

De Novo Allergy and Immune-Mediated Disorders Following Solid-Organ Transplantation—Prevalence, Natural History, and Risk Factors

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Objectives To describe the prevalence, natural course, outcome, and risk factors of post-transplant de novo allergy and autoimmunity.

Study design A cross-sectional, cohort study of all children (<18 years) who underwent a solid-organ transplantation, between 2000 and 2012, in a single transplant center, with a follow-up period of 6 months or more post-transplant and without history of allergy or immune-mediated disorder pretransplant.

Results A total of 626 eligible patients were screened, and 273 patients (160 males; 59%) met the inclusion criteria; this included 111 liver, 103 heart, 52 kidney, and 7 multivisceral recipients. Patients were followed for a median period of 3.6 years. A total of 92 (34%) patients (42 males, 46%) developed allergy or autoimmune disease after transplantation, with a high prevalence among liver (41%), heart (40%), and multivisceral (57%) transplant recipients compared with kidney recipients (4%; $P < .001$). Post-transplant allergies included eczema ($n = 44$), food allergy (22), eosinophilic gastrointestinal disease (11), and asthma (28). Autoimmunity occurred in 18 (6.6%) patients, presenting mainly as autoimmune cytopenia ($n = 10$). In a multivariate analysis, female sex, young age at transplantation, family history of allergy, Epstein–Barr virus infection, and elevated eosinophil count >6 months post-transplantation were associated with an increased risk for allergy or autoimmunity. Two patients (0.7%) died from autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis, and 52 episodes of post-transplant allergy, autoimmunity, and immune-mediated disorders (37%) did not improve over time.

Conclusions Allergy and autoimmunity are common in pediatric liver, heart, and multivisceral transplant recipients and pose a significant health burden. Further studies are required to clarify the mechanisms behind this post-transplant immune dysregulation. (*J Pediatr* 2017;■■■:■■■–■■■).

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Allergic and immune-mediated disorders have been reported sporadically in pediatric recipients of solid-organ transplantation (SOT) and are associated with mild-severe morbidity and rarely with mortality. The reported clinical spectrum of SOT-associated allergies is variable, ranging from asymptomatic eosinophilia, through food allergies, eosinophilic gastrointestinal disorders (EGIDs), atopic dermatitis, allergic rhinitis, and asthma to anaphylaxis.^{1–6} Likewise, a variety of SOT-associated immune-mediated disorders have been reported, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, neutropenia, and pancytopenia.^{7–11} These phenomena are attributed to an ongoing exposure of pediatric recipients of SOT to immunosuppressive medications and a unique immune milieu.

The prevalence of post-transplant allergy, autoimmunity, and immune-mediated disorders (PTAA) among pediatric transplant recipients is estimated at 8.5%–45%, with a high prevalence of allergies in liver recipients and low prevalence in kidney recipients; the prevalence of PTAA in heart transplant recipients is unknown.^{1–6} PTAA pathophysiology and whether post-transplant allergy and autoimmunity share common triggers and immune pathways also are unknown.

PTAA across all SOT recipients over a long period of follow-up has never been studied systematically, and gaps exist in our knowledge. We studied a large cohort

CNI	Calcineurin inhibitor
EBV	Epstein–Barr virus
EGID	Eosinophilic gastrointestinal disorder
HLH	Hemophagocytic lymphohistiocytosis
IBD	Inflammatory bowel disease
PTAA	Post-transplant allergy, autoimmunity, and immune-mediated disorders
PTLD	Post-transplant lymphoproliferative disease
SOT	Solid-organ transplantation

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of pediatric recipients of liver, heart, kidney, and multivisceral transplants in a single center to assess the clinical spectrum of PTAA, the prevalence among different organs, clinical course, risk factors, and outcomes.

Methods

We conducted a retrospective, cross-sectional, single-center study of all children (<18 years of age) who underwent a primary liver, heart, kidney, intestine, or multivisceral transplantation at the Hospital for Sick Children, Toronto, Canada, between January 2000 and December 2012. Data were retrieved from the patients' prospectively collected electronic charts, available at our center since 2000. Patients were excluded from the study in cases of allergy (excluding drug allergy) and/or immune-mediated disorder before SOT; pretransplant exposure to immunosuppressive medications or chemotherapy; post-transplantation follow-up <6 months; or incomplete data in the patient's chart. Collected data included patient demographics, medical history, and clinical course; immunosuppressive regimens; PTAA and their treatment; complications; and outcome. Blood test results included eosinophil counts, immunoglobulins, microbiologic studies, and allergy testing. Transplant protocols varied according to organ and year of transplant; however, tacrolimus and steroids were the standard post-transplant immunosuppressive treatment and were used in all cases unless specified. The study was reviewed and approved by the local ethics committee.

PTAAs were identified according to the reported diagnoses in the patient's electronic chart based on compatible clinical and laboratory findings. Charts of all patients diagnosed with PTAA were reviewed by 3 physicians to avoid over- or incorrect diagnoses. Cases of disagreement were discussed, and patients were diagnosed with PTAA only on mutual agreement. Patients were determined allergic only if symptoms persisted, were followed by the relevant subspecialty service (eg, immunology, dermatology, pulmonology), or received ongoing treatment for their allergy. Food allergy was diagnosed clinically by an allergist or a gastroenterologist. IgE-mediated reactions were defined by the combination of clinical symptoms including anaphylaxis, urticaria, or angioedema and a positive skin prick testing, the presence of food-specific IgE antibodies, or a positive oral challenge test. Non-IgE-mediated

reactions were diagnosed clinically, ie, the presence of vomiting or diarrhea that responded to elimination diet. Allergic rhinitis, asthma, eczema, and atopic dermatitis were all diagnosed clinically. EGIDs were diagnosed by compatible clinical and histologic findings.^{12,13} Peripheral blood eosinophilia was analyzed by patient ages according to reference ranges provided by the SickKids laboratory service in Toronto, Canada (0-3 months $>1 \times 10^9$, 3-12 months $>0.7 \times 10^9$, >1 year $>0.5 \times 10^9$ eosinophils/L, respectively), and recorded categorically as normal/abnormal at 3, 6, and 12 months post-transplant. Autoimmune and immune-related disorders were diagnosed according to accepted criteria for each of these pathologies.

Statistical analysis was computed with SPSS (V. 21.0; IBM Corp, Armonk, New York). Student *t* test and Fisher exact tests (for $n < 10$) were used for continuous variables, and the χ^2 test was used for categorical variables; all tests were performed with 2-sided tails with a CI of 95%. Kendall tau-B test was used to assess categorical trends. Survival was calculated with the Mantel-Cox test and logistic regression was used for multivariate analysis with a CI of 95%.

Results

A total of 626 patients who underwent their first SOT at our center during the study period were screened. Of those, 353 patients were excluded: 47 due to an immune-mediated etiology of their original disorder (31 kidney, 10 liver, and 6 heart transplant recipients); 61 due to a previous state of allergy (49 kidney and 12 heart transplant recipients), and 5 patients who underwent liver transplant were excluded due to pretransplant chemotherapy; the remaining 240 patients were excluded for short (<6 months) follow-up and were either transferred to another institution or lost to follow-up.

A total of 273 patients were included in the study cohort: 111 liver recipients, 103 heart, 52 kidney, and 7 patients who underwent multivisceral transplantation. Male subjects (160, 59%) predominated with a male/female ratio of 1.4 ($P < .01$); primarily because of male predominance among kidney transplant recipients (Table I). The overall median age at transplantation was 2.9 (IQR 0.7-10.3) years, with median ages for liver (1.7 year) and heart (1.2 year) recipients significantly lower than kidney recipients (10.8 years, $P < .001$). The median post-

Table I. Patient demographics by organ

Characertistics	Organ				Total
	Liver	Heart	Kidney	Multivisceral	
Patients, n (%)	111 (40)	103 (38)	52 (19)	7 (2.6)	273 (100)
Male, n (%)	63 (57)	56 (54)	37 (71)*	4 (57)	160 (59)
Age at transplantation, y, median (IQR)	1.7 (0.8-6.9)	1.2 (0.4-9.2)	10.8 (6.3-15.5)*	1.2 (0.9-1.6)	2.9 (0.7-10.3)
Length of follow-up, y, median (IQR)	3.2 (1.6-5.8)	4.5 (2.8-6.8)	2.4 (1.2-6.0)	4.8 (1.6-5.5)	3.6 (1.7-6.3)
Age at last follow-up, y, median (IQR)	7.0 (3.7-12.0)	9.0 (5.7-15.1)	17.5 (11.3-18.0)*	7.0 (4.5-7.3)	9.2 (5.2-15.6)

* $P < .05$.

transplantation follow-up was 3.6 (IQR 1.7-6.3) years and was not statistically different between the different organs (Table I). Forty-seven (42.3%) liver and 30 (57.7%) kidney recipients were transplanted with living donor organs.

Post Transplantation Allergy, Autoimmunity, and Immune-Mediated Disorders

Overall, 140 separate PTAA were diagnosed in 92 patients (42 males, 45.7%), a prevalence of 33.7%. PTAA was significantly more common among liver, 45 (40.5%); heart, 41 (39.8%); and multivisceral transplant recipients, 4 (57%) than kidney recipients 2 (3.8%). The majority of patients who developed PTAA, $n = 87$, had allergies, including 13 patients who were codiagnosed with autoimmunity/immune-mediated disorders; only 5 patients suffered exclusively from autoimmunity/immune-mediated disorders.

Prevalence of allergy among liver and heart recipients was 38.7% and 38.8%, respectively ($P = .43$), compared with 28.6% among multivisceral recipients ($P = .7$) and only 3.8% among kidney recipients ($P < .01$). Prevalence of autoimmunity in liver and heart recipients was 4.5% and 9.7%, respectively ($P = .01$), compared with none among kidney recipients and 42.9% among multivisceral recipients (Figure 1).

In-depth analysis of the 87 patients with allergic manifestation following SOT demonstrated that 44 (50.5%) had eczema, 28 (32.2%) had asthma, and 15 (17.2%) had rhinitis (Table II). Food allergies were diagnosed in 22 (25.3%) patients, including 4 (4.6%) who had 1 or more episodes of anaphylaxis. Eleven patients (12.6%) were diagnosed with EGID, including eosinophilic esophagitis, gastritis, and/or enteritis.

Interestingly, asthma was more prevalent following heart (15.5%) than liver (9%) transplantation ($P = .03$); in contrast, a greater prevalence of liver recipients (15.3%) compared with heart recipients (4.9%) were identified with food allergies ($P < .01$), anaphylaxis (2.7% vs 1% respectively, $P = .04$), and EGID (7.2% vs 2.9%, $P < .01$).

Autoimmunity and immune-mediated disorders were diagnosed in 18 (6.6%) patients. Of those, 9 patients had autoimmune cytopenias; 6 de novo inflammatory bowel disease (IBD); 2 patients had vasculitis, presenting as livedo reticularis in 1 and rash, arthralgia, and mouth ulcers in the other; 1 patient was diagnosed with hemophagocytic lymphohistiocytosis (HLH); and 1 with alopecia areata. A single patient was codiagnosed with IBD and cytopenia. Ten (9.7%) heart recipients had autoimmunity compared with 5 (4.5%) liver recipients ($P = .04$). Similarly, 5 (4.9%) heart recipients were diagnosed with post-transplantation IBD-like compared with only 1 (0.9%) liver recipient ($P = .03$). No statistical difference was noted between these 2 organs regarding autoimmune cytopenias. Recipients of multivisceral transplantation had a high prevalence of autoimmunity ($n = 3$, 42.9%), with 2 patients diagnosed with cytopenia and 1 with HLH; albeit a small cohort, the prevalence was significantly greater compared with liver and heart recipients (Table II).

The PTAA episodes presented after a median of 7 (mean 14) months post-transplantation. Of the 92 patients eventually diagnosed with PTAA, 40 (89%) of the affected liver recipients, 29 (71%) of the affected heart recipients and all kidney and multivisceral recipients, were diagnosed within 2 years after transplantation ($P =$ not significant). Only a single recipient

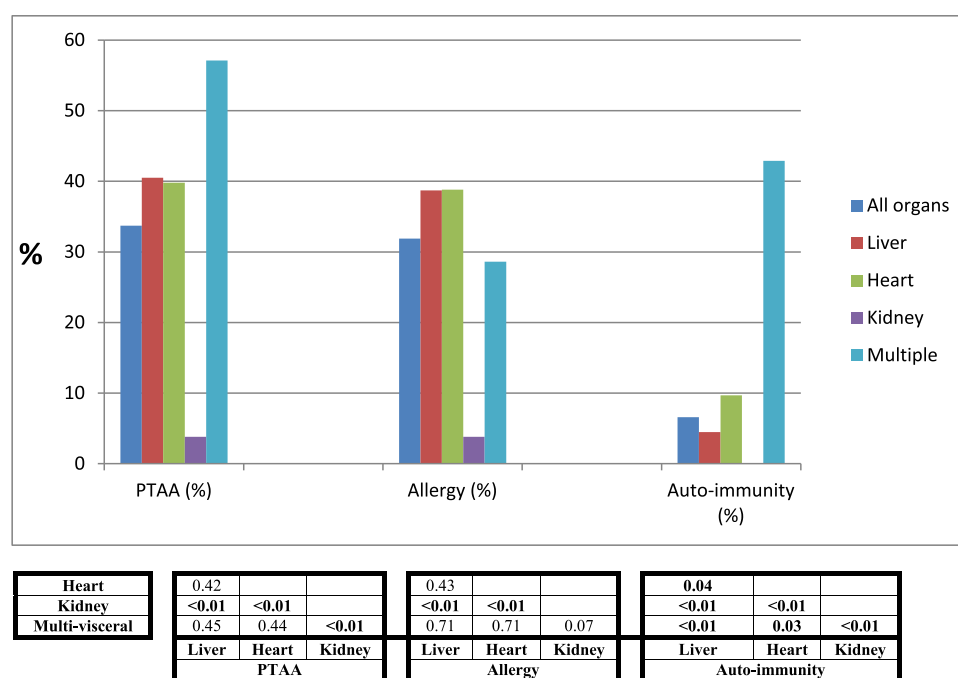


Figure 1. Prevalence of PTAA in 273 recipients of SOTs. (See Tables I-IV for statistical analysis; P value).

Table II. Allergies and immune-mediated disorders in 273 solid-organ recipients by organ, n (%)

Disorders	All organs (n = 273)	Liver (n = 111)	Heart (n = 103)	P value (liver vs heart)	Kidney (n = 52)	P value (kidney vs liver)	P value (kidney vs heart)	Multivisceral (n = 7)	P value (multivisceral vs liver)	P value (multivisceral vs heart)
Allergic disorders	87 (31.9%)	43 (38.7%)	40 (38.8%)	.43	2 (3.8%)	<.01	<.01	2 (28.6%)	.7	.7
Atopy	71 (26%)	30 (27%)	37 (35.9%)	.03	2 (3.8%)	<.01	<.01	2 (28.6%)	1.0	1.0
Asthma	28 (10.3%)	10 (9%)	16 (15.5%)	.03	1 (1.9%)	.18	.012	1 (14.3%)	.5	1.0
Eczema	44 (16.1%)	22 (19.8%)	21 (20.4%)	.42	—	<.01	<.01	1 (14.3%)	1.0	1.0
Rhinitis	15 (5.5%)	5 (4.5%)	9 (8.7%)	.07	1 (1.9%)	.67	.17	—	1.0	1.0
Food allergy	22 (8.1%)	17 (15.3%)	5 (4.9%)	<.01	—	<.01	.17	—	.6	1.0
Anaphylactic shock	4 (1.5%)	3 (2.7%)	1 (1%)	.04	—	.55	1.0	—	1.0	1.0
EGID	11 (4%)	8 (7.2%)	3 (2.9%)	<.01	—	.06	.55	—	1.0	1.0
Autoimmune disorders	18 (6.6%)	5 (4.5%)	10 (9.7%)	.04	—	<.01	<.01	3 (42.9%)	<.01	.03
Cytopenias	9 (3.3%)	2 (1.8%)	5 (4.9%)	.08	—	—	—	2 (28.6%)	.02	.06
Anemia	5 (1.8%)	1 (0.9%)	2 (1.9%)	.25	—	—	—	2 (28.6%)	<.01	.02
Thrombocytopenia	4 (1.5%)	—	3 (2.9%)	.04	—	—	—	1 (14.3%)	.06	.2
Neutropenia	3 (1.1%)	1 (0.9%)	2 (1.9%)	.25	—	—	—	—	1.0	1.0
IBD	6 (2.2%)	1 (0.9%)	5 (4.9%)	.03	—	—	—	—	1.0	1.0
Vasculitis	2 (0.7%)	1 (0.9%)	1 (1%)	.43	—	—	—	—	1.0	1.0
HLH	1 (0.4%)	—	—	—	—	—	—	1 (14.3%)	.06	.06
Alopecia areata	1 (0.4%)	1 (0.9%)	—	1	—	—	—	—	1.0	1.0

GI, gastrointestinal.
Bold values are statistically significant.

of liver and a single heart recipient (2.2% and 2.4% respectively) developed PTAA 5 years or later after transplantation (**Figure 2**; available at www.jpeds.com).

Risk Factors for the Development of PTAA

A multivariate logistic regression model was used to identify independent risk factors for the development of PTAA. Data on family history of allergy were available in only 85 (31%) patients. Based on these data, the OR of a positive family history of allergy for the development of PTAA was 5.0 ($P = .01$). Family history of autoimmunity was only rarely reported and therefore was not analyzed. Other risk factors identified included female sex (OR = 2.2), young age at transplantation (OR = 1.2 per age year), eosinophilia, and positive post-transplantation Epstein-Barr virus (EBV) Polymerase chain reaction (PCR). The association of blood eosinophilia and PTAA reached statistical significance only when the transplant recipient was ≥ 6 months of age, demonstrating the nonspecific nature of abnormally high eosinophil counts during the first months of life. This association was further strengthened by time after transplantation, with an OR of 2.8 6 months post-transplantation compared with OR of 5.8 for eosinophilia at 12 months post-transplantation; these data suggest a potential detrimental effect of prolonged activation of the eosinophilic-associated immune arms. Categorical test of trend (Kendall tau-B) demonstrated ordinal relationship between the frequency of elevated eosinophils and age ($P < .001$). Post-transplantation infection with EBV also was found to be a risk factor, with an OR of 2.0; this OR increased to 2.3 if the infection occurred at age 2 years or older (**Table III**; available at www.jpeds.com).

Factors not found to be associated independently with risk for PTAA development included length of post-transplantation steroidal treatment, presence and frequency of acute rejections, organ type (living donor vs cadaveric), donor/recipient blood type and compatibility, and non-EBV infections. Post-transplant lymphoproliferative disease (PTLD) was identified in 30 patients; 21 of them had PTAA. However, only 1 patient was diagnosed with PTLD before the PTAA, and an additional 2 patients were diagnosed with PTLD and PTAA concurrently. PTLD was not found to confer risk for PTAA. The specific type of post-transplantation immunosuppression regimen was neither associated nor protective of PTAA, including the presence of induction protocol with either antithymocyte globulin or anti-interleukin-2 receptors, and maintenance therapy with either mycophenolate mofetil, prednisone, or sirolimus. However, a significant limitation was our inability to assess the effect of tacrolimus, as nearly all the cohort (97.8%) was treated with this medication (**Table III**).

PTAA Outcome

Of the 92 PTAA-affected children, 10 (11%) were observed and followed conservatively without further intervention; 65 (71%) were treated medically as per customary treatment for their PTAA type, and in 17 (18%) patients, the immunosuppressive therapy was changed following a failure of medical treatment to control symptoms. These 17 patients had a high burden

of PTAA: 33 episodes in total. The immunosuppression change resulted in improvement in 9 PTAA and complete resolution in 7; however, 13 PTAA were not affected by the change, and 4 worsened, including 2 PTAA-associated mortalities.

The outcome of the 140 different diagnoses was as follows: 73 (52%) disorders improved and 15 (11%) completely resolved; however, 43 (31%) disorders did not change during follow-up and 9 (6%) worsened, including 2 mortalities secondary to PTAA: a child with resistant autoimmune hemolytic anemia and a child with post-transplant HLH. Time to PTAA from the day of transplant did not impact the PTAA outcome (mean time to PTAA was 25.4 ± 27.7 months in PTAA episodes that improved vs 32.9 ± 32.7 in the other groups; $P = .17$).

During the study period, 13 (4.8%) patients died: 8 (7.8%) heart, 3 (2.7%) liver, and 2 (28.6%) multivisceral transplantation recipients. Of those, 6 (6.5%) were patients affected by PTAA, including the 2 who died as a direct result of PTAA.

Discussion

The development of PTAA following SOT in children is a known transplant-related morbidity. Understanding of the prevalence, clinical spectrum, risk factors, and outcome of PTAA is limited by the nature of previous reports that focused on one organ or one specific PTAA and often described a limited number of patients. The current study approached PTAA with a broader perspective, describing PTAA in a large nonselective cohort of pediatric SOT recipients over a decade. The findings highlight the high prevalence of PTAA in heart, liver, and multivisceral recipients and the increased morbidity of patients with PTAA. The diverse spectrum of PTAA raises the possibility that these phenomena represent a unique state of post-transplant immune dysregulation with shared pathogenesis.

PTAA prevalence reached 40% of liver and heart transplant recipients, 57% in multivisceral, and only 4% in kidney transplant recipients. Although no study has looked at the aggregate prevalence of PTAA, similar trends have been noted for specific disease types or organ groups. High prevalence of allergic disorders in general (up to 40%), food allergies (5.6-38%), and autoimmune cytopenias (2.4%) were reported in liver transplant recipients.^{2-6,14-18} High prevalence of 23.5% of autoimmune cytopenia was described in one cohort of multivisceral transplant recipients, resembling our finding of 25%.¹⁶ Likewise, similar prevalence discrepancies of food allergy between kidney (0%-0.5%) and liver (6%-27%) transplant recipients have been described.^{5,14} However, data on heart and multivisceral transplant recipients are scarce and were only anecdotally reported in small cohorts.^{16,17,19}

The reasons for the prevalence discrepancy between organ groups is unclear and probably relates to the pathogenesis that governs PTAA. Age at transplant was significantly lower in heart and liver transplant recipients in our cohort compared with kidney recipients, with a median age of 1.2, 1.7, and 10.8 years, respectively. Indeed, young age at transplant was found as a significant risk factor for PTAA with OR of 1.2 per year in our study and others.^{2,18} Young age is associated with immature

Table IV. Prevalence of common allergies and autoimmunity in 273 solid-organ recipients compared with the general population*

PTAA	Liver (%)	Heart (%)	Kidney (%)	Multivisceral (%)	General population* (%)
Eczema	20	20	0	14	12-25
Asthma	9	16	2	14	13
Food allergy	15	5	0	0	3-5
EGID	7	3	0	0	0.04
Autoimmunity	4.5	10	0	43	0.01

*Canadian/North American pediatric population.²⁰⁻²⁴

immune system with a Th1/Th2 milieu that favors allergy-related Th2 responses. Early introduction of immunosuppressive therapy in infants may further predispose them to a greater risk of PTAA. This may partially explain the discrepancy in PTAA prevalence between liver and heart recipients vs kidney recipients.

Long-term maintenance therapy with steroids in addition to calcineurin inhibitors (CNIs) is common in our heart and kidney cohorts but not in liver transplant recipients; thus, the long-term use of prednisone post-transplant will not explain the differences between the groups and indeed was not found as a risk factor in our multivariate analysis. Further studies to elucidate the mechanism and pathogenesis of PTAA are required to explain the prevalence differences between the organ groups.

Comparison of specific diseases in our cohort with the general Canadian population shows a significantly greater prevalence of food allergy, EGID, and autoimmune diseases in liver, heart, and multivisceral transplant recipients (Table IV).²⁰⁻²⁴ Asthma prevalence was not significantly greater in our cohort compared with the general population, and a similar trend was observed for eczema. However, eczema developed at an older age in our cohort (mean age following liver and heart transplantation was 36 and 27 months, respectively), even though it usually presents before 2 years of age in the general population.²⁵ Interestingly, the vast majority of PTAA episodes occurred within the first 2 years post-transplant (89% of liver and 71% of heart PTAA), suggesting a direct effect of transplantation and the associated medications in the pathogenesis of PTAA.

Use of tacrolimus was not found in our analysis as a risk factor for PTAA. This is probably related to the fact that >90% of our patients were maintained on tacrolimus therapy, thus preventing sufficient power for risk analysis. However, recent reports on the resolution of autoimmune cytopenias post-transplant through the conversion of tacrolimus to the mTOR inhibitor sirolimus provide an indirect evidence to the potential importance of CNI in the pathogenesis of PTAA.^{8,16} CNIs were implicated as a potential trigger of PTAA through few proposed mechanisms: (1) Induction of autoreactivity through abnormal thymic T-cell maturation²⁶⁻²⁸; (2) abnormal T-regulatory cell function and number in CNI-treated animals and patients²⁹⁻³¹; and (3) Th1/Th2 imbalance with predominance of Th2 responses leading to allergic tendency.^{32,33} Donor-related factors such as passive transfer of B lymphocytes that

produce food-specific IgE and food allergy have been described in the past but are unlikely to account for the large number of PTAA cases more than 6 months post-transplant.³⁴⁻³⁶

Our analysis yielded additional risk factors for PTAA, including high eosinophil count at 6 and 12 months post-transplant, family history of allergy, and EBV DNAemia. Peripheral eosinophilia and elevated IgE are associated with the use of tacrolimus in liver transplant recipients and were reported in 28%-50% of patients under this therapy.^{1,37} The cause and effect of this peripheral eosinophilia and its relation to allergies post-transplant are unclear and require further research. EBV DNAemia also has been associated with eosinophilia, presence of eosinophilic colitis, and was found by us and others as an independent risk factor for PTAA.^{2,3,38} More recently, EBV-driven PTLT was reported in association with eosinophilic esophagitis after heart transplantation.^{39,40} The association of EBV with PTAA may simply reflect a state of overimmunosuppression; however, EBV itself has the potential to influence the host's immune system to create an environment characterized by predominance of Th2 cytokine activity with less cytotoxic T lymphocyte control.⁴¹⁻⁴³ Taken together, these additional risk factors in combination with CNI therapy may predispose transplant recipients to PTAA and explain the higher prevalence in young heart and liver transplant recipients.

Our findings demonstrate the significant health burden of PTAA on liver, heart, and multivisceral transplant recipients. PTAA led to a variety of chronic symptoms ranging from diarrhea, vomiting, failure to thrive, rash, and pruritus to life-threatening anaphylaxis, anemia, and neutropenia. Seventy-one percent of our affected patients required conventional therapies for allergies and/or autoimmune diseases, and 18% required a change in their immunosuppression regimens. Although 60% of PTAA episodes improved following a directed therapy, 37% did not respond or even worsened. Moreover, 2 patients have died as a result of PTAA, one due to uncontrolled hemolytic anemia and one due to post-transplant HLH. These data support the notion that PTAA spectrum should be recognized as a major health determinant in pediatric transplant recipients' outcome and a clinical and research focus for pediatricians.

Our study is limited by its retrospective nature. Relying on clinical diagnoses found in patients' charts may lead to bias through over or underdiagnosis of PTAA. To mitigate this bias, all patients were assessed independently by 3 authors, and patients were included in the study only if agreed on. Indeed, the similar prevalence of asthma and eczema in liver and heart recipients with those reported in nontransplanted children supports the reliability of our findings. The low prevalence of PTAA compared with the general population in kidney transplant recipients probably reflects the older age at transplant in this group and exclusion from the study of kidney transplant recipients with history of allergy pretransplant.

In summary, our findings show that PTAA are common in pediatric liver and heart recipients and pose a substantial health burden, with significant morbidity and mortality of recipients. The diverse spectrum of PTAA is likely a result of a shared

common pathogenesis and may represent a unique state of post-transplant immune-dysregulation. Further research is required to better understand the pathogenesis of PTAA to improve patient care, their quality of life and long-term outcome. ■

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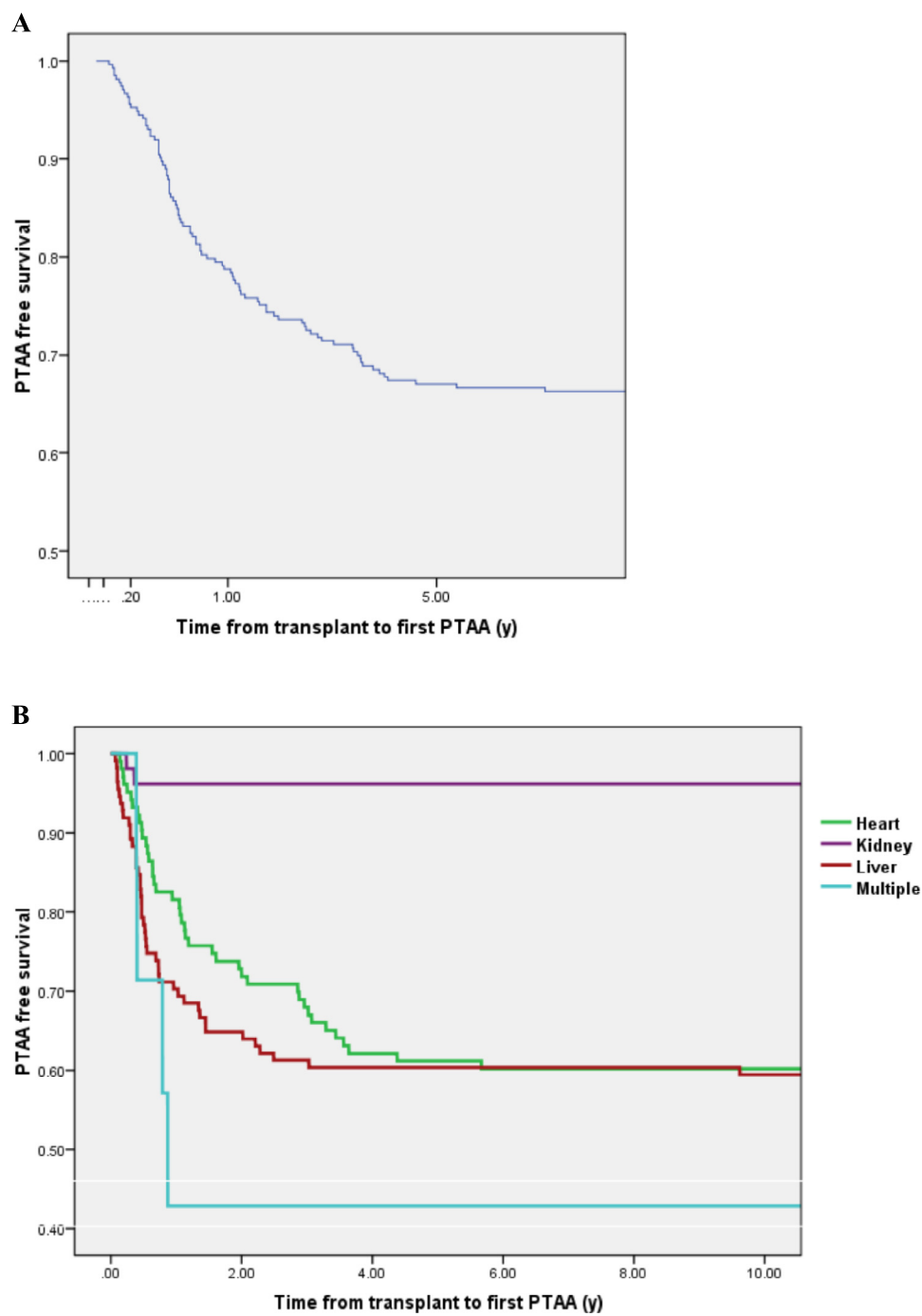


Figure 2. PTAA-free survival following SOT. **A**, PTAA-free survival—all organs. **B**, PTAA-free survival—by organ type.

Table III. Risk factors for the development of post-transplant allergy and autoimmunity among 273 solid-organ recipients

Risk factors	OR	P
Sex (female)	2.2	<.01
Family history of allergy	5	.01
Age (young) at transplantation	1.2 (per year)	<.001
EBV infection		
Overall	2	.029
>2 y of age at transplantation	2.3	.01
Eosinophilia		
6 m post-transplantation (age at transplantation >6 m)	2.8	<.01
12 m post-transplantation (age at transplantation >6 m)	5.8	<.001
Type of immunosuppression (excluding tacrolimus)*		n/s
Length of post-transplant steroidal treatment		n/s
Non-EBV infections		n/s
Acute rejection		n/s
PTLD		n/s
Blood type		n/s

n/s, nonsignificant.

*Induction therapy and maintenance therapy with either mycophenolate mofetil, prednisone, or sirolimus.