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Immunosuppressive Therapy Does Not Prevent the Occurrence of Immunoglobulin E–Mediated Allergies in Children and Adolescents With Organ Transplants

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ABSTRACT

BACKGROUND. Allogeneic organ transplantation has become a common procedure in acute and chronic organ failure. The major limitation, rejection of the allograft by the host's immune system, can be limited by various immunosuppressive drugs that target the adaptive T-cell response. Most of these drugs are used in the treatment of allergic diseases as well, suggesting that transplant recipients under long-term immunosuppressive therapy should not develop any sensitizations or at least not show any clinical signs of allergy. Surprisingly, organ-transplanted children and adults do report symptoms of type 1 allergies, such as allergic rhinoconjunctivitis, bronchial asthma, and food allergies. Thus far, mainly case reports and series on the occurrence of allergy after orthotopic liver transplantation exist.

OBJECTIVE. Our purpose with this study was to evaluate in a cross-sectional design the prevalence of immunoglobulin E-mediated sensitizations and type 1 allergies in solid organ–transplanted children and adolescents and to identify risk factors.

METHODS. Seventy-eight organ-transplanted subjects (50 kidney, 9 lung, 19 liver; mean age: 14.06 ± 5.94 years; range 1.42 to 24.25 years) were studied by standardized interviews (modified International Study of Asthma and Allergies in Childhood [ISAAC] criteria), skin-prick tests, and measurement of specific and total serum immunoglobulin E.

RESULTS. Nineteen patients (24.4%) were found to be sensitized to ≥1 common inhalant or food allergens, as reflected by elevated specific immunoglobulin E levels and/or positive skin-prick test results, and 8 subjects (10.3%) additionally reported a corresponding present history of atopic diseases. No severe anaphylactic reactions were reported. No statistically significant associations with gender, kind of transplanted organ, distinct immunosuppressive therapies, and age at time of transplantation or age at investigation were found (χ^2 test, Fisher's exact test, and

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Key Words

transplantation, sensitization, allergy, IgE, immunosuppression, children

Abbreviation

IgE—immunoglobulin E

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Wilcoxon rank-sum test, respectively). Multiple logistic-regression analysis did not identify any independent risk factor either.

CONCLUSION. This study demonstrates that therapeutic immunosuppression does not control sensitizations and clinical manifestation of type 1 allergies in organ-transplanted children and adolescents.

IN RECENT YEARS, allogeneic transplantation of solid organs has become a successful procedure to enhance the survival of patients suffering from acute and chronic organ failure. However, a wide range of complications and disorders can follow organ transplantation, such as the risk of transmitting diseases from the donor to the recipient^{1,2} and adverse effects of the immunomodulatory medication given to limit rejection of the allograft by the host's immune system.³ Interestingly, there are also reports on the occurrence of immediate-type allergic reactions to common allergens after organ transplantation in patients with no known allergy before transplantation.⁴⁻¹³ Hypotheses on the pathogenesis are diverse; for example, for liver transplantation, adoptive transfer of immunoglobulin E (IgE) antibody-loaded mast cells in the vascular pool of the allograft from allergic donors^{9,11,13} and an allergy-promoting effect of distinct immunosuppressors (namely, the calcineurin inhibitor tacrolimus) have been discussed.^{4,8,10,14,15}

Because the immunosuppressive drugs used to prevent allograft rejection (steroids, calcineurin inhibitors, and proliferation inhibitors) strongly suppress the cellular immune system, in particular T and B lymphocytes,¹⁶ which play a key role in IgE-mediated immediate-type allergic reactions as well,¹⁷ it was expected that transplant recipients would not develop sensitizations or, at least, no clinical signs of allergy. Moreover, the same immunosuppressors are even used to treat severe cases of allergic diseases such as atopic dermatitis and bronchial asthma.¹⁸⁻²⁵

Because so far mainly case reports and series on the occurrence of allergy after orthotopic liver transplantation exist, our aim with this cross-sectional study was to investigate the prevalence of sensitizations and type 1 allergies in pediatric and adolescent recipients of allogeneic liver, kidney, and lung transplants and to identify potential risk factors.

METHODS

Study Population and Study Design

Seventy-eight recipients of kidney, liver, or lung allografts at the Medical University of Vienna from 2004 to 2005 were evaluated in this study (32 male, 46 female; aged 1.42 to 24.25 years; mean age at enrollment: 14.06 $\pm$ 5.94 years). Patients were treated by individual combinations of steroids (prednisolone), proliferation inhib-

itors (azathioprine, mycophenolate mofetil), and kinase and phosphatase inhibitors (cyclosporin A, tacrolimus, and rapamycin).

In a cross-sectional study design, patients' medical charts were checked for date of transplantation and immunosuppressive therapy (immunosuppressor and duration of treatment). Patients (or parents of minors) completed a structured interview based on the International Study of Asthma and Allergies in Childhood (ISAAC) criteria on personal and family history of atopic diseases²⁶ as well as history of immunosuppressive medication. Allergic sensitizations were surveyed by serum-IgE measurements and skin-prick testing. A patient was classified as "sensitized" when presenting with a positive skin-prick test and/or specific IgE >0.35 kU_A/L to at least 1 of the tested allergens, and as "allergic" when additionally reporting a corresponding present history of atopic diseases such as allergic rhinitis, rhinoconjunctivitis, asthma, or atopic eczema.

This project was approved by the local ethics committee, and patients (or parents of minors) gave informed consent.

Total and Specific Serum IgE

Total serum IgE and specific IgE to a standardized panel of inhalant and nutritive allergens were measured by using a solid-phase immunoassay (CAP System, Pharmacia Diagnostics, Uppsala, Sweden). Panels tested in all patients comprised timothy grass, rye, birch, and mugwort pollen, house dust mite, cat and dog dander, and *Cladosporium herbarum* for inhalant allergens, and hen's egg white, cow's milk, codfish, wheat flour, soy bean, peanut, hazelnut, Brazil nut, almond, and coconut for nutritional allergens. When indicated by history, other sensitizations were tested as well. Specific IgE levels >0.35 kU_A/L were considered positive. To account for age, total serum-IgE levels were converted into z units.²⁷

Skin-Prick Testing

After consent of the subject or his or her parents, a standardized panel of allergens was tested in a skin-prick test (birch pollen, 6-grass-pollen mix, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, peanut, cat and dog dander, and hen's egg; Alk-Scherax, Hamburg, Germany) according to manufacturer recommendations. Histamine chloride (10 mg/mL) and sodium chloride (0.9%) were used as positive and negative controls, respectively. The skin-prick test was considered positive if the wheal diameter after 15 minutes was at least 3 mm²⁸ and at least half the diameter of the positive control. Patients were advised to pause antihistamines for at least 2 weeks before skin-prick testing. When indicated by history, additional allergens were included in the panel.

Statistical Analysis

Data were analyzed with SAS for Windows (SAS Institute Inc, Cary, NC). Categorical variables were compared by using the χ^2 test or Fisher's exact test when indicated. The Wilcoxon rank-sum test was used to analyze numeric variables. To evaluate independent risk factors, multiple logistic-regression analysis (enter method) was performed by using "positive skin-prick test," "positive specific IgE," or "allergy" as dependent variables and transplanted organ, age on enrollment, age at transplantation, duration of immunosuppression, first immunosuppressive medication after transplantation, and current medication as independent variables. A P value of $<.05$ was considered significant.

RESULTS

The study population ($n = 78$) consisted of 50 kidney, 19 liver, and 9 lung allograft recipients (mean ages: 13.45 ± 5.5 , 12.57 ± 6.36 , and 20.58 ± 2.65 years, respectively). All patients (or their parents) consented to take part in the structured interview and serum-IgE measurements, but 20 subjects refused to undergo skin-prick testing (25.6%).

Among the 78 patients, 19 (24.4%) were found to be sensitized to inhalant and/or nutritive allergens, with 16 patients (84.2%) showing specific serum IgE and 13 subjects (68.4%) having a positive skin-prick test to at least 1 allergen (Table 1). Eight patients (8 of 78 [10.3%]) additionally reported a corresponding clinical history of type 1 allergic diseases and therefore were designated "allergic" (seasonal rhinitis/rhinoconjunctivitis, $n = 5$; seasonal rhinitis with wheezing, $n = 2$; angioedema on peanut ingestion, $n = 1$; atopic eczema, $n =$

1; Table 2). No severe anaphylactic reactions were reported. The prevalence of both sensitization and allergy was similar among kidney-, liver-, and lung-transplanted patients (Fig 1), whereas the spectrum of sensitizations was diverse between these subgroups: kidney and liver recipients were sensitized to nutritive as well as inhalant allergens, whereas lung recipients displayed sensitizations to inhalant allergens exclusively (Fig 2).

Sensitized patients did not differ significantly from their nonsensitized counterparts in terms of gender, age on enrollment to the study, age at transplantation, family history of allergies, or total time of immunosuppressive medication (Table 1; χ^2 , Fisher's exact, and Wilcoxon rank-sum tests, respectively). Analyzing the immunosuppressive medication in detail, no statistically significant differences were found for any of the immunosuppressors (prednisolone, azathioprine, mycophenolate mofetil, cyclosporine A, tacrolimus, and rapamycin) in terms of prevalence (Fig 3) or duration of treatment (Table 1; Wilcoxon rank-sum test).

Comparing allergic and nonallergic subjects did not reveal significant results either.

To identify independent risk factors for sensitization and allergy, multiple logistic-regression analysis was performed on the total study sample. However, no significant associations between "positive skin-prick test," "positive specific IgE," or "allergy" and any of the independent variables (transplanted organ, age on enrollment, age at transplantation, duration of immunosuppression, first immunosuppressive medication after transplantation, or current medication) were found.

TABLE 1 Patient Characteristics

	Sensitization		Allergic Symptoms	
	Yes	No	Yes	No
N (%)	19 (24.4)	59 (75.6)	8 (10.3)	70 (89.7)
Gender, male/female, n/n (%)	6/13 (31.6/68.4)	25/34 (42.4/57.6)	3/5 (37.5/62.5)	28/42 (40/60)
Age, mean $\pm$ SD, y	14.65 $\pm$ 5.71	13.78 $\pm$ 6.08	14.41 $\pm$ 3.7	13.95 $\pm$ 6.2
Age at transplant (mean $\pm$ SD)	8.95 $\pm$ 5.88	8.61 $\pm$ 5.81	9.33 $\pm$ 5.1	8.62 $\pm$ 5.82
Positive family history, n (%)	11 (57.9)	25 (42.4)	6 (75)	30 (42.9)
Total IgE, median (range), z units	0.66 (−1.17 to 2.88)	−0.46 (−2.07 to 2.85)	0.61 (−0.87 to 2.88)	−0.25 (−2.07 to 2.85)
Positive skin-prick test ($n = 58$), n (%)	13 (68.4)	0	8 (100)	5 (7.1)
Positive specific IgE, n (%)	16 (84.2)	0	7 (87.5)	9 (12.9)
Transplanted organ, n (%)				
Kidney ($n = 50$)	11 (57.9)	39 (66.1)	5 (62.5)	45 (64.3)
Liver ($n = 19$)	5 (26.3)	14 (23.7)	2 (25)	17 (24.3)
Lung ($n = 9$)	3 (15.8)	6 (10.2)	1 (12.5)	8 (11.4)
Immunosuppression, median (range), mo				
Immunosuppression	59 (13 to 181)	56 (2 to 252)	50.5 (16 to 131)	56 (2 to 241)
Prednisolone	44 (10 to 181)	42 (2 to 252)	50.5 (16 to 96)	42 (2 to 252)
Azathioprine	0 (0 to 91)	0 (0 to 145)	1.5 (0 to 90)	0 (0 to 145)
Mycophenolate mofetil	13 (0 to 78)	9 (0 to 93)	24 (0 to 59)	9 (0 to 93)
Cyclosporin A	10 (0 to 181)	19 (0 to 252)	4.5 (0 to 91)	19 (0 to 252)
Tacrolimus	9 (0 to 81)	7 (0 to 81)	18.5 (0 to 55)	7 (0 to 81)
Rapamycin	0 (0 to 36)	0 (0 to 49)	0 (0 to 36)	0 (0 to 49)

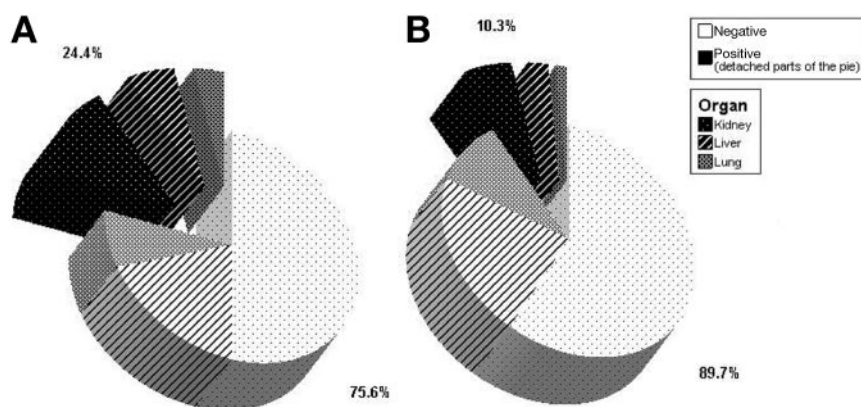
TABLE 2 Characteristics of Sensitized Patients

No.	Organ	Gender	Age, y	Total IgE		Specific IgE (RAST/CAP-Class)		Skin-Prick Test		Symptoms	Current Medication
				kU/L	z units	Inhalant	Nutritive	Inhalant	Nutritive		
1	Kidney	F	18	532	2.88	GP (3), R (3), BP (2), M (1), CI (2), HDM (6), D (1)	HE (1), W (1)	BP, GP, Df, D, C, A	HE	RC, WH	Pred, Aza, Rapa
2	Kidney	F	20	228	2.14	—	CM (2)	—	—	—	Pred, CsA
3	Kidney	M	4	6.68	0.23	—	P (1)	A	P	—	Pred, MM, TAC
4	Kidney	M	11	9.63	−1.68	GP (2), R (1)	—	GP, R	H	RC	Pred, MM, TAC
5	Kidney	M	16	32.7	0.43	GP (3), R (2), C (2)	—	BP, GP, R, C	—	RC	Pred, MM, Rapa
6	Kidney	F	22	42.7	0.66	HDM (2)	—	Skin-prick test	Denied	—	Pred, Rapa, TAC
7	Kidney	F	20	28.1	0.30	—	—	GP, Dp	—	—	Pred, Aza, CsA
8	Kidney	F	16	115	1.53	GP (4), R (4), C (2)	—	GP, A, C, Df	—	RC, WH	Pred, Aza
9	Kidney	F	15	28.5	0.31	HDM (2)	—	Skin-prick test	Denied	—	Pred, MM, Rapa
10	Kidney	F	10	101	1.00	HDM (3)	—	Df	—	—	Pred, MM, CsA
11	Kidney	M	7	44	0.79	—	HE (1), P (2), H (1)	—	P	AN	Pred, Aza, TAC
12	Liver	M	17	440	2.71	GP (2), R (1), BP (3), HDM (5), C (2)	—	BP, GP, Dp, Df, C	—	—	CsA
13	Liver	F	4	28.8	1.00	C (2)	HE (3), SB (1)	Skin-prick test	Denied	—	TAC
14	Liver	F	12	224	1.73	C (3), D (1)	CM (2)	C	—	AE, RC	Pred, Aza
15	Liver	F	15	15.7	−0.22	HDM (3)	—	Dp, Df	—	RC	Pred, MM, TAC
16	Liver	F	7	69.7	1.09	—	HE (1), CM (2)	Skin-prick test	Denied	—	CsA
17	Lung	F	18	7.42	−0.87	—	—	GP	—	RC	Pred, MM, TAC
18	Lung	M	21	5.28	−1.17	—	—	BP, GP	—	—	Pred, MM, TAC
19	Lung	F	20	7.18	−0.9	Asp (1)	—	—	—	—	Pred, TAC, Rapa

F indicates female; M, male; A, *Alternaria tenuis*; Asp, *Aspergillus fumigatus*; BP, birch pollen; C, cat; CI, *Cladosporium herbarum*; CM, cow's milk; D, dog; Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; GP, grass pollen; H, hazelnut; HDM, house dust mite; HE, hen's egg; M, mugwort; P, peanut; R, rye; SB, soy bean; W, whey; AN, angioedema; AE, atopic eczema; RC, allergic rhinoconjunctivitis; WH, seasonal wheezing; Pred, prednisolone; Aza, azathioprine; MM, mycophenolate mofetil; CsA, cyclosporine A; TAC, tacrolimus; Rapa, rapamycin; —, nil.

FIGURE 1

Prevalence of sensitization (A) and allergy (B) among kidney- ($n = 50$), liver- ($n = 19$), and lung-transplanted ($n = 9$) patients. "Sensitization" means a positive skin-prick test and/or specific IgE >0.35 kU/L to ≥ 1 inhalant or food allergens; "allergy" is defined by sensitization and an additional corresponding present history of atopic diseases.



DISCUSSION

In this cross-sectional study we have shown that despite immunosuppressive treatment, solid organ-transplant recipients of pediatric and adolescent age show specific sensitizations to common inhalant and food allergens and even suffer from allergic diseases. The prevalences of sensitization and allergy found in the present study (24.4% and 10.3%, respectively) were actually comparable to random samples of pediatric/adolescent subjects in Europe.^{29,30} Among allergic subjects, seasonal rhinitis and rhinoconjunctivitis with/without wheezing were the predominant symptoms reported (7 of 78 [9%]; Table 2), which likewise is analogous to the Austrian population of similar age.³¹

Type 1 allergic reactions to the point of life-threaten-

ing anaphylaxis to common food allergens have increasingly been reported in transplant recipients, mainly in orthotopic liver-transplanted children.^{5,8–11,13–15} In most cases, the calcineurin inhibitor tacrolimus seemed to be the cause of the de novo development of posttransplant allergies.^{4,8,10,14,15} Underlying immunologic mechanisms could be a suppression of the T helper 1–dedicated cytokine interleukin 2, thereby promoting a shift toward the T helper 2 phenotype,^{8,10} or an increased antigen uptake via the intestinal mucosa, because tacrolimus impairs the permeability of the intestinal epithelium.³² In our study, neither tacrolimus nor any other immunosuppressive drug was statistically associated with the occurrence of sensitizations or allergies (χ^2 test; Fig 3), and no anaphylactic reactions were reported. However,

FIGURE 2
Sensitization patterns of kidney- ($n = 11$), liver- ($n = 5$), and lung-transplanted ($n = 3$) patients to inhalant and/or nutritive allergens.

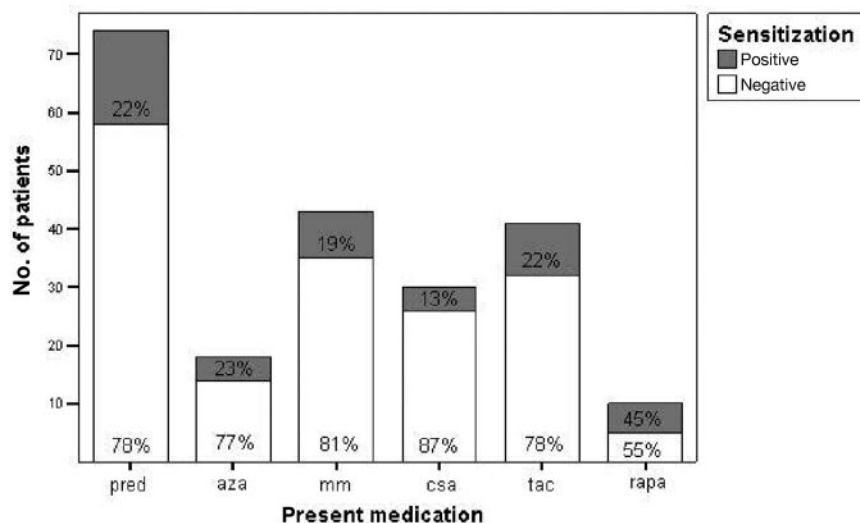
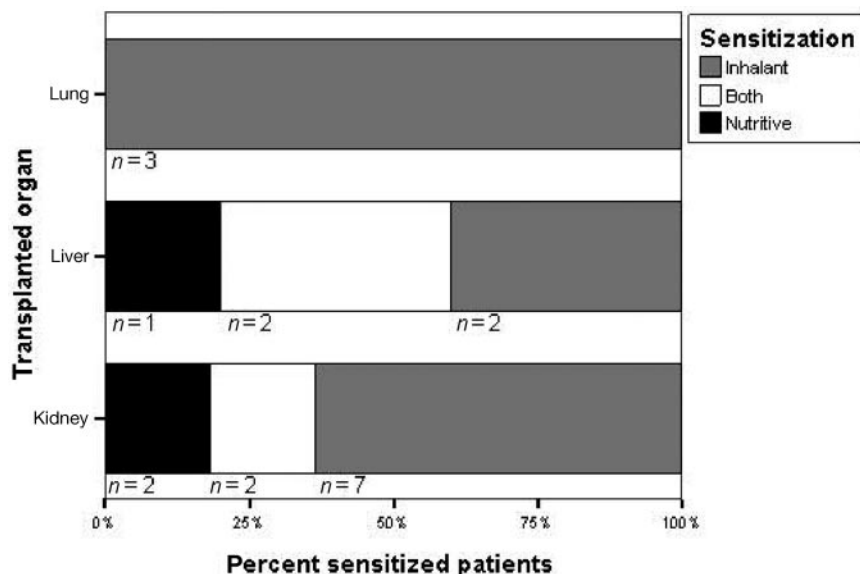


FIGURE 3
Present immunosuppressive medication and sensitization. pred indicates prednisolone; aza, azathioprine; mm, mycophenolate mofetil; csa, cyclosporine A; tac, tacrolimus; rapa, rapamycin.

because tacrolimus is thought to contribute to the development of transplantation-associated food allergy strongest in the setting of the rather immature immune system of infants and young children,^{10,14} it has to be considered that in our study the mean age at transplantation, and in particular the mean age at liver transplantation, was higher than in most of the cited reports (8.69 and 5.96 years, respectively). One tacrolimus-treated kidney-transplant recipient reported angioedema on peanut ingestion and revealed a positive skin-prick test and radioallergosorbent test/CAP class 2 to peanut (Table 2), but it could not be evaluated whether he developed these symptoms under therapy or whether they were already present before this medication. Tacrolimus has also been shown to strongly increase total serum-IgE levels in vivo,³³ thereby potentially favoring the atopic phenotype, but in our study,

total IgE levels did not differ significantly between those treated with tacrolimus and those who were not (Wilcoxon rank-sum test, data not shown).

The diagnoses “sensitization” and “allergy” were distributed equally among the 3 subgroups of organ recipients (kidney, liver, and lung), indicating no impact of the transplanted organ on the prevalence of sensitization or allergy (Fig 1). Interestingly, subgroups revealed distinct patterns of sensitization, with lung-transplant recipients showing sensitizations exclusively to inhalant allergens, whereas the other 2 subgroups presented with a mixed sensitization pattern to nutritive and inhalant allergens (Fig 2). However, this finding is most likely a surrogate for the higher age of lung-transplanted patients at the time of investigation (mean ages: 13.45 ± 5.5 , 12.57 ± 6.36 , and 20.58 ± 2.65 years, for kidney-, liver-, and lung-transplant recipients, respectively); in

addition, the very low numbers of subjects in the subgroups have to be considered.

Sensitized and nonsensitized subjects did not differ significantly in terms of gender, age at investigation, age at transplantation, family history of allergies, total time of immunosuppressive therapy, kind of immunosuppressor, and treatment periods with the various immunosuppressive drugs (χ^2 , Fisher's exact, and Wilcoxon rank-sum test, respectively). To account for different susceptibilities to sensitizations and allergy depending on the transplanted organ, univariate analyses were also performed in the subgroups of kidney-, liver-, and lung-transplanted patients, and results were identical to those obtained in the whole study population (data not shown). However, the small sample sizes, especially in lung-transplant recipients ($n = 9$), certainly limit this analysis.

Trying to identify independent risk factors for sensitization and allergy by multiple logistic-regression analysis did not reveal any significant results, which can possibly be explained by the rather small and inhomogeneous study sample.

CONCLUSIONS

This cross-sectional study demonstrates that pediatric and adolescent solid organ-transplant recipients, although receiving potent long-term immunosuppressive therapy, display allergic sensitizations and symptoms of atopic diseases comparable to the unselected adolescent population. It remains to be established in a longitudinal investigation whether allergy is already present before transplantation and cannot be controlled by immunosuppressive drugs or whether it develops de novo during therapy and to identify risk factors such as a preceding personal history of allergies or the intake of distinct immunosuppressors.

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Immunosuppressive Therapy Does Not Prevent the Occurrence of Immunoglobulin E-Mediated Allergies in Children and Adolescents With Organ Transplants

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