REVIEW

# Pathophysiology of De Novo Food Allergies After Solid Organ Transplant in Pediatric Patients

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## Abstract

De novo food allergy is a common phenomenon among pediatric solid organ recipients (8.5%-57%) when compared with the general population (0.45%-10%). Other associated disorders include non–IgE-mediated immune reactions and clinical predisposition to asthma and alterations in the oral mucosa. Originally, passive mechanisms (passive transfer of IgE and immune cells) were thought to be responsible for acute, transient cases of food allergies with a previous history of sensitization for a specific allergen in the donor. Recently proposed pathophysiological mechanisms to explain de novo allergies include $T_H2$/B-cell imbalance, regulatory T-cell (Treg) disruption, gastrointestinal immaturity, and altered gastrointestinal permeability. Recent studies also suggest that immunosuppressive drugs, especially tacrolimus, promote naïve T-cell differentiation into $T_H2$ cells, IgE-promoting cytokine production, decreased IL-5 and IL-10 levels, increased IgA levels, and Treg disruption. Such immunological interactions, in conjunction with altered intestinal permeability, intestinal immaturity in children, history of viral infection, and a personal history of allergies or eczema, are thought to explain most clinical cases of pediatric de novo food allergy after solid organ transplantation reported in the literature. A better understanding of the immunological mechanisms underpinning organ donors and recipients may unveil some of the caveats concerning therapeutic management and improve the quality of life of affected individuals.

Key words: Allergies. Transplant. Pediatric. Calcineurin inhibitors. Treg. $T_H17$. $T_H2$.

## Resumen

El desarrollo de alergias *de novo* es un fenómeno común (8,5%-57%) en la población pediátrica receptora de trasplantes de órganos sólidos en comparación con la población general (0,45-10%). Otros fenómenos relacionados incluyen las reacciones no mediadas por inmunoglobulina (IgE), la predisposición al asma y alteraciones de la mucosa oral. Originalmente se han descrito mecanismos de carácter pasivo (transferencia pasiva de IgE, transferencia pasiva de células inmunes) que pueden ser responsables de casos de alergias alimentarias agudas y transitorias en pacientes con historia de sensibilización a ese específico alérgeno en el donante. Recientemente, se han descrito mecanismos fisiopatológicos que pueden explicar estas alergias *de novo*: desbalance entre $T_H1/T_H2$, disrupción de los linfocitos T reguladores (Treg), inmadurez gastrointestinal y alteración de la permeabilidad gastrointestinal. Estudios recientes también han demostrado que los fármacos inmunosupresores, especialmente el tacrolimus, promueven la diferenciación de los linfocitos T nativos en linfocitos $T_H2$, producción de citoquinas potenciadoras de la vía IgE, disminución de los niveles de interleucina (IL) 5 e IL-10, aumento de los niveles de IgA y disrupción de los Treg. Estas alteraciones junto con modificaciones en la permeabilidad intestinal, la inmadurez intestinal, la historia previa de infecciones virales y los antecedentes personales de alergias o eczema, explican la mayor parte de los casos clínicos publicados de alergias alimentarias *de novo* después de trasplantes de órganos sólidos en pacientes pediátricos. Un mejor conocimiento de los mecanismos inmunológicos subyacentes en donante y receptor puede ser útil para describir advertencias respecto al manejo terapéutico que pueden ayudar a mejorar la calidad de vida de estos pacientes.

Palabras clave: Alergias. Trasplante. Pediátrico. Inhibidores de la calcineurina. Treg. $T_H17$. $T_H2$.

## Introduction

Food allergies comprise a spectrum of clinical syndromes characterized by an excessive or anomalous immune response aimed at specific food allergens and involving IgE-mediated mechanisms, non–IgE-mediated mechanisms, or both. Posttransplant food allergies, both passive and active, have been reported in the literature for more than 40 years in pediatric and adult solid organ transplant recipients, especially liver recipients [1-11].

The worldwide prevalence of food allergy ranges from 0.45% to 10%, and the condition usually develops during childhood. In recent years, studies have reflected an increasing incidence with a far-reaching impact on health care systems and wellbeing [7,8]. Given that the reported incidence of food allergies among pediatric transplant recipients (from 8.5% to 57%) is higher than in the general population, several studies have concluded that organ transplants may play a role in these phenomena [1-6].

Development may take from days to years after transplantation, depending on the suspected pathophysiological mechanism involved [1-5,12-16]. Recent literature exploring larger pediatric transplant cohorts shows no differences in the development of de novo food allergies between different types of solid organ transplants, except for kidney transplant having the lowest frequencies [3,17,18].

The most common manifestations include angioedema and gastrointestinal symptoms [5,19,20]. Other clinical signs reported to be associated with solid organ transplantation are gastrointestinal eosinophilia, atopic dermatitis, allergic rhinitis, asthma (no more frequent than in the general pediatric population), anaphylaxis, and even non–IgE-mediated immune disorders [3,5,7,8,15,21-23], the last of which are much more common in the multiorgan transplant group. The incidence of each of these phenomena differs with the various types of organ transplant [3]. Interestingly, these changes may persist for years with no identifiable cause, except for nonspecific immune dysregulation [6,24,25].

IgE-mediated food allergy is considered a type 1 hypersensitivity disorder that can be divided into 2 processes: sensitization (with new development of food-specific IgE [sIgE] but not symptoms) and allergic reaction [26,27].

Failure of tolerance mechanisms drives dendritic antigen presentation to CD4 T cells, which differentiate into $T_H2$ lymphocytes that ultimately produce IL-4 (Figure 1). The latter is responsible for the phenotypic change from B cells to

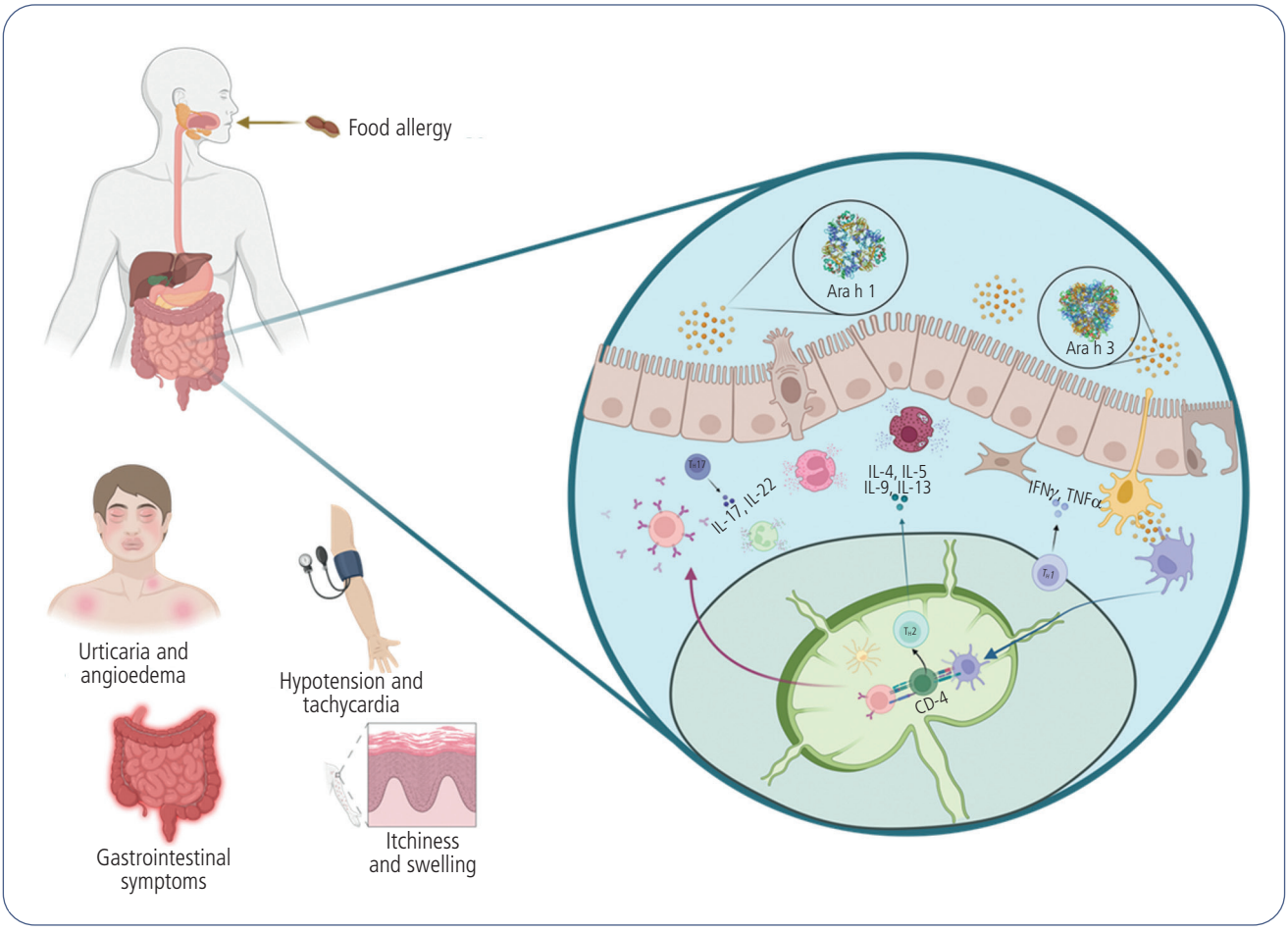


**Figure 1.** Type I hypersensitivity disorder: allergy. Clinical manifestations of food allergies include itching, urticaria, and angioedema. A disturbance in tolerance mechanisms produces an imbalance towards $T_H2$ differentiation resulting in increased IL-4, along with the development of IgE plasma cells. These cells are responsible for the sensitizing mast cells and basophils, which are in turn responsible for the clinical spectrum.

IgE plasma cells. These secrete sIgE, which bind and sensitize mast cells and basophils. During the allergic reaction, we can differentiate between an immediate phase, led by these mast cells, and a late phase, led by eosinophils attracted to the site of inflammation by production of $T_H2$-secreted IL-5 and other chemokines [26-28].

Studies have also suggested the involvement of other cell types, such as T follicular helper cells [7], which play a pivotal role in fostering immune tolerance to self-antigens and exerting regulatory influence over the extent of damage caused by immune cells during allergic reactions. Murine models have revealed that depletion of these cells and genetic mutations causing alterations in their function disrupt tolerance. T follicular helper cells exert this function by secreting immunosuppressive cytokines (eg, IL-10), blocking the release of proallergic substance by mast cells, and interfering in the suppression of the lymphocyte response [29,30].

## Pathophysiology of De Novo Food Allergies

Theories proposed to explain these allergies can be divided into passive processes (which include hypotheses 1 and 2) and active processes (which account for the remaining hypothesis mentioned below) (Figure 2).

Passive processes should not be considered de novo food allergies but instead transferred food allergies. Nevertheless, their presence in the literature as possible pathophysiological mechanisms requires them to be included in this manuscript.

### *Hypothesis 1: Transfer of allergen-specific IgE*

Allergen-specific IgE are transferred to the recipient during the transplant, causing a type 1 hypersensitivity reaction [1,17].

The hypothesis has been supported for many years, although the fact that the half-life of unbound IgE is a few days and that of cell-bound IgE is up to 120 days makes this theory unviable for explaining the cause of de novo food allergies, as most develop within the first 2 years and persist for up to 8 years. Some studies have also reported recovery of allergen-specific IgE levels to normal values after transplant, reflecting IgE cell-bound depletion [2-4,6,12,15,18,21,27].

Several studies have been carried out to test this hypothesis, finding posttransplant serum total and allergen-specific IgE levels higher than previous values. Nevertheless, increased IgE levels would only account for sensitization to food if they were not associated with clinical symptoms [1]. Moreover, IgE has also been found in the donated organ [21].

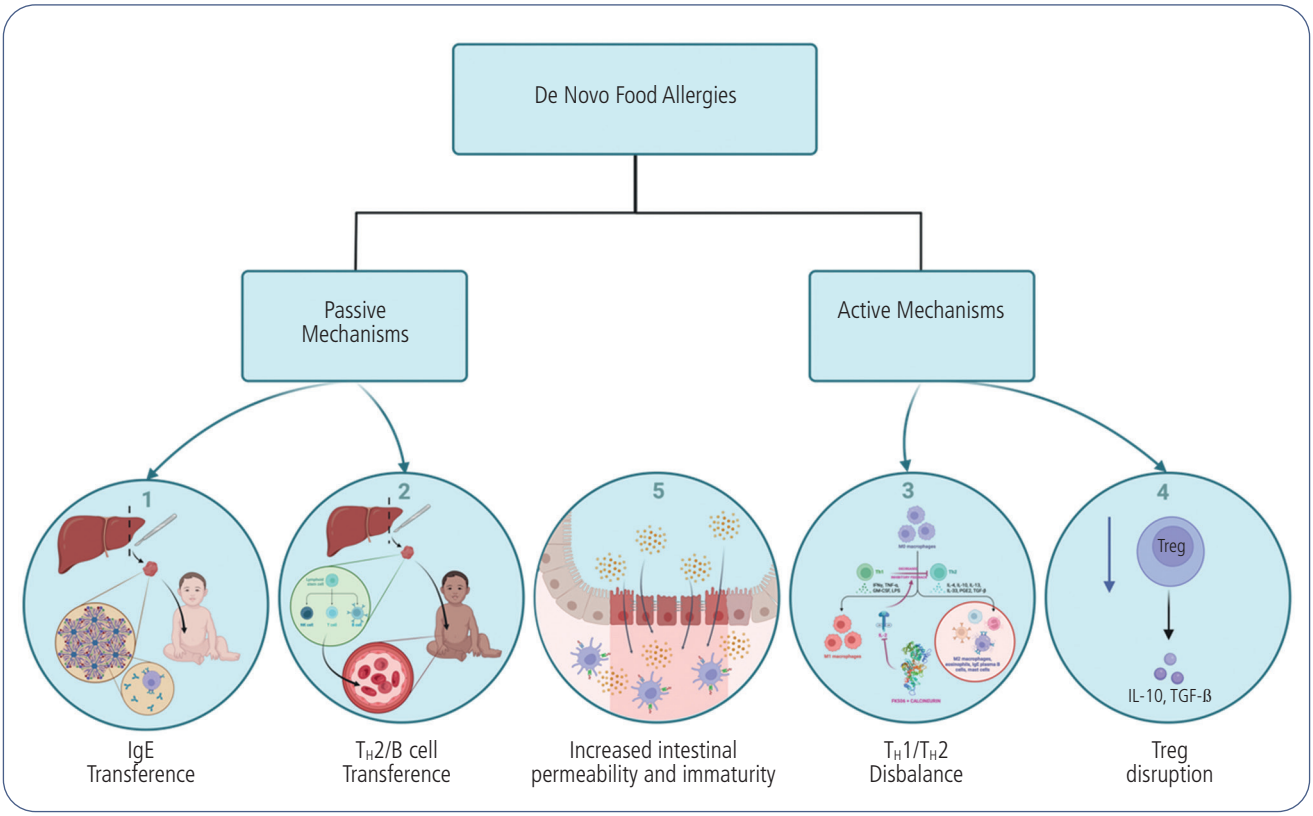


**Figure 2.** Hypothesis proposed to explain the development of de novo food allergies: *1*) Transfer of IgE, proposed to be responsible for the passive transfer of allergies between donor and recipient; *2*) $T_H2$/B-cell transfer, proposed as an alternative hypothesis to explain de novo food allergies, especially for chronic allergies; *3*) Increased intestinal permeability and immaturity, proposed as a cofactor that explains the higher prevalence of de novo food allergy in the pediatric population and a possible mechanism that alters Treg function; *4*) $T_H1/T_H2$ imbalance, proposed as the main mechanisms responsible for de novo food allergy and the association with immunosuppressive drugs; *5*) Treg disruption, a new mechanism that is complementary to the $T_H1/T_H2$ imbalance and the effect of immunosuppressive drugs.

Increased pretransplant serum IgE levels in patients with liver dysfunction and lower IgE levels in hemodialysis patients waiting for an organ have also been used, among other findings, to explain the higher risk of developing de novo food allergies in liver recipients than in kidney recipients [1].

This hypothesis could account for the few case reports on transient, acute food allergies with a previous history of food allergy and increased pretransplant serum IgE levels in the donor. Cases of acute anaphylaxis, caused by food allergens may be explained by the transfer of allergen-specific IgE bound to mast cells or basophils. Nevertheless, the hypothesis fails to explain how these allergies can be transferred to some recipients but not to others, and most studies did not include measurement of specific IgE levels before transplant in the recipient [1,21,31]. Ozbek et al [16] did not find donor-positive skin prick tests for those allergens responsible for the phenomena in the recipients they assessed.

New studies measuring allergen-specific IgE levels in solid organ recipients before and after surgery are required to determine the percentage of cases of de novo food allergies that can be accounted for by passive transfer.

### *Hypothesis 2: Transfer of lymphocytes*

Donor-derived stem cells in the liver can sustain long-term hematopoiesis in the recipient. Therefore, it was proposed that lymphoid tissue be transplanted during liver and small bowel procedures, suggesting that the development of these phenomena is caused by the transfer of allergen-sensitized T and B cells [1,12,17,21,27].

This hypothesis has also been used to explain the higher incidence of de novo food allergies in liver recipients than in other transplant recipients, since liver cells seem to be involved in phenotypic changes in lymphocytes. Besides, the probability of receiving pluripotent hematopoietic stem cells is higher in larger organs. Transfer of mast cells or basophils has been hypothesized to play a role in lung transplants, in which the transfer of immune cells is limited. A similar phenomenon has been described for small bowel transplants [12,21].

Ambiguous results have been reported from molecular studies based on the analysis of leukocyte HLA microchimerism (using DNA extracted from peripheral blood cells and from skin cells to identify HLA-DRB1 alleles) [1,32]. Animal-based studies have demonstrated that the liver may be involved in allergen-specific $T_H2$ selection, since hepatic sinusoidal endothelial cells and dendritic cells lead to differentiation of T cells into $T_H2$ cells on exposure to food allergens transported by the portal vein. Mouse models have demonstrated that these $T_H2$ cells are involved in the response to food antigens [1,12,21].

However, we encounter similar problems to those reported for the passive transfer of allergen-specific IgE, as these cells have a limited lifetime, and this hypothesis does not explain those cases of de novo food allergies with no previous history in the donor.

### *Hypothesis 3: Drug-mediated mechanisms*

$T_H1$ cells are involved in the activation of macrophages, whereas $T_H2$ cells activate IgE B cells, eosinophils, and mast cells. It has been demonstrated that immunosuppressive drugs are responsible for this imbalance, since they block the action of IL-2, causing decreased inhibitory feedback from $T_H1$ and, thereby, increasing the $T_H2$ response (Figure 3). Furthermore, calcineurin inhibitors promote $T_H17$ differentiation [1,12,33].

As reported elsewhere, the calcineurin inhibitors cyclosporine A and tacrolimus are the most common drugs in maintenance regimens. Calcineurin inhibitors bind to immunophilins, which are cyclophilins for cyclosporine A, and tacrolimus binds to FKBP12. A molecular complex is then formed between these proteins and calcineurin, inhibiting its phosphatase activity by preventing activation of NFAT1c and, therefore, synthesis of IL-2 and IFN-$\gamma$ (inhibiting cellular immunity and, to a lesser extent, humoral immunity) (Figure 4). Other pathways affected include phosphatase I and NO synthase (involved in degranulation and leukocyte apoptosis), dendritic cell function, and leukocyte migratory capacity [34,35].

These drugs have different oral absorption patterns with high interindividual variability, as they are substrates of CYP3A4/CYP3A5 and P glycoprotein [35]. This imbalance is more prevalent during therapy with tacrolimus than with cyclosporine, as is increased production of IgE-promoting cytokines and eosinophilia. These findings may explain the increased incidence of de novo food allergies in patients treated with tacrolimus. Differences in this pharmacological effect have been demonstrated after switching therapy.

Kawamura et al [36] found that serum IgE levels are proportional to tacrolimus plasma levels, although this does not seem to be related to IL-4. Low doses of cyclosporine seem to increase IgE levels (through inhibition of IL-4 and IFN), whereas

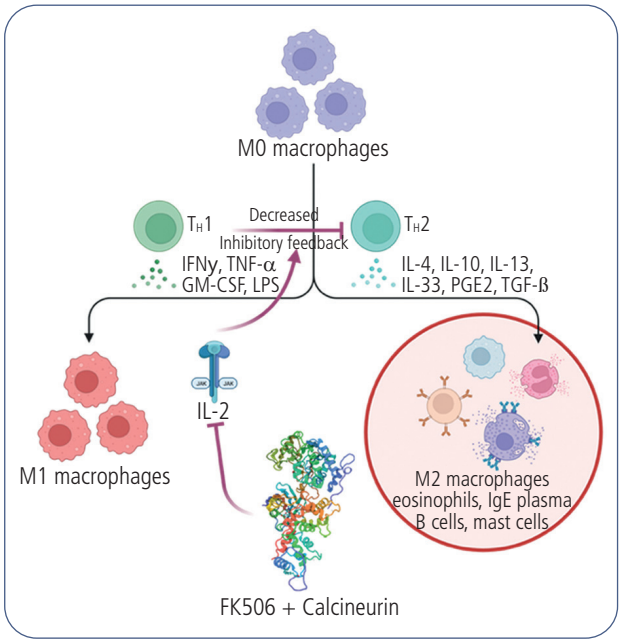


**Figure 3.** Imbalance in T-cell subsets. Tacrolimus is considered to produce an increase in the $T_H2$ population, leading to an imbalance in T-cell populations, an increased inflammatory response, and decreased control over this. It has also been suggested that this imbalance produces an increase in the $T_H17$ subset and a decrease in Treg cells. All these factors contribute to the production of proinflammatory cytokines and the suppression of anti-inflammatory processes.

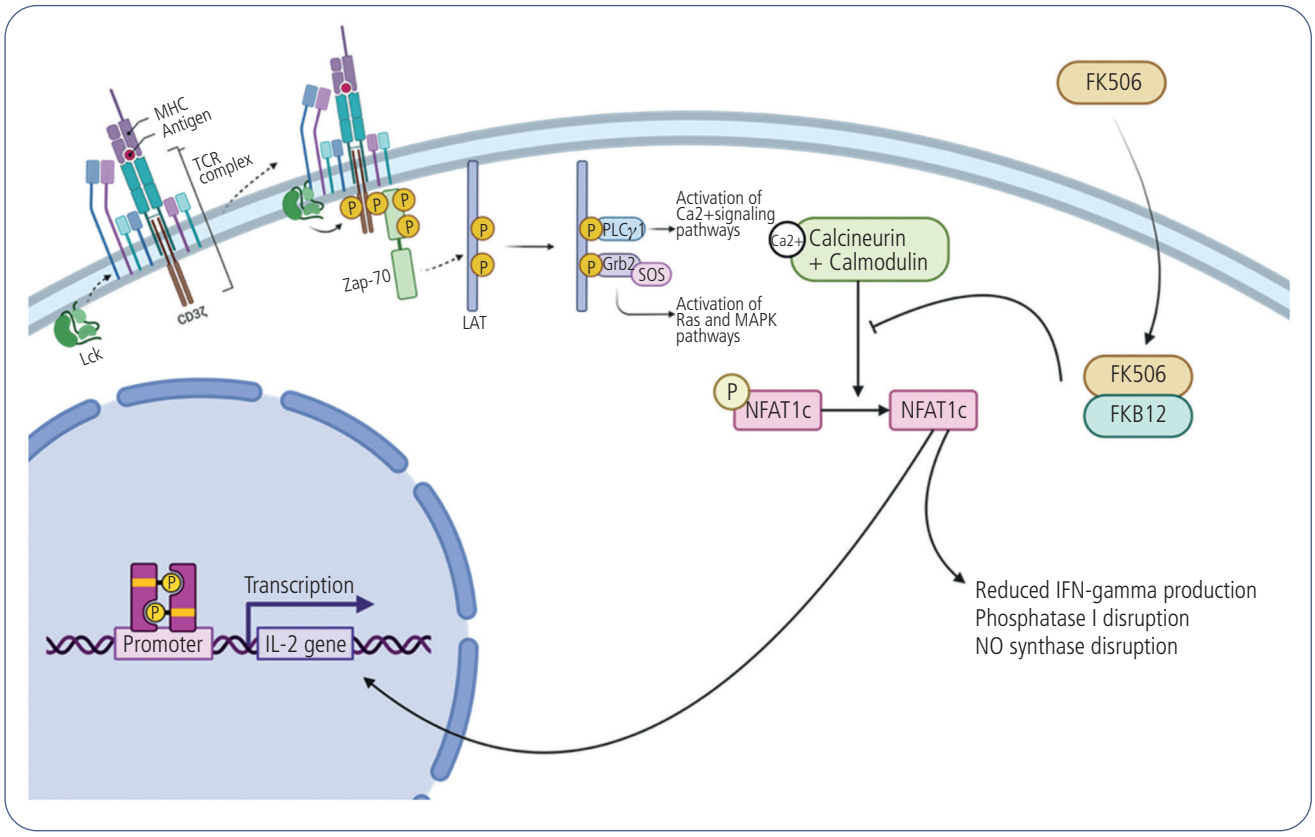


**Figure 4.** Mechanism of action of tacrolimus. It acts by inhibiting activation of NFAT1 and thus reducing the production of IFN-$\gamma$, phosphatase 1, and NO synthase. These pathways play a key role in the function of leukocytes and dendritic cells.

high doses decrease IgE levels. Mast cells and basophils may be important in these mechanisms.

Tacrolimus has been shown to be inefficient for suppressing the $T_H17$ subset, and these cells may be involved in chronic rejection [37,38]. Nevertheless, it should be important to consider the effect this may have on the development of de novo food allergies, since recent studies have demonstrated increased IL-17 levels in pediatric patients with food allergy, asthma, and atopy [39]. Its mechanism of action consists of an increased production of proinflammatory cytokines such as IL-1, IL-6, and IL-18 (Figure 5). Some authors even suggest that IL-17 could be used as a marker of severity or as a marker of response to immunotherapy in allergic patients [39,40].

The $T_H17$ subset has been defined as a plastic cell population dependent on microenvironmental changes. The polarization of these cells can be driven towards a $T_H2$ phenotype. Therefore, the involvement of $T_H17$ should be considered when analyzing this interplay between immune factors, immunosuppressive drugs, and de novo food allergies [41-44].

To overcome this $T_H17$ imbalance in other pathologies where tacrolimus is used as an immunosuppressant, several therapeutic options have been proposed, one of them being the use of *Lactobacillus acidophilus* to regulate the $T_H17$ and Treg populations through the intracellular adhesion molecule 3–grabbing nonintegrin homolog-related 3 (SIGNR3) pathway [45,46]. Another therapeutic option is the combination of metformin with tacrolimus [47].

Currently, it is difficult to say whether there are clinical differences between tacrolimus and cyclosporine, as most patients are treated with tacrolimus. Some patients benefit from switching therapy whereas others do not [3,6,17,19,20,27,48]. Clinically, tacrolimus is preferred over cyclosporine because of its efficacy and the numerous adverse effects of cyclosporine A (eg, hypertrichosis, gingival hyperplasia) [49].

Given the difference in prevalence between different types of solid organ transplant, many authors have suggested that the immunosuppressive pharmacological regimens used for solid organ transplants may help to explain these differences, along with other factors (see above).

Mycophenolate mofetil is obtained from *Penicillium brevicompactum* and works by selectively and reversibly inhibiting inosine monophosphate dehydrogenase (which regulates de novo guanine synthesis) and thus reducing GMP, GTP, and dGTP, which are essential for T- and B-cell proliferation [35].

Mycophenolate mofetil has been shown to reduce IgE levels and, therefore, has been used to explain the differences between liver transplant and kidney transplant, where the use of this drug is more frequent. Nevertheless, as studies may report contradictory results, its involvement in pathophysiology remains unclear [1,50].

In 2023, Haflidadottir et al [51] reported a decreased prevalence of this phenomenon among patients treated with mycophenolate mofetil, attributing it to its effect on DNA

synthesis in B and T cells and on its ability to induce immune tolerance through upregulation of Treg. Furthermore, when used in combination with tacrolimus, it can also inhibit IL-17, thus reducing this subset imbalance that may favor de novo allergies [52].

Further studies are required to determine the effect of this drug, although this may be difficult, given that the frequency of use is decreasing owing to its frequent adverse effects in the pediatric population.

Prednisone is a corticosteroid that is commonly used as an immunosuppressive drug, as it disrupts leukocyte migration, fibroblast function, and endothelial cell function and suppresses numerous cytokines (IL-1, IL-6, TNF-α) through various pathways. It also reduces serum eosinophil and basophil levels, as well as eosinophil and mast cell counts in inflammation. Moreover, it reduces all T-cell subset levels [35].

Therefore, prednisone may be involved in kidney transplants by reducing mast cell degranulation and, thus, decreasing the incidence of de novo food allergies [21]. Even though Marcus et al [3] found a lower prevalence of these allergies among kidney recipients, they did not report significant results for post-transplant immunosuppression regimen in their multivariate analysis. Moreover, these authors reported significant differences in the incidence of de novo food allergies between kidney and heart recipients (both having prednisone in their immunosuppression regimen).

Sirolimus is an mTOR inhibitor produced by *Streptomyces hygroscopicus* that hampers progression from G1 to S, thus affecting T- and B-cell proliferation. Furthermore, it blocks calcium-dependent T-cell proliferation, IL-promoted

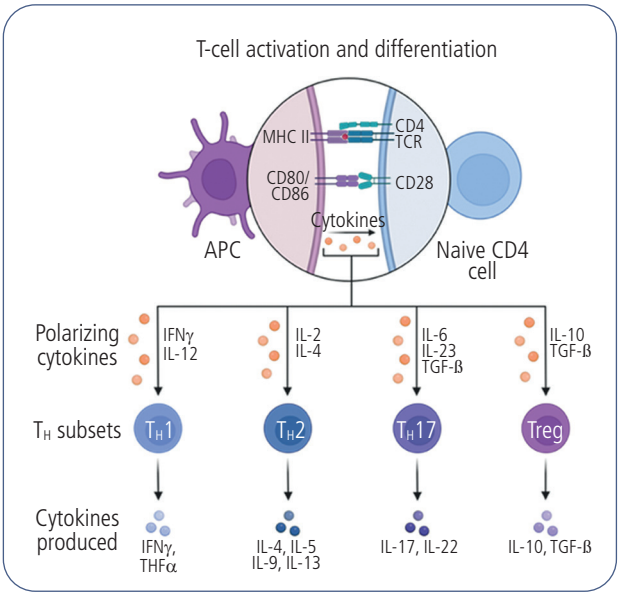


**Figure 5.** T-cell subsets and their cytokine production. $T_H1/T_H2$ imbalance is proposed as one of the mechanisms responsible for de novo food allergy. The increased $T_H2$-cell count is associated with increased production of IL-4 and other cytokines that play a pivotal role in the development of allergic processes. $T_H17$ was recently proposed as a possible agent involved in de novo food allergies by producing inflammatory cytokines. Disruption of Treg function and decreased Treg levels may also be involved.

immunoglobulin production, and growth factor production in nonimmune cells. Some of its mechanisms include the inhibition of IL-9, thus disrupting the pathway by which IL-9 promotes mast cell survival and function (potentially beneficial for allergies, since IL-9 acts as a $T_H2$ cytokine cell promotor) and the increase in the number of functional Treg cells [6,35]. This increase may counteract the decrease in the Treg population caused by tacrolimus.

Reports regarding the resolution of autoimmune cytopenia when switching from tacrolimus to sirolimus highlight differences in the mechanisms of action of these 2 drugs and the potential use of sirolimus as an alternative treatment for patients who develop de novo food allergies [3,6]. The switch is associated with considerable adverse effects (eg, hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, leukopenia) and with an increased risk of acute rejection during conversion and maintenance therapy.

Although this interplay between immunosuppressor and $T_H$ subset imbalance may be sufficient to explain these phenomena, the complexity of the pathophysiological mechanism is extraordinary. Furthermore, recent studies suggest functional heterogeneity among $T_H$ subsets leading to plasticity in cytokine production [41].

When thinking about switching therapy, it is necessary to consider both drawbacks and benefits [6,35]. These phenomena usually resolve by adapting diet, although complex cases may require further action [6].

### *Hypothesis 4: Treg disruption*

Other mechanisms proposed include disruption of Treg, given that some studies have found Treg levels to be decreased in patients treated with tacrolimus [38,45-47]. Treg play an important role in the pathophysiology of allergic phenomena, as they are responsible for the maintenance of immune tolerance to allergens [53,54].

Some studies in liver transplant recipients have found decreased IL-5 and IL-10 levels but increased IgA levels (which, according to animal studies, are involved in the development of food allergies). Tacrolimus seems to be more efficient for inhibiting IL-2 than cyclosporine [1,21,27,55-58].

Gallon et al [59] compared the effect of tacrolimus and sirolimus on $T_H$ subsets, showing that tacrolimus decreased the number of Treg, whereas sirolimus exerted the opposite effect and was even able to avoid the effect of tacrolimus on this subset when used in combination.

### *Hypothesis 5: Intestinal permeability*

Tacrolimus has been demonstrated to increase intestinal permeability without histological alterations and, therefore, increases the risk of de novo food allergies [1,5,21,27,57]. Studies based on permeability to sugar probes have shown increased permeability, probably via a transcellular pathway, in patients treated with calcineurin inhibitors. This permeability has been associated with mitochondrial impairment [60-64].

Data from the literature showed that peanut allergy was transferred to a pediatric recipient but not to an adult recipient, thus highlighting the presence of mechanisms that explain the differences in incidence between children and adults [1].

Therefore, it is also important to consider the immaturity of the gastrointestinal tract and immune system (owing to the presence of a $T_H1/T_H2$ imbalance that favors $T_H2$ allergic responses), since the incidence of this phenomena is higher in children than in adults. Several studies have shown that increased permeability enhances the stimulation of submucosal immune cells by food allergens, thus promoting the development of oral food allergies [65].

Intestinal barrier maturation takes place during the first 2 years. Some studies have even found a correlation between age and the incidence of these phenomena, reporting an improvement over the years. Differences in age between kidney transplant recipients and other organ transplant recipients have been used to explain the scarce cases reported for the former [1,3,14,21,48].

De novo food allergies have been reported after viral infection, probably owing to an increase in intestinal permeability [66].

### *Hypothesis 6: Microbiota*

Recent studies highlight the role of microbiota in the development of food allergies through imprinting of Treg cell pathways [54,67,68], leading to a loss of tolerance of these antigens to specific food allergens. Furthermore, the intestinal microbiota has been shown to be less diverse in children with allergies [65]. Disruption of microbiota due to previous liver dysfunction has also been suggested as a possible mechanism [48].

## Impact of Medical and Family History

Among the risk factors associated with these phenomena, we can find a previous history of food allergies and atopy in either the donor or the recipient [7,8,12,21,69].

The latter seems to support passive mechanisms, although it can also account for the development of pre-existing food allergies in the recipient after recovery of liver function, since liver impairment may lead to the absence of clinical manifestations [12,21]. While this may explain some of the reported cases of de novo food allergies in liver recipients, it cannot account for such cases in other solid organ recipients.

Young age is also important. Immunological mechanisms that may be responsible for this increased tolerance, and thus the increased prevalence of food allergies among children, include decreased IgA or CD8 T cells, disrupted intestinal permeability due to poor development, and the effect of drugs or viruses [16].

## Clinical Management and Other Considerations

An initial approach based on an allergy-focused clinical history from both donor and recipient prior to solid organ transplantation (SOT) is recommended. This enables us to understand the immunological scenario while emphasizing any reported cause of previous history of food allergies, atopy, and/or predisposition to immune-mediated disorders. It is essential to further explore any severe allergic reaction to food, hymenoptera venom, and drugs with the family of the donor, although specific recommendations are difficult to establish in view of limited data. As with organ recipients, a detailed allergy work-up based on qualitative serological screening and measurement of specific IgE is advisable. Blood testing should include eosinophil counts, liver and kidney function, and immunoglobulins. The interpretation of results should consider the significance of other allergic comorbidities, immunologic cross-reactivity, genetic susceptibility, and current/previous medications and past immunizations [3,70].

After SOT, specific attention should be given to any previous reported risk of allergy, and periodic reassessment should guide investigation of new, developing allergies. Given that the frequency and clinical consequences of recipients are currently poorly understood, some studies have advocated following up the sensitization profile. In the cases of transfer of donor-related IgE-mediated sensitization, clinical symptoms should be monitored in conjunction with skin prick test and total IgE results, all starting within the first week after transplant. If specific IgE-mediated food allergy is demonstrated, recommendations to avoid food allergens should be based on the findings of the allergy work-up. Food challenge should be considered only in circumstances when skin prick testing and IgE results have turned negative. In cases of remaining positivity for food-specific IgE, a food challenge may be considered safe when IgE is persistently below the positive threshold curve [71].

Ideally, a documented immunological scenario facilitates understanding of immune interactions. However, limitations at this point arise from restricted understanding of several factors and from disparities in the pathophysiological response after transplant. Several studies report the presence of preexisting food allergies in the recipient after recovery of liver function, since it seems that liver impairment may lead to the absence of clinical manifestations [12,21]. In fact, recipients with a previous history of food allergies were excluded from the study by Marcus et al [3] to rule out the development of pseudo–de novo food allergies [19]. Nevertheless, the authors found a high correlation between the development of these phenomena and family history of food allergies, thus highlighting the importance of genetic factors.

Other factors suggested to be involved are female sex, young age, eosinophilia (associated with tacrolimus and with Epstein-Barr virus [EBV] infection, along with increased IgE levels) and positive PCR results for EBV (possibly related to overimmunosuppression or to the development of $T_H2$ predominance). On the other hand, no correlation has been found between resolution and time to development, organ type, acute rejection, compatibility, or other infectious diseases [3,16, 72, 73].

An increased prevalence of eosinophilia has been reported after solid organ transplantation, thus potentially supporting the development of these phenomena. There is insufficient evidence to determine whether this long-term eosinophilia (caused by calcineurin inhibitors or other agents) is responsible for de novo food allergies owing to a disrupted immune system or whether the development of the de novo food allergy (due to the hypothesis described above) is the main cause of

eosinophilia as part of the allergic response. It is important to consider that since nonspecific high eosinophils levels are found during the first 6 months of life, this correlation is only valid for individuals older than 6 months. Moreover, the increasing frequency of eosinophilia has been associated with older age, and a longer period with eosinophilia has been correlated with an increased risk of de novo food allergy, as eosinophils levels and IgE levels are higher in transplant patients with food allergies than in those without food allergies [3,16,19,70]. Romero et al [74] suggest eosinophilia develops around 1 year after transplant. Therefore, eosinophilia may be useful as a predictive marker of potential risk.

Other posttransplantation, allergy, autoimmunity, and immune-mediated disorders (PTAA) that have been reported after SOT include autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and other types of cytopenia. Early introduction of immunosuppressive therapy after SOT may also further predispose patients to a greater risk of PTAA. However, whether posttransplant food allergies and autoimmune mechanisms share common pathways remains unknown. Interestingly, some clinical cases of angioedema with overinfection by *Staphylococcus aureus* and other microorganisms or tongue edema/scrotal tongue/fissured tongue have also been associated with altered food tolerance mechanisms, although some authors recommend considering oral mucosa alterations as a different entity [21,75-78]. A complete allergy history, together with follow-up and skin prick testing and determination of allergen-specific IgE levels as the first-line approach should be considered. Ultimately, histopathology may be necessary to determine the etiology of the lesions.

## Disease Burden

De novo food allergies have a considerable impact on the dosage of immunosuppressive therapy, since they affect mucosal absorption and defensive functions, as well as bioavailability. Several authors recommend the inclusion of the allergy history in the medical records of both the donor and the recipient. Further studies involving multiple centers and more patients are required. De novo food allergies should be considered a health determinant in transplant recipients, since they produce significant morbidity and worsen quality of life.

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*Conflicts of Interest*

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