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EDITORIAL

New developments in transplant-acquired allergies

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Abstract

Transplant-acquired allergy (TAA) was firstly described as transplant-acquired food allergy (TAFA) after bone marrow transplantations and mostly observed in a transient form. The picture is complicated by numerous case reports of TAFA after the receipt of liver grafts from donors with no documented history of food allergy. The estimated prevalence of TAFA among young children in the literature has been documented in various studies ranging from 6% to 57%. Although TAA is mostly found to be associated with liver transplantation; it has been recently reported to be related with heart, intestinal, lung and even renal transplantations in adults. Previous reviews of published cases of liver TAA misleadingly emphasized the predominance of children and the absence of TAA in cardiac, pulmonary, and renal transplant recipients. In different studies, the male/female ratio is equal. Literature data suggest that children with TAFA typically present within the first year after surgery and are typically allergic to multiple foods. The pathogenesis of TAA is not still completely understood. Most of the studies support the concept that the functioning liver itself, and not only tacrolimus immunosuppression, is one of the main contributors to TAA in these patients. In the light of recent findings, other possible mechanisms can be summarized as following: (1) the recovery of delayed type hypersensitivity; (2) late manifestation of food allergy; (3) intestinal injury as well as inhibition of cellular energy production by tacrolimus; and (4) transfer of food-specific IgE or lymphocytes. Thus, interplay between hematopoietic cells from the transplanted organ and recipient specific factors (*e.g.*, younger age and atopic background) seem to underlie the development of TAA. Most patients will have symptomatic improvement following reduced immunosuppression and an appropriately restricted diet. Nevertheless, some studies suggest that atopic diseases occur in some of pediatric liver transplant recipients, with manifestations including food allergy, eczema, allergic rhinitis, and asthma. More studies would be needed including greater number of patients to determine whether TAA is transient or not in pediatric/adult solid organ recipients.

Key words: Cyclosporine A; Tacrolimus; Liver; Transplantation; Donor; Recipient; Atopy; Children

Core tip: Transplant-acquired allergy (TAA) was firstly described after bone marrow transplantation and mostly observed in a transient form. Although TAA is mostly found to be associated with liver transplantation; it has been recently reported to be related with heart, intestinal, lung and even renal transplantations in adults. Most studies suggest that the functioning liver itself, and not only tacrolimus immunosuppression, is one of the main contributors to TAA in these patients. Most patients will have symptomatic improvement following reduced immunosuppression and diet. Nevertheless, recent studies suggest that allergic diseases (*e.g.*, eczema, rhinitis and asthma) occur in some of pediatric transplant recipients.

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BACKGROUND

The transfer of allergy from a food allergic solid organ

such as liver donor to a previously non-allergic transplant recipient was firstly reported in 1990's, and has subsequently been reported in one further case[1-3]. The phenomenon is consistent with previous findings of allergy transfer *via* bone marrow transplantation, and the finding that donor-derived stem cells present in a transplanted liver can sustain long-term hematopoiesis in a recipient[4]. The picture is complicated by numerous case reports of transplant-acquired food allergy (TAFA) after the receipt of liver grafts from donors with no documented history of food allergy. An association between tacrolimus therapy after liver transplantation and development of food allergy, TAFA, was first suggested by Lacaille *et al*[1].

What is transplant-acquired allergy?

Transplant-acquired allergy (TAA) was firstly described as TAFA after bone marrow transplantations and mostly seen in a transient form[4]. The estimated prevalence of TAFA among young children in the literature has been documented in various studies ranging from 6% to 57%. TAFA is described mainly after liver, but also after small bowel/intestinal, lung and heart transplantations[5-9]. In different studies, the male/female ratio is equal[1-9]. Literature data suggest that children with TAFA typically present within the first year after surgery and they are typically allergic to multiple foods[4,5,8].

PATHOGENESIS OF TAA

The pathogenesis of TAA is not still completely understood. Most of the studies support the concept that the functioning liver itself, and not only tacrolimus immunosuppression, is one of the main contributors to TAA in this patient population[10-13]. Animal models suggest hepatic mechanisms may be really important for immune tolerance to orally ingested antigens, but there is little direct evidence for this in humans. Watanabe *et al*[14] showed in a mouse model that the liver is found to be one of the sites at which T-helper (Th) 2 lymphocytes specific to a food antigen develop.

A recent study evaluated paired pre- and post-liver transplant sera from children aged 0-36 mo treated at a single centre during 2001-2008. Thirty-five of 50 cases had IgE sensitization to ⩾ 1 food pre-transplant and 18 post-transplant. Food sensitization pre-transplant was associated with severity of liver dysfunction. Young children with severe liver dysfunction appear to have a high prevalence of food sensitization. Hepatic mechanisms may therefore be important for establishing immune tolerance to dietary antigens in humans. However, these findings were not replicated in the renal transplant group[13].

Association with the type of transplantation: liver vs kidney

Liver TAFA has been widely reported now, and is estimated to affect nearly 10% of children who receive a liver transplant. For example, Legendre *et al*[7] described 4 of the 65 children (6%) who underwent liver or combined liver and kidney transplantation acquiring a new-onset food allergy postoperatively. The majority of cases reported have been in young children receiving tacrolimus immunosuppression, and in only a few cases with passive transfer of food allergy from an allergic donor have been documented. Nevertheless, the only reports of liver TAFA in adults have occurred *via* passive transfer from a food allergic liver donor.

Table 1 Predisposing factors for transplant-acquired allergy development in different types of organ transplantation

Predisposing factors	Type of organ transplantation	
	Liver	Renal
Use of MMF/prednisone	-	+
Delayed manifestation of food allergy in recipient	+	+
Recovery of delayed type hypersensitivity	++	+
Transfer of hematopoietic stem and dendritic cells	+	±
Transfer of food-specific IgE	+	+
Passive transfer of food-specific lymphocytes	++	+
Atopic background of recipient	+	+
Younger age of recipient	+	+
Allergy of donor	+	+

MMF: Mycophenolate mofetil; -: No effect; ±: Suspicious effect; +: Positive effect; ++: Strong positive effect.

The accumulating data shows that mostly liver transplantations seem to be associated with new onset TAA suggesting the hematopoietic tissue and dendritic cells play a role in this phenomenon. Pluripotential hematopoietic stem cells and dendritic cells are known to be normally resident in the liver. T-cell activation by antigens migrating through the portal vein occurs in the liver and some liver-resident dendritic cells and liver sinusoidal endothelial cells (LSEC) direct naive $CD4^+$-T cells preferentially to Th2 differentiation. Furthermore, it was recently shown in a mouse model that helper $CD4^+$-T cells in the liver induced an IgE response to a food antigen[14].

At the same time, it could be argued that children with kidney transplants receive more prednisone than children with liver transplants, which may down regulate mast cell degranulation in response to exposure to allergenic foods. Furthermore, unlike children with liver transplants, they receive mycophenolate mofetil, which also suppresses humoral immunity, and, thereby, IgE production. Hällgren *et al*[15] also showed the low IgE concentrations in uremia are suggested to reflect altered T-cell regulation of the IgE production in renal transplant recipients (Table 1).

Relation with the type of immunosuppressant: tacrolimus vs cyclosporine A

Another main contributor to TAA in this patient population is immunosuppressant used in prevention of graft rejection. Tacrolimus is a macrolide agent that is now the primary immunosuppressant utilized in transplant recipients. It has been found to be superior to cyclosporine A (CsA) for rescue therapy as well as for earlier weaning of steroids. Both tacrolimus and CsA share similar toxicity profiles; however, their gastrointestinal side effects have received little attention. An increased prevalence of food

Table 2 Side effects of immunosuppressive agents help developing transplant-acquired allergies in solid organ recipients

Types of side effects	Immunosuppressive agents	
	Tacrolimus	Cyclosporine A
Intestinal injury	+	-
Inhibition of cellular energy production in intestine	+	-
Th1/Th2 imbalance	++	+
IL-2 production	↓↓	↓
IL-5 production	↑↑	↑
IL-10 production	↑↑	↑
IL-13 production	↑↑	↑
IgE production	↑↑	↑
Immunosuppression	++	+

IgE: Immunoglobulin E; IL: Interleukin; Th: T-helper cells; -: No effect; +: Positive effect; ++: Strong positive effect; ↓: Decrease; ↑: Increase; ↓↓: Strong decrease; ↑↑: Strong increase.

allergy noted specifically in children receiving tacrolimus immunosuppression supports the hypothesis that selective suppression of Th1 lymphocytes by the interleukine (IL)-2 inhibitor immunosuppressants such as CsA, and the more potent drug, tacrolimus, promotes Th2 lymphocytes and an allergic immune response. Tacrolimus, however, is more potent than CsA and, in addition, augments the production of IL-5 and IL-13-eosinophil- and IgE-promoting cytokines. It is also known to increase intestinal permeability, which may lead to increased exposure to allergenic proteins and a further shift toward Th2 cytokines and IgE production against these proteins[11,12]. As a result; the immunomodulatory effects of tacrolimus, including its propensity to skew toward a Th2 phenotype by inhibiting production of IL-2, as well as its effects on intestinal permeability, are potentially important (Table 2).

It looks like that under the tacrolimus or immunosuppressive therapy, independent of transplantation type; there is always a chance for TAA development. Insufficient control of allergen-specific responses *via* the Treg-cell compartment under systemic immunosuppression has recently been demonstrated by Eiwegger *et al*[16] as one of the triggering factors.

A present study by Gruber *et al*[17] directly compared the occurrence of allergic sensitization and disease under tacrolimus- *vs* CsA-based immunosuppressive therapy in kidney-transplanted patients. The rate of clinically relevant allergy in patients receiving tacrolimus was twice that in patients receiving CsA (15% *vs* 8%). Their results suggest that post-transplant immunosuppression with tacrolimus is associated with an increased occurrence of IgE-mediated sensitization and probably manifestation of allergic disease.

A recent study by Granot *et al*[18] was performed to demonstrate an association with asymptomatic eosinophilia, elevated total and specific IgE levels under tacrolimus immunosuppression. This study was undertaken to characterize the IgE-mediated immune response, in CsA and tacrolimus-treated, post- orthotopic liver transplanted children. Thirty children and adolescents aged 2-21 years, (6-year post-transplantation), were studied. Immunosuppression-CsA: 10 patients, tacrolimus; 20 patients. Eosinophilia was present in 10/20 of patients treated with tacrolimus and 1/10 treated with CsA. IgE levels were found to be elevated in 8/10 tacrolimus-treated patients and in 2/10 CsA patients. Specific IgE levels to a wide panel of food allergens were positive in 5 tacrolimus-treated patients and to both food and inhaled allergens in 3 patients (2, tacrolimus-, 1, CsA-treated). Four children (tacrolimus-treated) had symptoms of food allergy.

Other mechanisms for TAA

In addition, none of the hypotheses would clearly explain why food allergy develops specifically in tacrolimus- but not CsA-immunosuppressed children if the mechanism was only the Th1/Th2 imbalance and immunosuppression. I think that Th1/Th2 imbalance caused by tacrolimus could not be the only cause for TAA. Although the exact mechanism is still not clear, the reported series confirm their role in triggering allergy in post transplant children. In the light of recent findings, possible mechanisms can be summarized as following: (1) the recovery of delayed type hypersensitivity in patients who could have been in a state of relative immune deficiency, *e.g.*, cirrhosis before transplantation[19]; (2) delayed manifestation of food allergy may be due to limited exposure to dietary allergens prior to transplant, which happens especially in the context of anergy caused by chronic liver disease. Acute and chronic liver disease particularly cirrhosis have long been recognized to be associated with absent delayed cutaneous hypersensitivity responses, which is called as the immune anergy of liver failure. Thus, some food allergic children fail to manifest their food allergy due to the immune anergy caused by their liver failure; (3) intestinal injury as well as inhibition of cellular energy production by tacrolimus in the intestine plays a significant role allowing penetration of protein antigens and skewing the immune response towards Th2 *via* induction of cytokines like IL-10[20-22]; and (4) transfer of food-specific IgE or lymphocytes with specificity for particular food antigens from donors.

In summary, interplay between hematopoietic cells from the transplanted organ and recipient specific factors underlie the development of TAA.

RISK FACTORS?

Transplant recipient-specific factors

Some cases presented in the literature are remarkable for the discordant development of liver TAA in two recipients of the same liver[23]. This highlights the importance of transplant recipient specific factors in this condition.

Younger age: These studies suggest that immature infant immune responses play an important part in their predisposition to allergic disease. Most of the children were less than 1 year of age at the time of transplantation, and the appearance of allergy might be explained by their limited exposure to dietary antigens[13,23]. The reported cases sug-

gest that liver TAA occurs when patients with immature immunoregulatory responses undergo transplantation and fail to suppress the clinical expression of new food allergies.

Atopic background: Those who develop liver TAA may also have greater background risk of allergic disease than those who fail to develop TAA. The majority of patients had a family history of atopy, which might be another risk factor for food allergy after transplantation[13,24].

Transplant donor-specific factors

The occurrence of TAA has also found to be associated with young donor age and donor's atopic diseases[7,11,24].

OTHER ROUTES FOR DEVELOPING TAA: HEMATOPOIETIC STEM CELL, CORD BLOOD STEM CELL, LUNG, HEART TRANSPLANTATIONS

Previous reviews of published cases of liver TAA misleadingly emphasized the predominance of children and the absence of TAA development in cardiac, pulmonary, and renal transplant recipients. Although TAA is mostly found to be associated with liver transplantation; it has been recently reported to be related with heart and even adult renal transplantations[6-9].

Consistently, the absence of new-onset food allergy in the children with isolated kidney transplants is compatible with the earlier literature. Search of the literature till 2006 by Dehlink *et al*[24] yielded only one report of food allergy in a child after kidney transplantation receiving tacrolimus therapy. Furthermore, a recent article by Chehade *et al*[8] reported *de novo* food allergy after intestinal transplantation.

The finding that mostly liver and small bowel transplantations seem to be associated with new onset TAA suggests that the pluripotent hematopoietic stem cells and dendritic cells play a role in this phenomenon. The nature of these transplants also involves transfer of mature donor lymphocytes into recipient tissues. Transfer of donor Th2-B lymphocytes producing specific IgE antibodies in recipient tissue can result in ongoing cellular and humoral activity against the allergen. Transferred cell populations are not deleted by post-transplant immunosuppression[24].

Given the histology of lung tissue, lung transplantation results in limited transfer of pluripotent hematopoietic cells and mature lymphocytes into recipient tissues. As a result, the mechanism of allergy transfer following lung transplantation was postulated to involve passive transfer of IgE-sensitized donor mast cells within the transplanted lung into the recipient. Schuller *et al*[9] reported a case transferring of peanut allergy following lung transplantation. They supposed two mechanisms may explain the observations described for the patient reported in this study: *de novo* development of peanut allergies after transplantation, or passive transfer of peanut allergies from a peanut-sensitized organ donor. Moreover, Bhinder *et al*[25] reported a case developing transient peanut allergy following lung transplantation as well. An alternate mechanism was proposed for passive transfer of immunoglobulin E-sensitized mast cells and/or basophils within the transplanted tissue that subsequently migrate into recipient tissues. The gradual decline in the magnitude of the peanut skin prick test and its return to negative over the course of 1 year suggested the gradual depletion of sensitized cells (B lymphocytes and, possibly, mast cells) in the recipient and supported the initial passive transfer of sensitized cells from donor tissue during transplantation.

We described one of the first patients developing TAA after heart transplantation. This patient was receiving tacrolimus subsequent to heart transplantation and developed angioedema after consumption of dairy products at 12 mo after transplantation. The patient was found to be allergic to multiple foods by both radioallergosorbent test and Immuno Solid-phase Allergy Chip tests[26].

An interesting patient, 2-mo-old Japanese male, developed hemophagocytic lymphohistiocytosis. At 7 mo of age, cord blood stem cell transplantation was performed. He developed veno-occlusive disease (VOD) on day 6 after transplantation. Liver damages due to VOD might contribute to the development of TAFA in this case. It has been shown that Kupffer cells, LSEC and liver dendritic cells uptake and present gut-derived antigens, including food allergens, to naïve T cells, thus resulting in immune tolerance both in $CD8^+$-T cells and $CD4^+$-T cells. Therefore, it is possible that VOD -associated damages to the liver, especially to these cells that can induce immune tolerance, might have suppressed oral tolerance to food allergens and promoted the development of TAFA in these patients[27].

VARIOUS CLINICAL PRESENTATIONS OF TAA

Is this just happening as a food allergy or allergy to other substances such as airborne allergens?

Current literature data suggest that children developing TAA typically present to be allergic to multiple foods and aeroallergens[4,5,8]. For instance: Dehlink *et al*[24] showed food allergy in 2, both food and inhalant allergy in 2; inhalant allergy in 7 cases after different solid organ transplantations.

Eosinophilic gastroenterocolitis

New-onset TAA, whether immediate hypersensitivity type or eosinophilic gastroenteropathy, is an infrequent but potentially serious complication of organ transplantation. Eosinophilic gastroenteropathy is common after transplantation and should be considered in all children with gastrointestinal symptoms undergoing transplantation. The colitis in a study appeared to be mediated by food allergies. Most of the patients had symptomatic improvement following reduced immunosuppression and an appropriately restricted diet[23,28].

Urticaria/angioedema

Our group described one of the first patients developing TAA after heart transplantation. This patient presented

to us with angioedema after consumption of dairy products at 12 mo after transplantation[26].

Atopic disease (atopic dermatitis, allergic rhinitis and asthma)

Shroff *et al*[29] demonstrated presentation of atopic disease in a large cohort of pediatric liver transplant recipients. Food allergy and atopic skin disease symptoms were present in 40% and 56% of cases, respectively. Asthma, allergic rhinitis, or both were found in 66% of cases. The onset of symptoms of food allergy and eczema (median, 12 mo post-transplantation) preceded symptoms of allergic rhinitis and asthma (median of 27 and 30 mo post-transplantation, respectively).

LONG-TERM OUTCOME OF TAA?

The long-term prognosis of TAA after solid organ transplantations is currently obscure. As you imagine, TAA may be transient or persist long period of time and turn into manifestation of an atopic disease.

Transient TAA

Several modes of TAA may be envisaged. Some reports in adults and children with liver transplants attributed the development of food allergy to passive transfer of food-specific IgE antibodies from the allergic donors to the recipients. Passive transfer of food allergy has been described in association with bone marrow transplants and solid organ (liver, combined liver and kidney) transplants, all in adult patients. Passive transfer of donor IgE is unlikely, because the half-life of IgE is only a few days, whereas the allergic reaction occurred 3-12 mo after transplantation. However, it cannot be ruled out the possibility that donor IgE bound to the recipient's mast cells and basophils could have persisted for more than a few days.

The findings were explained by the presence of specific IgE-producing B cells in the donor bone marrow and by the presence of IgE producing B cells and specific IgE antibodies or sensitized mast cells with allergen-specific IgE in the donor organ. For transient cases of anaphylaxis occurring only shortly after transplantation, it has been postulated that passive transfer of donor mast cells or basophils sensitized by donor allergen-specific IgE occurred from donor to recipient *via* transplanted tissues[1-3,7]. The transfer of allergen-specific donor lymphocytes is a more likely possibility[9,19,20,25]. In mice, a secondary hapten-specific IgE response can be elicited by the adoptive transfer of primed B lymphocytes, T lymphocytes, or both[30]. The occurrence of immune hemolytic anemia and autoimmune thrombocytopenia after liver transplantation from donors with such diseases indicates that the transfer of functionally active donor-type B or T lymphocytes can occur in humans.

Persistent TAA

Some studies describe the long-term outcome of food allergy in this population, demonstrating that although a substantial number of food sensitivities are lost, most children remain sensitized to at least a subset of foods for an extended period. For instance: Mavroudi *et al*[31] reported long term outcome of acquired food allergy in 3 pediatric liver recipients as a single center experience. The symptoms of food allergy persisted for 8 years in one of the cases and for 2 years in the other two cases. The long-term prognosis in their cases was excellent and food allergy resolved in all the patients. In Granot *et al*'s[18] study, eosinophilia was present in up to 50% of children and adolescents receiving tacrolimus immunosuppression. The majority of these patients also had elevated levels of total and specific (mainly to food allergens) IgE antibodies. However, most patients were asymptomatic and did not manifest food allergy or asthma[18,32,33].

Nevertheless, Shroff *et al*[29] utilized for 176 orthotopic liver transplanted pediatric recipients at a single institution for manifestations of allergic disease. They demonstrated that atopy occurs in approximately 14% of pediatric liver transplant recipients, with manifestations including food allergy, eczema, allergic rhinitis, and asthma.

CONCLUSION

At the end, most patients will have symptomatic improvement following reduced immunosuppression and an appropriately restricted diet. Nevertheless, some studies show that atopic diseases may occur in some of pediatric liver transplant recipients, with manifestations including food allergy, eczema, allergic rhinitis, and asthma. I think that more studies would be needed including greater number of patients to determine whether TAA is transient or not in pediatric/adult solid organ recipients.

REFERENCES

1 **Lacaille F**, Laurent J, Bousquet J. Life-threatening food allergy in a child treated with FK506. *J Pediatr Gastroenterol Nutr* 1997; **25**: 228-229 [PMID: 9252915 DOI: 10.1097/00005176-199708000-00019]

2 **Phan TG**, Strasser SI, Koorey D, McCaughan GW, Rimmer J, Dunckley H, Goddard L, Adelstein S. Passive transfer of nut allergy after liver transplantation. *Arch Intern Med* 2003; **163**: 237-239 [PMID: 12546616 DOI: 10.1001/archinte.163.2.237]

3 **Lee Y**, Lee YM, Kim MJ, Lee SK, Choe YH. Long-term follow-up of de novo allergy in pediatric liver transplantation--10 yr experience of a single center. *Pediatr Transplant* 2013; **17**: 251-255 [PMID: 23405954 DOI: 10.1111/petr.12051].]

4 **Shalit M**, Amar A, Or R. Allergy development after bone marrow transplantation from a non-atopic donor. *Clin Exp Allergy* 2002; **32**: 1699-1701 [PMID: 12653158 DOI: 10.1046/j.1365-2222.2002.01511.x]

5 **Storek J**, Vliagoftis H, Grizel A, Lyon AW, Daly A, Khan F, Bowen T, Game M, Larratt L, Turner R, Huebsch L. Allergy transfer with hematopoietic cell transplantation from an unrelated donor. *Bone Marrow Transplant* 2011; **46**: 605-606 [PMID: 20562922 DOI: 10.1038/bmt.2010.150]

6 **Niemeier V**, Passoth PR, Krämer U, Bauer J, Oschmann P, Kupfer J, Gieler U. Manifestation of atopic eczema in children after heart transplantation in the first year of life. *Pediatr Dermatol* 2005; **22**: 102-108 [PMID: 15804295 DOI: 10.1111/j.1525-1470.2005.22203.x]

7 **Legendre C**, Caillat-Zucman S, Samuel D, Morelon S, Bismuth H, Bach JF, Kreis H. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney trans-

plant. *N Engl J Med* 1997; **337**: 822-824 [PMID: 9297112 DOI: 10.1056/NEJM199709183371204]
8 **Chehade M**, Nowak-Wegrzyn A, Kaufman SS, Fishbein TM, Tschernia A, LeLeiko NS. De novo food allergy after intestinal transplantation: a report of three cases. *J Pediatr Gastroenterol Nutr* 2004; **38**: 545-547 [PMID: 15097447 DOI: 10.1097/00005176-200405000-00017]
9 **Schuller A**, Barnig C, Matau C, Geny S, Gosselin M, Moal MC, Champion G, Atal L, de Blay F, Massard G, Kessler R. Transfer of peanut allergy following lung transplantation: a case report. *Transplant Proc* 2011; **43**: 4032-4035 [PMID: 22172896 DOI: 10.1016/j.transproceed.2011.08.088]
10 **Hinds R**, Dhawan A. Food allergy after liver transplantation - is it the result of T-cell imbalance? *Pediatr Transplant* 2006; **10**: 647-649 [PMID: 16911484 DOI: 10.1111/j.1399-3046.2006.00563.x]
11 **Levy Y**, Davidovits M, Cleper R, Shapiro R. New-onset post-transplantation food allergy in children--is it attributable only to the immunosuppressive protocol? *Pediatr Transplant* 2009; **13**: 63-69 [PMID: 18179638 DOI: 10.1111/j.1399-3046.2007.00883.x]
12 **Arikan C**, Kilic M, Tokat Y, Aydogdu S. Allergic disease after pediatric liver transplantation with systemic tacrolimus and cyclosporine a therapy. *Transplant Proc* 2003; **35**: 3039-3041 [PMID: 14697973 DOI: 10.1016/j.transproceed.2003.10.033]
13 **Brown C**, Haringman N, Davies C, Gore C, Hussain M, Mieli-Vergani G, Vergani D, Warner JO, Marks SD, Boyle RJ. High prevalence of food sensitisation in young children with liver disease: a clue to food allergy pathogenesis? *Pediatr Allergy Immunol* 2012; **23**: 771-778 [PMID: 23050587 DOI: 10.1111/pai.12011]
14 **Watanabe T**, Katsukura H, Shirai Y, Yamori M, Chiba T, Kita T, Wakatsuki Y. Helper CD4+ T cells for IgE response to a dietary antigen develop in the liver. *J Allergy Clin Immunol* 2003; **111**: 1375-1385 [PMID: 12789242 DOI: 10.1067/mai.2003.1466]
15 **Hällgren R**, Fjellström KE, Odlind B. Total serum IgE in uremia and after renal transplantation. *Scand J Urol Nephrol* 1983; **17**: 365-368 [PMID: 6359389 DOI: 10.3109/00365598309182147]
16 **Eiwegger T**, Gruber S, Geiger C, Mayer E, Dehlink E, Bannert C, Frischer T, Kasper D, Jaksch P, Klepetko W, Akdis C, Szépfalusi Z. Impact of systemic immuno-suppression after solid organ transplantation on allergen-specific responses. *Allergy* 2011; **66**: 271-278 [PMID: 21208218 DOI: 10.1111/j.1398-9995.2010.02475.x]
17 **Gruber S**, Tiringer K, Dehlink E, Eiwegger T, Mayer E, Konstantin H, Kikic Z, Graf A, Szépfalusi Z. Allergic sensitization in kidney-transplanted patients prevails under tacrolimus treatment. *Clin Exp Allergy* 2011; **41**: 1125-1132 [PMID: 21545550 DOI: 10.1111/j.1365-2222.2011.03761.x]
18 **Granot E**, Yakobovich E, Bardenstein R. Tacrolimus immunosuppression - an association with asymptomatic eosinophilia and elevated total and specific IgE levels. *Pediatr Transplant* 2006; **10**: 690-693 [PMID: 16911492 DOI: 10.1111/j.1399-3046.2006.00542.x]
19 **O'Rourke M**, Post J, Fernandez M, Ferran D, Sheiner P, Mor E, Schwartz M, Berner J, Miller C. Recovery of delayed-type hypersensitivity following liver transplantation. *Transplant Proc* 1995; **27**: 1150-1151 [PMID: 7533369]
20 **Perico N**, Remuzzi G. Prevention of transplant rejection: current treatment guidelines and future developments. *Drugs* 1997; **54**: 533-570 [PMID: 9339960 DOI: 10.2165/00003495-199754040-00003]
21 **Perry I**, Neuberger J. Immunosuppression: towards a logical approach in liver transplantation. *Clin Exp Immunol* 2005; **139**: 2-10 [PMID: 15606606 DOI: 10.1111/j.1365-2249.2005.02662.x]
22 **Kawamura N**, Furuta H, Tame A, Kobayashi I, Ariga T, Okano M, Sakiyama Y. Extremely high serum level of IgE during immunosuppressive therapy: paradoxical effect of cyclosporine A and tacrolimus. *Int Arch Allergy Immunol* 1997; **112**: 422-424 [PMID: 9104801 DOI: 10.1159/000237491]
23 **Wisniewski J**, Lieberman J, Nowak-Węgrzyn A, Kerkar N, Arnon R, Iyer K, Miloh T. De novo food sensitization and eosinophilic gastrointestinal disease in children post-liver transplantation. *Clin Transplant* 2012; **26**: E365-E371 [PMID: 22694084 DOI: 10.1111/j.1399-0012.2012.01670.x]
24 **Dehlink E**, Gruber S, Eiwegger T, Gruber D, Mueller T, Huber WD, Klepetko W, Rumpold H, Urbanek R, Szépfalusi Z. Immunosuppressive therapy does not prevent the occurrence of immunoglobulin E-mediated allergies in children and adolescents with organ transplants. *Pediatrics* 2006; **118**: e764-e770 [PMID: 16950967 DOI: 10.1542/peds.2006-0370]
25 **Bhinder S**, Heffer MJ, Lee JK, Chaparro C, Tarlo SM. Development of transient peanut allergy following lung transplantation: a case report. *Can Respir J* 2011; **18**: 154-156 [PMID: 21766079]
26 **Ozdemir O**, Arrey-Mensah A, Sorensen RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation. *Pediatr Transplant* 2006; **10**: 380-383 [PMID: 16677366 DOI: 10.1111/j.1399-3046.2005.00474.x]
27 **Inoue Y**, Ochiai H, Hishiki T, Shimojo N, Yoshida H, Kohno Y. Food allergy after cord blood stem cell transplantation with tacrolimus therapy in two patients who developed veno-occlusive disease. *Allergol Int* 2012; **61**: 497-499 [PMID: 22722810]
28 **Saeed SA**, Integlia MJ, Pleskow RG, Calenda KA, Rohrer RJ, Dayal Y, Grand RJ. Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: role of potential food allergies in pathogenesis. *Pediatr Transplant* 2006; **10**: 730-735 [PMID: 16911498 DOI: 10.1111/j.1399-3046.2006.00538.x]
29 **Shroff P**, Mehta RS, Chinen J, Karpen SJ, Davis CM. Presentation of atopic disease in a large cohort of pediatric liver transplant recipients. *Pediatr Transplant* 2012; **16**: 379-384 [PMID: 22489822 DOI: 10.1111/j.1399-3046.2012.01684.x]
30 **Hamaoka T**, Katz DH, Benacerraf B. Hapten-specific IgE antibody responses in mice. II. Cooperative interactions between adoptively transferred T and B lymphocytes in the development of IgE response. *J Exp Med* 1973; **138**: 538-556 [PMID: 4125546 DOI: 10.1084/jem.138.3.538]
31 **Mavroudi A**, Xinias I, Deligiannidis A, Parapanissiou E, Imvrios G. Long term outcome of acquired food allergy in pediatric liver recipients: a single center experience. *Pediatr Rep* 2012; **4**: e6 [PMID: 22690312]
32 **Frischmeyer-Guerrerio PA**, Wisniewski J, Wood RA, Nowak-Wegrzyn A. Manifestations and long-term outcome of food allergy in children after solid organ transplantation. *J Allergy Clin Immunol* 2008; **122**: 1031-1033.e1 [PMID: 18922566 DOI: 10.1016/j.jaci.2008.08.032]
33 **Rietz H**, Plummer AL, Gal AA. Asthma as a consequence of bone marrow transplantation. *Chest* 2002; **122**: 369-370 [PMID: 12114384 DOI: 10.1378/chest.122.1.369]

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