

Review Article

Food allergies developing after solid organ transplant

Needham JM, Nicholas SK, Davis CM. (2015) Food allergies developing after solid organ transplant. *Pediatr Transplant*, 19: 827–835. DOI: 10.1111/ptr.12613.

Abstract: The development of food allergy is an increasingly recognized form of morbidity after solid organ transplant. It occurs more commonly in liver transplant recipients, although it has also been reported in heart, lung, kidney, and intestinal transplants. Pediatric transplant recipients are more likely to develop symptoms compared to adults, and reports of frequency vary widely from 5% to 38% in pediatric liver transplant recipients. Multiple mechanisms have been proposed in the literature, although no single mechanism can yet account for all reported observations. As food allergy can have at worst potentially fatal consequences, and at best require lifestyle adjustment through food avoidance, it is important for recipients to be aware of the donor's food allergies and particularly in pediatrics, the possibility of completely *de novo* allergies. This review explores the recent reports surrounding food allergy after solid organ transplant, including epidemiology, proposed mechanisms, and implications for practice.

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Key words: pediatric liver transplantation – practice guidelines – T lymphocytes – tacrolimus – immunosuppression – solid organ transplantation

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Accepted for publication 27 August 2015

The development of food allergy is an increasingly recognized form of morbidity after solid organ transplant, ranging from mild, localized symptoms to anaphylaxis or death. This can have a significant impact on quality of life as well as transplant outcomes. The wide variation in case and cohort reporting, both in terms of data measured as well as results reported, makes it challenging to identify trends, to suggest causative mechanisms or simply to counsel patients on managing this new diagnosis. We will review the epidemiology of food allergy in transplantation, methods of identification, possible mechanisms described for this phenomenon, and specific practice implications for transplant physicians.

Identification of post-transplantation food allergies is important because the allergies may be life-threatening and cause significant morbidity, jeopardizing a good quality of life. In fact, the first case report of food allergies developing after transplant involved a donor who suffered from a fatal anaphylactic reaction to peanuts (1), and similarly, severe allergies have developed in recipients (2). A national registry established by the American Academy of Allergy, Asthma and Immunology has reported that multiple foods may cause fatal anaphylactic reactions, and an analysis revealed that most of the individuals did not have epinephrine available at the time of their fatal reaction (3). The potential severity of the allergic reactions, coupled with the preventable nature of the deaths through food avoidance and availability of epinephrine, indicates the importance of recognition of the food allergy and of education for the allergic individuals.

Further, food allergies may affect immunosuppressive therapy dosing after transplantation. In

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; CDC, Centers for Disease Control and Prevention; CNI, calcineurin inhibitor; ENT, ear, nose and throat; GI, gastrointestinal; HLA, human leukocyte antigen; IgE, immunoglobulin E; UNOS, United Network for Organ Sharing.

a retrospective review of 24 patients, 12 patients with a clinical history of food allergies required higher levels of tacrolimus or cyclosporine after undergoing pediatric liver transplantation compared to 12 non-allergic patients. Once an appropriate food avoidance diet was implemented, drug doses required to obtain the same serum levels of immunosuppressants were lower (4). This decrease was attributed to the impact of food allergies on mucosal immunity (5, 6), with subsequent alteration of the gastrointestinal barrier affecting absorption and thus bioavailability of immunosuppressive drugs. This result suggests a possible consequence of food allergy on the dosing of immunosuppressive therapy, and after institution of an appropriate food avoidance diet, the resulting reduction in dose could also lead to a reduction in adverse side effects (4).

Subsequently, this review article will summarize epidemiological data, review possible mechanisms, and discuss the implications for practice for solid organ transplantation. It will not cover blood transfusions, bone marrow transplants, or stem cell transplants, which are reviewed elsewhere (7).

Identification of food allergy

The AAAAI and the American College of Allergy, Asthma, and Immunology define a food allergy as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (8). Adverse health effects of IgE-mediated food allergy may include cutaneous manifestations (e.g., angioedema or urticaria), gastrointestinal symptoms (e.g., vomiting or diarrhea), respiratory symptoms (e.g., wheezing or shortness of breath), hypotension, and laryngeal edema, occurring separately or together. Anaphylaxis is a multi-organ system allergic reaction that may involve the respiratory, cardiovascular, dermatologic, and other organ systems. The elicited history of IgE-mediated food allergy may have three additional characteristic features: (i) rapid symptom onset from food ingestion (within minutes), (ii) severe reactions from even small amounts of food, and (iii) continued reactions with re-exposure (9). These features (Table 1) help differentiate food allergies from the broader differential diagnosis; drug side effects such as angioedema from a CNI may be mistaken for food allergy if a careful history is not performed (10).

After obtaining a detailed history, the best way to diagnose an IgE-mediated reaction is to obtain a positive serum test result for specific IgE

Table 1. Food allergy definition, manifestations, and characteristic history

Food allergy manifestations	Characteristic history
IgE-mediated	
<i>Cutaneous</i> (angioedema, urticaria)	Rapid symptom onset within minutes of food ingestion
<i>Gastrointestinal</i> (vomiting, diarrhea)	Severe reactions from even small amounts of food ingestion
<i>Respiratory</i> (wheezing, shortness of breath)	Continued allergic reactions with food re-exposure
<i>Hypotension</i>	
<i>Laryngeal Edema</i>	
<i>Anaphylaxis</i> : multi-organ system involvement	
Non-IgE-mediated	
<i>Cutaneous</i> (eczema)	Delayed symptom onset within hours to days of food ingestion
<i>Gastrointestinal</i> (nausea, vomiting, diarrhea, abdominal pain, haematochezia)	Reactions from large amounts of food ingestion Continued allergic reactions with food re-exposure

Food allergy, an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.

antibodies, followed by a positive food challenge, with a double-blind, placebo-controlled food challenge having the highest positive predictive value (9). The food challenge is necessary to differentiate true food allergy from food sensitization, in which specific IgE is elevated without a clinical reaction (8). Patients with only food sensitization have no risk of anaphylaxis. Importantly, patients whose initial allergic reaction was anaphylaxis should not receive a food challenge after finding elevated specific IgE serum levels; the risk of a potentially severe reaction during a food challenge outweighs the now low pretest probability of ruling out the food allergy. Patients who have clinical reactions to food without elevated specific IgE may have non-IgE-mediated food allergies and should undergo a trial of elimination, which is avoiding the specific food trigger for 4–8 wk while monitoring for symptom improvement. Non-IgE-mediated food allergies present more commonly with gastrointestinal symptoms, including nausea, vomiting, diarrhea (with and without hematochezia), and abdominal pain. The manifestations and characteristic history of non-IgE-mediated food allergies are summarized in Table 1. The differential diagnosis of these non-IgE-mediated food allergy symptoms includes food protein-induced enterocolitis syndrome and eosinophilic gastroenteritis (11).

Food allergies are reported in the literature by a variety of surrogate measurements, which can potentially confound reported epidemiology if food allergy is not carefully defined, or if confir-

matory testing is not available, as in retrospective reviews. In addition, retrospective reviews may have a specific information bias as patient or parental reports of adverse food reactions also include food intolerance, rather than exclusively reporting true food allergy. Another surrogate measure often reported is the immediate hypersensitivity skin test, where the skin is pricked or punctured with a sample of the suspect food. Although a positive skin test may indicate food allergy, it has a positive predictive value of <50%. Skin tests better serve to rule out an IgE-mediated mechanism as negative predictive values are >95%. Given the need for a reliable history and supportive testing, it can be challenging to definitively identify food allergy and make comparisons across the literature.

Epidemiology

In 1997, the first two case reports of food allergy developing after solid-organ transplantation were published. The first case report involved an adult donor who died of anaphylaxis due to peanut allergy, and the liver and kidney transplant recipient subsequently developed peanut allergy. The case was additionally notable because a second recipient, who received the pancreas and other kidney, did not develop food allergies, despite having the same donor (1). The second case report was a seven-month-old child who developed a milk allergy after a living-related liver transplant from her father, who did not have a history of food allergies (12). These two cases demonstrate the wide variety of food allergy presentation.

More common after liver transplantation

Food allergies are most common after liver transplantation, but have also been reported to develop after intestinal, kidney, heart, and lung transplants. This frequency is not simply a reflection of the frequency with which transplants are performed. UNOS data from 2014 reported that the most common transplant surgery performed was kidney (58%), followed by liver (23%), heart (9%), lung (7%), and pancreas (1%). Intestinal transplants accounted for <1%, with the remaining fraction accounted for by multi-organ transplant surgeries. These values suggest that there may be some unique aspect of liver transplantation or underlying pathology that contributes to the development of food allergies.

As kidney transplants are performed in greater numbers, many authors have remarked on the relative absence of food allergies after kidney transplant compared to liver or liver–

kidney transplant. In a retrospective review of 124 kidney transplant recipients and 65 liver or liver–kidney transplant recipients, none of the kidney recipients developed food allergies, while two of the liver recipients and three of the liver–kidney recipients did develop food allergies (13). This observation was supported by another retrospective review and patient questionnaire that found that 13 of 49 liver recipients developed food allergies, while none of the 21 kidney recipients did (14). To understand this discrepancy, a study of young children with severe liver dysfunction revealed high pretransplant total IgE with both pre- and post-transplant food sensitization (15). At the same time, a different study found that total IgE levels in uremic patients on hemodialysis are low, and decrease further after transplantation, although this study was performed before modern immunosuppressive regimens were implemented (16). Alternatively, it has been suggested that a potential contributor is mycophenolate mofetil; it is part of the immunosuppressive regimen in renal but not liver transplantation and is known to suppress IgE production (17). One case report found that the addition of mycophenolate to tacrolimus was associated with decreased food-specific IgE (18). However, another case report describes a liver transplant recipient who received mycophenolate with tacrolimus but subsequently developed food allergies (19). Thus, the presence of mycophenolate does not completely account for the differences seen between liver and kidney transplant recipients. Although the mechanism is unknown, the literature supports the predominance of liver transplantation in the development of post-transplant food allergies.

Because development of food allergies is most common after liver transplantation, epidemiological data about other types of organ transplants are only available from case reports. After liver transplantation, the reported frequency of food allergy varies from 5.6% to as high as 38%. Shroff et al. reported a rate of 5.6% after 176 cases of liver transplantation at a large, tertiary-care children's hospital based on retrospective review with a follow-up telephone interview. Lee et al. found a rate of 38% in their prospective cohort of 93 South Korean patients undergoing pediatric liver transplant. Other studies report rates of food allergy between these extremes (2, 13, 20). Studies report the frequency of allergy development among their cohort, but incidence is not known as the presentation may occur between a few

months to a few years after the transplant has occurred (20–22).

In the general population, the prevalence of food allergies is 3–4% in late childhood and adulthood, with a peak of 6–8% at one yr of age with a subsequent decline (23–26). Because the reported frequency of food allergies after transplantation exceeds the rates of the general population, such allergies are assumed to be in part attributed to the transplantation or post-transplant immunosuppressive regimen. An additional factor is the increasing prevalence of food allergy in children; according to the CDC, the prevalence has increased from 3.4% in 1997–1999 to 5.1% in 2009–2011 (27). Most epidemiological studies to date are limited by their retrospective nature and lack of case-control trials to eliminate the possible confounding of the increasing prevalence of food allergy in the United States.

More common after pediatric transplantations

While food allergies have been reported after both adult and pediatric transplants, the development of food allergies has been noted at a higher frequency after pediatric compared to adult transplantation. In a case report of a split liver graft from a 15-yr-old donor with a questionable history of peanut allergy, the right lobe was given to a 35-yr-old recipient who developed no allergy, while the left lobe was given to a 19-month-old recipient who developed both peanut and egg allergy (28). Topal et al. (29) described a prospective study of 29 pediatric and 136 adult liver transplant recipients who had no history of atopic disease. Twenty-one patients developed atopic diseases, including allergic rhinitis, asthma, eczema, and food allergy. Food allergy was found to be more common in children ($p = 0.009$), although the other manifestations of atopic disease were found to be similar between children and adults. Even among children aged 0–17 yr, younger ages of both recipient and donor correlated with the development of food allergies after liver transplantation (14). Risk factors for the development of food allergies

Table 2. Risk factors for the development of food allergy after solid organ transplantation

Risk factors
Recipient of liver transplantation
Younger age of recipient
Younger age of donor
Donor with history of food allergy
Recipient family history of atopy

after solid organ transplantation are summarized in Table 2.

Food allergies developing after transplant generally do not progress, and many of the allergies resolve completely. Lee et al. followed 42 patients found to have atopic symptoms, including 35 with food allergy after liver transplantation for a median of 70 months and reported allergy improvement in 69%. Allergy improvement was defined as a symptom-free state without any kind of medical intervention and absent symptomatic aggravation after antigen re-challenge. They also found that older recipients were more likely to have allergy improvement according to their Cox proportional hazard analysis (22). Similarly, a case series found complete resolution in all three patients, but for the youngest recipient, transplanted at age 16 months, resolution required eight yr. The older patients, aged 3 and 16 yr, had resolution after two yr (30). The most common food allergies seen after transplantation include eggs, cow's milk, peanuts, soy, and wheat, but may also include other foods (20, 31). These specific food allergens mirror those most frequently found in the general population. It has not been reported whether there is a relationship between the resolution of allergies with donor allergic status or with number of recipient food allergies.

Mechanisms

While a unifying mechanism has not been found, four different mechanisms have been proposed to explain the development of food allergies after solid organ transplantation (Table 3).

First mechanism: donor allergen-specific, bound IgE

The first mechanism is the passive transfer of donor allergen-specific IgE. In response to the first case report of food allergy developing after liver transplant (1), it was suggested that the

Table 3. Potential mechanisms for the development of food allergies after solid organ transplantation

Four potential mechanisms	Description
Donor allergen-specific, bound IgE	Passive transfer, directly leading to transient allergy
Donor allergen-specific B or T cells	Passive transfer, indirectly leading to transient allergy
Immunosuppressive agents, especially tacrolimus	Suppression of Th1 cellular response, shifting to primarily Th2 cellular response and thus activating cells responsible for allergy
Immature GI tract and immune system of children	GI tract is more permissive for intact food antigens.

donor's liver may have contained peanut-specific IgE, which passed to the liver/kidney recipient, to explain why the pancreas/kidney recipient did not develop peanut allergy. While the half-life of unbound IgE is only a few days, the half-life extends to over 120 days when bound to cells, which could explain the delay of several months between the transplant surgery and development of allergies (32). Although multiple studies have demonstrated elevated post-transplant total and food-specific IgE levels (20, 33, 34), only two studies also measured pretransplant total IgE levels, finding these to be elevated as well in their populations of pediatric liver transplant recipients (15, 35). In addition, the presence of elevated IgE without clinical reactivity is known as IgE food sensitization and is not a true food allergy (19). Thus, it is unlikely that the passive transfer of IgE can completely account for the development of post-transplant food allergies.

Second mechanism: donor allergen-specific B or T cells

Rather than transfer of immunoglobulins, the second mechanism is the transfer of donor allergen-specific B or T cells. In a mouse model, the liver was found to be one of the sites at which Th2 lymphocytes specific to food allergen might be selected (36). The presence of carrier lymphocytes would also account for the time delay in the development of food allergy (37, 38). Hematopoietic lymphoid tissue is transplanted during bone marrow, liver, and small bowel transplants, all of which have been increasingly associated with peanut sensitization (39). One case report describes the food allergies from a multi-organ donor developing in the liver and pancreas–kidney recipients, but not in the kidney-only recipient. It is noted that a section of the donor duodenum is included in pancreas transplantation to drain the pancreatic exocrine secretions, and this difference in transfer of lymphoid tissue could be the reason why the solitary kidney recipient did not develop food allergies (40). Conflicting reports have been made in attempts to verify this mechanism through testing for peripheral microchimerism, which includes detecting donor-specific leukocytes through polymerase chain reaction for comparison of HLA genotypes. In two separate case reports of recipients who both developed food allergies after receiving liver transplants from donors with anaphylaxis from peanut allergy, peripheral microchimerism was found in the skin of one patient (1) but not in the skin or blood of the other patient (41). Overall, the passive transfer of both IgE and the passive transfer of B and T cells can explain the food allergies of recipients

who develop the same allergy as their donor, but they do not account for food allergies that develop from allergy-free donors, or the development of different allergies than donors, such as in the first case report of the infant developing cow's milk allergy from a non-allergic donor (12).

Third mechanism: immunosuppressive agents, especially tacrolimus

The third potential mechanism is the shift to a primarily Th2 cellular immune response as a result of immunosuppressive agents. Th1 and Th2 cellular immune responses are complementary pathways that balance each other through negative feedback. The Th1 response ultimately results in the activation of macrophages, while the Th2 response results in the activation of cells responsible for allergic reactions, namely B cells, which produce IgE, as well as eosinophils and mast cells. Immunosuppressive agents prevent organ rejection by blocking interleukin-2, part of the Th1 cell response. However, in the process of suppressing the Th1 response, immunosuppressive agents also prevent the negative feedback mechanism by which the Th1 response inhibits the Th2 response. Thus, the immune system shifts to a Th2 response, which predisposes the patient to allergic disease (5, 33, 42).

Tacrolimus has especially been implicated in the development of allergies after organ transplant (22, 43). Cyclosporine has been used since 1984, with tacrolimus introduced in 1989 as salvage therapy (44). Although reports of food allergies after transplantation do occur with primary cyclosporine therapy (1, 35, 45), the number of reports increased substantially after the broader introduction of tacrolimus (45). In one study, pediatric liver transplant recipients who developed clinical food allergy were placed on an elimination diet and either switched to cyclosporine or had their tacrolimus dosage reduced. Of the patients switched to cyclosporine, all were able to tolerate the allergen, whereas allergic symptoms recurred in half of the children who remained on tacrolimus (20). Two studies have found that tacrolimus increases intestinal permeability, which exposes the body to more allergens, and thus may increase the development of allergy in predisposed individuals (5, 46). No data are available about the effects on intestinal permeability of cyclosporine in the early post-transplant period, although one study found no decrease in intestinal permeability with either tacrolimus or cyclosporine two to three yr after liver transplantation in adult patients (47).

While the discussion of specific immunosuppressive regimens is outside of the scope of this article, multiple trends have been documented that reflect the changing nature of the field. First, although corticosteroids are administered to the majority of patients, steroid-avoidance and steroid-withdrawal protocols are becoming increasingly common (48). Second, by 2001, the CNI used for maintenance immunosuppression had shifted from cyclosporine to tacrolimus for most organ transplants. Some authors note that cyclosporine remained the CNI of choice for heart transplants after this time (48–50), but in recent years, the shift to tacrolimus has also occurred in immunosuppressive regimens after heart transplantation (51). Third, a trend was noted in the change of antimetabolite choice from azathioprine to mycophenolate mofetil (50). Finally, induction therapy was least common in liver transplants at 18%, compared to as high as 70% in other transplants (49). The changing nature of immunosuppression regimens may be significant given their potential contribution to the development of food allergies.

Fourth mechanism: immature GI tract and immune system of children

The fourth mechanism is the immature GI tract, and immune system of children is permissive for intact food antigens. This mechanism is largely supported by the increased prevalence of food allergies in children compared to adults as previously discussed. Further, Boyle et al. describe a case report of a split liver graft; a donor with questionable history of peanut allergy donated

the left lobe to a child (19 months) who developed egg/peanut allergy, and the right lobe to an adult (35 yr old) who did not develop food allergies (28). Although the only case report of its kind, it does suggest that there is some mechanistic contribution apart from innate immune properties of the liver or the immunosuppressive regimen. Certainly, some food allergies in children may be attributable to the late development of food allergies, coinciding with but not causally related to the transplantation. However, as previously discussed, the rates of food allergies after transplantation (6–38%) exceed those in the general population at all age groups (peak of 6–8% at age 1), and so one or more of these mechanisms must be considered to explain the many observations of food allergies that develop after organ transplantation.

Impact to practice

Suggestions to impact practice include the detection and treatment of food allergies, as well as the screening of organ donors. Knowledge about the possibility of food allergies should prompt providers to elicit allergic symptoms in both the pretransplant and post-transplant history, particularly for pediatric liver transplant recipients given the high prevalence in this population. Specific questions in the history should include a wide review of systems (ENT, respiratory, dermatologic, and gastrointestinal symptoms) as well as the onset, severity, and frequency of symptoms. If symptoms are noted in the pretransplant period, practitioners can utilize the algorithm (Fig. 1) described below. New

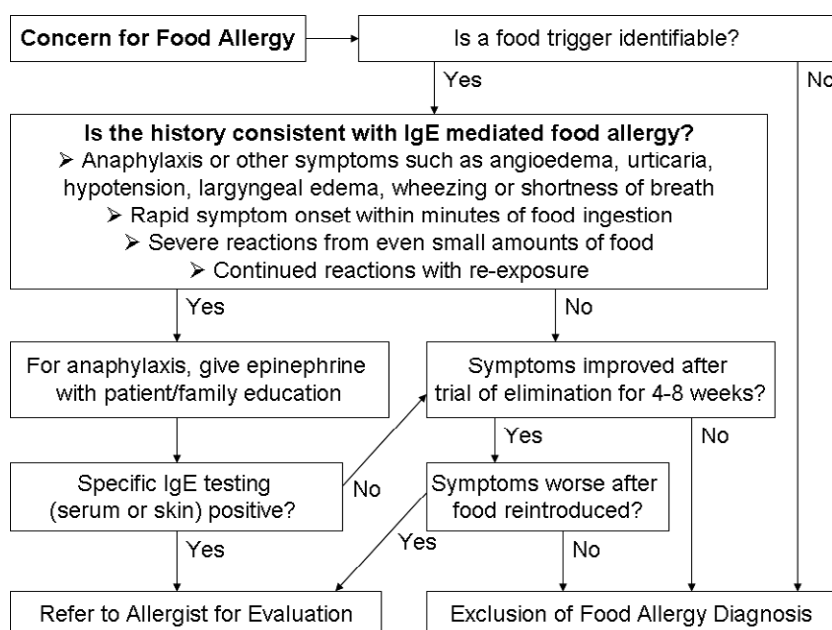


Fig. 1. Algorithm for the diagnosis and management of food allergy for the non-allergist practitioner.

symptoms concerning for food allergy would be expected after the immediate post-transplant period, as studies have all found a delay in several months between the transplant itself and the development of food allergies. Physical exam may be unremarkable if recent exposure has not occurred, or may have longer lasting cutaneous manifestations, such as dermatitis or urticaria.

Treatment algorithm

An algorithm for the diagnosis and management of suspected food allergies is found in Fig. 1. The first-line treatment in food allergies is avoidance of the expected allergen, although the causal food may not always immediately apparent. If an immediate, life-threatening allergy is suspected, the practitioner could then prescribe auto-injectable epinephrine-containing device with patient and family education, and then refer to an allergist for specific testing and longitudinal treatment for the allergy. Beta-blockers may interfere with the efficacy of epinephrine for the treatment of anaphylaxis, so patients should be appropriately counseled and glucagon used in an emergency setting if epinephrine fails to be effective (52–54). Practitioners should consider monitoring serum levels of immunosuppressants after food avoidance has been instituted, as lower drug doses may be required (4). Patients can be reassured that most food allergies that develop after transplantation are transient, although many studies report improvement occurring over several years.

Multiple authors (4, 7, 20, 41) have suggested a standard screening process for food allergies in organ transplant donors. This is especially true for organ donors who died after anaphylaxis due to food allergy, as there are multiple reports of recipients developing the same food allergies as the donor, and there may be some component of passive transfer of these allergies to the recipient. If donor screening has been performed, the finding of donor food allergies could guide testing in the symptomatic recipient, given the increased pretest probability of those specific foods causing the allergy.

Future work

Much remains to be ascertained in this challenging area of research. Although trends have emerged in the presentation of post-transplant food allergies, there is still a lack of consensus on the exact prevalence of food allergy both in the more common scenario of pediatric liver transplantation as well as adult and pediatric non-liver transplantation. The mechanism of the

development of food allergy is also unclear, and thus, explanations for the observed trends are speculative. Particularly relevant to practice is the question of the role of immunosuppressants both in the development of food allergies and as dosing is impacted by food allergy. Large-scale, multicenter, prospective randomized controlled trials are needed to elucidate the true prevalence, severity, and morbidity of disease. Multispecialty cooperative studies would help minimize the potential reporting bias for food allergies by gastroenterologists vs. other transplant specialists. To better counsel transplant patients, longitudinal studies are needed to better understand the course of the allergies and potential for resolution. In addition, national organ registries could fulfill the standard screening of donors, which could give transplant patients more information about their potential risk of food allergy.

Conclusion

In summary, food allergies developing after solid organ transplantation have been increasingly reported since the 1990s. Food allergies are most common after pediatric liver transplantation, but case reports have described them after multiple different solid organ transplants in both adults and children. Allergies do not present until several months after transplant, and most resolve after several years without worsening. Four main mechanisms have been proposed, including the passive transfer of IgE, passive transfer of B and T cells, Th2 cellular immune response as a result of immunosuppressive agents, and the immature GI and immune systems of children. While food allergies may introduce serious morbidity into a patient's life, they can be managed with appropriate recognition and treatment.

Funding sources

Institutional (no outside funding).

Authors' contributions

J. M. Needham: Participated in concept/design, data collection, drafting of the article, critical revision of the article, and approval of the article; S. K. Nicholas: Participated in concept/design, drafting of the article, critical revision of the article, and approval of article; C. M. Davis: Participated in concept/design, data collection, drafting of the article, critical revision of the article, and approval of the article.

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