DR. PRIYA VERGHESE (Orcid ID : 0000-0002-8836-0881)
DR. ASHA MOUDGIL (Orcid ID : 0000-0002-9376-6659)
DR. KATHERINE TWOMBLEY (Orcid ID : 0000-0003-2073-2834)

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AUTHORS: Verghese PS[1], Luckritz KE[2], Moudgil A[3], Chandar J[4], Ranch D[5], Barcia J[6], Lin JJ[7], Grinsell M[8], Zahr R[9], Engen R[10], Twombley K[11], Fadakar P[12], Jain A[13], Al-Akash S[14], Bartosh S[15]

Affiliations:

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

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

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

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

[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

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

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

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

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

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

[11]Professor of Pediatrics, College of Medicine Professor, College of Graduate Medical Studies
Chief, Pediatric Nephrology, Interim Chief, Pediatric Neurology
Medical Director, Pediatric Kidney Transplant, Medical Director, Acute Dialysis Units,
Medical University of South Carolina, Charleston, SC

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

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

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

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Corresponding author contact information:

Priya Verghese, MD, MPH

225 East Chicago Avenue, Box 37

Chicago, Illinois 60611-2605

Email: pverghese@luriechildrens.org

Phone: 312-227-6167

Fax: 312-227-9405

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Verghese PS: 1. 2. 3. 4. 5.

Luckritz KE: 2. 3. 4. 5.

Moudgil A: 2. 3. 4. 5.

Chandar J: 2. 3. 4. 5.

Ranch D: 2. 3. 4. 5.

Barcia J : 2. 3. 4. 5.

Lin JJ: 2. 3. 4. 5.

Grinsell M: 2. 3. 4. 5.

Zahr R: 2. 3. 4. 5.

Engen R: 2. 3. 4. 5.

Twombley K: 2. 3. 4. 5.

Fadakar P: 2. 3. 4. 5.

Jain A: 2. 3. 4. 5.

Al-Akash S: 2. 3. 4. 5.

Bartosh S: 2. 3. 4. 5.

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Abstract

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

Materials & Methods: We performed a first of its kind multi-center study assessing prevalence of transplant nephrectomy, patient characteristics and outcomes in pediatric renal transplant recipients with graft failure from January 1st, 2006- December 31st, 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 demographics. Fifty three percent of graft nephrectomies were within a year of transplant. Graft tenderness prompted transplant nephrectomy in 91% ($p<0.001$). Patients that underwent nephrectomy were more likely to have a prior diagnosis of rejection within 3 months (43% vs 29%; $p = 0.04$). Nephrectomy of allografts did not affect time to re-listing, donor source at re-transplant but significantly decreased time to ($p=0.009$) and incidence ($p=0.0002$) 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%; $p=0.03$) and multiple rejections in first year after re-transplant (7% vs. 1%; $p=0.03$).

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; timing / frequency of immunosuppression withdrawal is significantly different with slightly increased risk for rejection following retransplant.

KEYWORDS: transplant nephrectomy, pediatric re-transplant

Abbreviations:

Pediatric Nephrology Research Consortium (PNRC)

Kidney transplant (KTx)

Donor specific antibody (DSA)

Human Luecocyte Antigen (HLA)

Panel Reactive Antibody (PRA)

Enzyme-Linked Immunosorbent Assay (ELISA)

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 a 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 retransplantation 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 1st, 2006- December 31st, 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.

METHODS

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 1st, 2006 and December 31st, 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 receipts were excluded. Center participation was approved by the respective individual site Institutional Review Boards.

Data/Specimen Analysis.

Data was 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 was 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 kidney transplant (KTx) outcomes in univariate analysis. P values <0.05 were considered statistically significant. All statistical analysis was performed with STATA/IC 11.0, College Station, Texas, USA.

RESULTS

Between January 1st, 2006 and December 31st, 2016, there were 186 pediatric transplant recipients who had graft failure from a total of 14 centers. Recipient characteristics are found on 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 7-30 days in 8 (11%), at 31-365 days posttransplant in 22 (29%), and after 1-year posttransplant in 36 (47%) [4 within 1-2 years posttransplant; 25 within 2-5 years posttransplant and 7 more than 5 years posttransplant]. 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 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%] versus 33/75 [44%] p=0.03).

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 <0.001].

Transplant nephrectomies performed in the first week and month posttransplant were most commonly for graft thrombosis (80% and 63% respectively). Indications for transplant nephrectomy after the first year posttransplant 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 = 0.04) [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=0.03).

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 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 = 0.118) nor maintenance immunosuppression (p = 0.1) were associated with the decision to perform a transplant nephrectomy [Table 3]. Steroid inclusive versus 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% versus 27%; p < 0.002) 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% versus 55% respectively; p = 0.6). 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 = 0.35), or retransplant rate (47% and 40% in patients that did and did not undergo transplant nephrectomy respectively; p = 0.98). Peak PRA prior to and PRA at retransplant was not significantly different between patients that had undergone previous transplant nephrectomy and not. Of the 82 patients that were retransplanted, 12 patients underwent de-sensitization: 7 had undergone previous transplant nephrectomy and 5 had not (p = 0.24). Donor source, living or deceased, was not significantly different (p=0.46) nor was time to retransplant (p=0.67).

Retransplantation 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 versus 8; p=0.03). There were a total of 9 graft failures: 5 were in the nephrectomy cohort with numbers being too small to be significant (p=0.5). 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.

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 Pediatric Nephrology Research Consortium (PNRC), provided us the platform to perform a multi-center retrospective study to assess current practice regarding transplant nephrectomy and the influence of transplant nephrectomy on re-transplant access and outcomes. 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 retransplant listing rate, the retransplant rate or the timing to retransplant. 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 retransplant 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 retransplant [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 retransplant, 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 retransplanted 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. 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 does 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 posttransplant was graft thrombosis which was intuitive but documented indications for transplant nephrectomy after the first year posttransplant, 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 versus 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 retransplant. 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.

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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%)	0.69
Race:			0.06
Caucasian	33 (43%)	53 (48%)	
African American	25 (33%)	23 (21%)	
Asian	2 (3%)	5 (5%)	
Hispanic	16 (21%)	19 (17%)	

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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	5 (63%)	8 (36%)	1 (3%)	
Tubulo-interstitial disease			7 (9%)	12 (11%)	
Unknown / Other			4 (5%)	9 (8%)	
Donor type:					0.16
Deceased Donor			54 (71%)	63 (57%)	
Living Related Donor			19 (25%)	40 (36%)	
Living Unrelated Donor			3 (4%)	7 (6%)	
Primary renal transplant			71 (93%)	103 (94%)	0.95
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	0.43

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 -	P value
Graft				
Poorl				
hyper				
Gross				
or without fever				
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%) -"severe AMR"	1 (5%) -"severe AMR"	0
Other causes	0	0	0	2 (5%) -to create surgical space -chronic pyelonephritis

		N=110	
Induction:			0.118
Thymoglobulin	35 (46%)	46 (42%)	
IL-2 Receptor Inhibitor	24 (32%)	42 (38%)	
Alemtuzumab	13 (17%)	21 (19%)	
Other / Unknown	4 (5.2%)	1 (0.9%)	
Maintenance:			0.44
Steroid inclusive	43 (57%)	62 (56%)	
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%)	

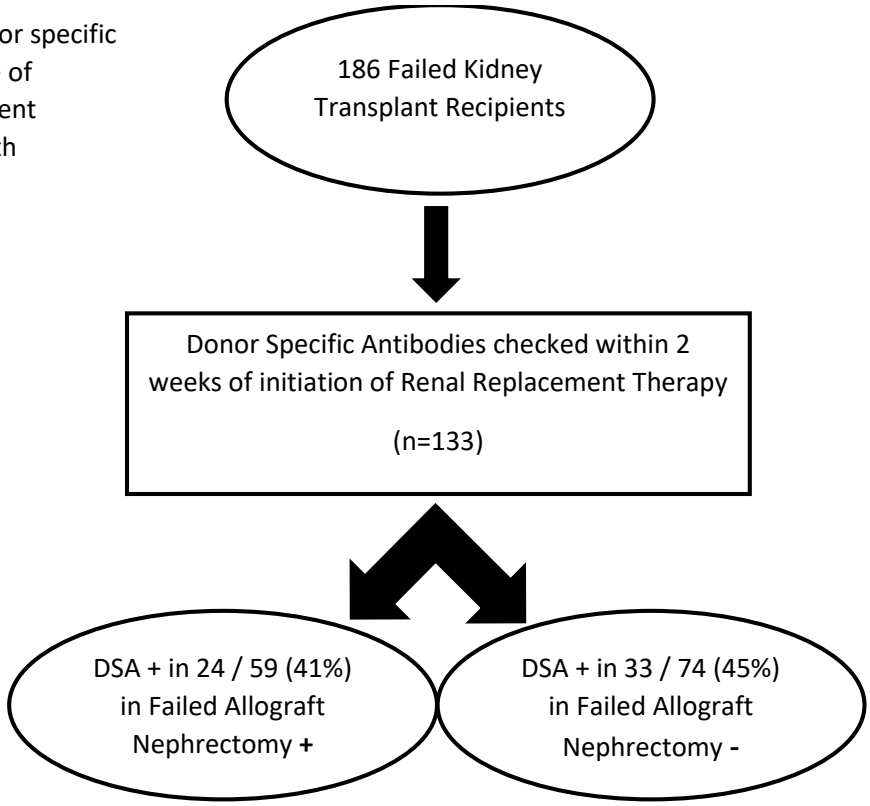
TABLE 4: Comparative analysis of outcomes in recipients with failed allografts that did and did not undergo transplant nephrectomy

	Failed Allograft Nephrectomy + N=76	Failed Allograft Nephrectomy - N=110	P value
Relisted for transplant	49 (64%)	61 (55%)	0.35
Time to relisting (mean in days)	495	436	0.67
PRA = 0% at time of	5 (7%)	14 (13%)	0.22

retransplant			
Peak PRA prior to retransplant **0%** **1-49%** **50 – 97%** **>=98%**	 3 (4%) 10 (13%) 8 (11%) 13 (17%)	 9 (8%) 7 (6%) 8 (7%) 12 (11%)	0.8*
De-sensitization prior to re-transplant	7 (9%)	5 (5%)	0.2
Re-Transplanted **DD** **LRD** **LURD**	36 (47%) 24 (32%) 6 (8%) 6 (8%)	46 (42%) 31 (28%) 7 (6%) 8 (7%)	0.46
Rejection in retransplanted kidney	14 (18%)	8 (7%)	0.03
Multiple rejection episodes (≥2) in first year after re-transplant	5 (7%)	1 (1%)	0.03
Antibody-mediated rejection	5 (7%)	3 (3%)	0.5
Indication biopsy after re-transplant	21 (28%)	21 (19%)	0.36
Re-transplant graft failure **Reasons:** **Recurrence of original disease** **Acute rejection** **Chronic rejection** **Death**	5 (7%) 3 (4%) 0 (0%) 1 (1%) 1 (1%)	4 (4%) 1 (1%) 3 (1 non-adherent) 0 (0%) 0 (0%)	0.48

*Please note there was large missing data for this variable

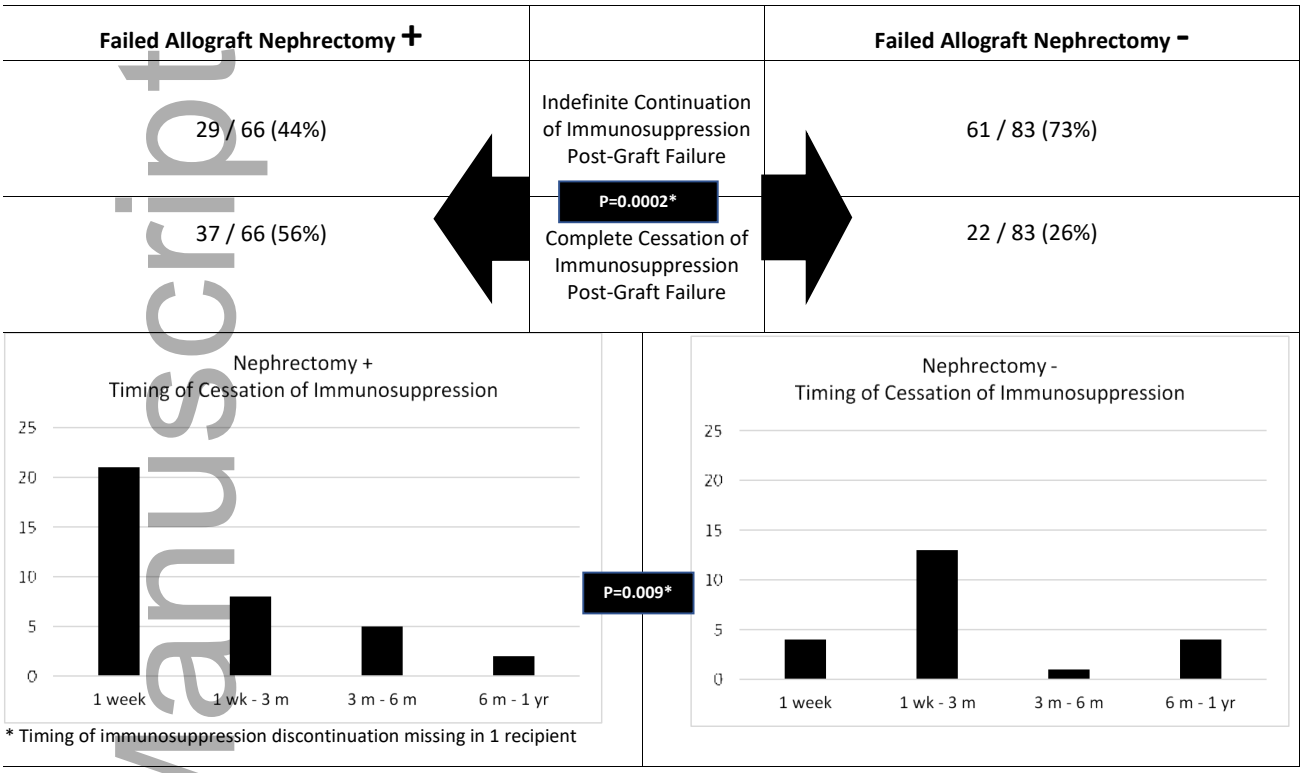
FIGURE 1: Incidence of donor specific antibodies assessed at time of initiation of renal replacement therapy and association with transplant nephrectomy



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



* Timing of immunosuppression discontinuation missing in 1 recipient