Tillou X. Impact of renal graft nephrectomy on second kidney transplant survival. *Int Urol Nephrol*. 2013;45(1):87-92.
18. Ahmad N, Ahmed K, Mamode N. Does nephrectomy of failed allograft influence graft survival after re-transplantation? *Nephrol Dial Transplant*. 2009;24(2):639-642.
19. Yagmurdur MC, Emiroglu R, Ayvaz I, Sozen H, Karakayali H, Haberal M. The effect of graft nephrectomy on long-term graft function and survival in kidney retransplantation. *Transplant Proc*. 2005;37(7):2957-2961.
20. Muramatsu M, Hyodo Y, Sheaff M, et al. Impact of Allograft Nephrectomy on Second Renal Transplant Outcome. *Exp Clin Transplant*. 2018;16(3):259-265.
21. Abouljoud MS, Deierhoi MH, Hudson SL, Diethelm AG. Risk factors affecting second renal transplant outcome, with special reference to primary allograft nephrectomy. *Transplantation*. 1995;60(2):138-144.
22. Graves RC, Fine RN. Kidney retransplantation in children following rejection and recurrent disease. *Pediatr Nephrol*. 2016;31(12):2235-2247.
23. Phillips BL, Callaghan CJ. Graft nephrectomy in children. *Pediatr Nephrol*. 2018;33(6):947-955.
24. Zerouali F, Levtchenko EN, Feitz WF, Cornelissen EA, Monnens LA. Renal transplant nephrectomy in children: can an aggressive approach be recommended? *Pediatr Transplant*. 2004;8(6):561-564.

How to cite this article: Verghese PS, Luckritz KE, Moudgil A, et al. Practice patterns and influence of allograft nephrectomy in pediatric kidney re-transplantation: A pediatric nephrology research consortium study. *Pediatr Transplant*. 2021;25:e13974. https://doi.org/10.1111/petr.13974