



Figure 1. Initial red cutaneous streaking in a 13-year-old girl starting from a mosquito bite on the volar aspect of her left wrist and progressing toward her axilla, with subsequent streaking starting the next day on her right arm and starting again from her wrist toward her antecubital fossa despite receiving no mosquito bites on the right wrist.

increased infestation with the nonnative *Aedes albopictus*, the so-called Asian tiger mosquito.⁹ Although there is significant cross-reactivity among antigens in the saliva from different *Aedes*

species,¹ some proteins are antigenically distinct.¹⁰ Therefore, another possibility is that she had a hypersensitivity reaction with streaking to the bite of one mosquito species and normal local reactions to others.

Practitioners should be aware that immediate-onset superficial lymphangitis to arthropod bites, in the absence of fevers, lymphadenopathy, or systemic symptoms, is likely allergic and should be treated with glucocorticoids and not antibiotics.

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References

1. Peng Z, Simons FER. Mosquito allergy: immune mechanisms and recombinant salivary antigens. *Int Arch Allergy Immunol*. 2004;133:198–209.
2. Meyer Sauter PM, Orban P, Theiler M. Recurrent superficial lymphangitis after insect bites. *Arch Dis Child*. 2018;103:296.
3. Ota M. Allergic lymphangitis. *BMJ*. 2016;355:i5726.
4. Piccolo V, Russo T, Picciocchi R, Diplomatico M, Ametrano O, Moscarella E. Superficial lymphangitis after insect bite. *J Pediatr*. 2013;163(1):299.e1.
5. Orange JS, Song LA, Twarog FJ, Schneider LC. A patient with severe black fly (Simuliidae) hypersensitivity referred for evaluation of suspected immunodeficiency. *Ann Allergy Asthma Immunol*. 2004;92(2):276–280.
6. Marque M, Girard C, Guillot B, Bessis D. Superficial lymphangitis after arthropod bite: a distinctive but underrecognized entity? *Dermatology*. 2008;217(3):262–267.
7. Aquino M, Rosner G. Systemic contact dermatitis. *Clin Rev Allergy Immunol*. 2019;56(1):9–18.
8. Rinn K, Schiffman K, Otero HO, Disis ML. Antigen-specific recall urticaria to a peptide-based vaccine. *J Allergy Clin Immunol*. 1999;104(1):240–242.
9. Metzger MD, Hardstone Yoshimizu M, Padgett KA, Hu R, Kramer VL. Detection and establishment of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) mosquitoes in California, 2011–2015. *J Med Entomol*. 2017;54(3):533–543.
10. Asada H, Saito-Katsuragi M, Niizeki H, et al. Mosquito salivary gland extracts induce EBV-infected NK cell oncogenesis via CD4+ T cells in patients with hypersensitivity to mosquito bites. *J Invest Derm*. 2005;125(5):956–961.

Pediatric posttransplantation food allergy experience at a large US tertiary care center



The first case of new-onset food allergy after transplantation was reported in 1997.^{1,2} Although posttransplantation food allergy (PTFA) is most common after liver transplantation, with a prevalence ranging from 5.6% to 38%, new-onset food allergy has also been described after bone marrow transplantation (BMT).^{2–4} Tacrolimus, a medication used less frequently in BMT compared with solid organ transplantation, has been identified as a potentially modifiable risk factor for PTFA.² Tacrolimus creates an immunologic imbalance that favors a T_H2 response and increases intestinal permeability, which may increase allergen exposure via the gut.^{2,3} Most studies evaluating the prevalence of PTFA and risk factors have included small patient populations, and none compare risks of PTFA after solid organ transplantation vs BMT.^{5–7} We sought to compare the association between tacrolimus exposure and PTFA in BMT and solid organ transplantation recipients in a large cohort from a pediatric tertiary care center.

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The electronic medical records (EMRs) at Ann & Robert H. Lurie Children's Hospital of Chicago were queried for *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) codes for transplantation from January 2007 to June 30, 2017. PTFA cases were defined as patients who had an ICD-9 or ICD-10 code for food allergy applied to their EMR after the application of the ICD-9 or ICD-10 code for transplantation. The EMRs were also queried to obtain indication for transplant, date and age at transplant, date and age at food allergy diagnosis, sex, exposure to tacrolimus, and date of tacrolimus exposure. This query revealed 2017 transplant recipients younger than 19 years at transplantation, of whom 52 had PTFA. A single physician systematically reviewed the EMRs of the 52 patients suspected of having PTFA, evaluating the following: food allergen, symptoms associated with food exposure, allergy clinic visit(s), testing performed, and epinephrine prescription(s). After this review, 11 PTFA cases were removed because of a lack of transplantation or a food allergy diagnosis before transplantation, and 8 PTFA cases were reclassified as controls because of lack of a food allergy diagnosis. Given that 19 of 52 patients (36.5%) suspected of having PTFA had incorrect ICD-9 or ICD-10 coding, a case-control cohort was generated. Approximately 95% of confirmed PTFA cases had a history of symptoms with ingestion for at least 1 documented allergen. The other 5% had evidence of sensitization, evaluation by an

Table 1

Examining Differences in Age at Transplantation, Sex, Tacrolimus Exposure, and Timing Variables Within the Final Cohort

Characteristic	BMT (n = 12)	Solid organ transplantation (n = 140)	P value ^a
Age at transplantation, median (IQR), y	6.83 (3.6–10.3)	2.20 (0.8–6.9)	.02
Sex, No. (% male)	4 (33.3)	80 (57.1)	.14
Tacrolimus, No. (% exposed)	3 (25.0)	124 (88.6)	<.001
Time between transplant and food allergy diagnosis, median (IQR), y (n = 37)	0.69 (0.2–0.8)	2.5 (1.0–5.1)	.04
Time between tacrolimus exposure and food allergy diagnosis, median (IQR), y (n = 34)	0.14 (0)	1.97 (0.7–5.0)	.14

Abbreviations: BMT, bone marrow transplant; IQR, interquartile range.

^aComparisons made using χ^2 , Fisher exact, and Wilcoxon rank-sum tests.

allergist, and/or a prescription for an epinephrine autoinjector. Confirmed PTFA cases were randomly matched to 3 controls on sex and transplant type. During a manual review of all matched controls, 5 additional cases of PTFA were added to the case population. The final cohort consisted of 38 cases and 114 controls (eFig 1).

Data analysis was performed using Stata statistical software, version 12.1 (StataCorp, College Station, Texas). Primary analyses used conditional logistic regression modeling to assess the odds of PTFA in patients exposed to tacrolimus and the association between age at transplantation and the odds of PTFA. Additional analyses considered associations between variables of interest and type of transplant. Continuous variables are presented as median and interquartile range (IQR). Dichotomous variables were compared using the χ^2 or Fisher exact test, and continuous variables were compared using Wilcoxon rank-sum tests. This study was approved by the institutional review board at the Ann & Robert H. Lurie Children's Hospital of Chicago.

There were 1399 solid organ recipients (69.4%) and 618 BMT recipients (30.6%) seen between 2007 and 2017. Of the 2017 transplantation recipients, 52 (2.6%) had PTFA based on ICD-9 or ICD-10 coding, 5 of 618 (0.8%) after BMT, 23 of 383 (6.0%) after liver transplantation, 23 of 1000 (2.3%) after other solid organ transplantation, and 1 type not specified; however, after EMR review, only 38 of the 52 PTFA cases were deemed to have likely IgE-mediated food allergy (3 after BMT and 35 after solid organ transplantation). As such, a well-defined case-control cohort was generated and used as the final cohort (N = 152). The foods implicated are displayed in eFigure 2. In this final cohort, the median age at transplantation was 2.3 years (IQR, 0.8–7.6 years). A total of 36 of the 38 PTFA cases (94.7%) and 91 of the 114 controls (79.8%) were exposed to tacrolimus. Patients who underwent BMT had an older median age at transplantation, were less often exposed to tacrolimus, and had a shorter time between transplantation and food allergy diagnosis compared with solid organ transplant recipients (Table 1). The prevalence of PTFA was significantly higher among those exposed to tacrolimus compared with those unexposed (Table 2). Conditional logistic regression modeling revealed that individuals exposed to tacrolimus were 9.1 times more likely to develop PTFA compared with those unexposed. For every year increase in age at transplantation, the odds of PTFA were reduced (Table 2). We present the odds ratios for tacrolimus exposure with caution because we have small numbers of PTFA cases without the exposure (n = 2).

In summary, the overall prevalence of PTFA in a large cohort of pediatric transplant recipients from a tertiary care center was 1.9% (38 of 2017 patients), lower than the prevalence reported in the general population and in the transplantation literature. Inclusion of multiple transplantation types and cohort size may

Table 2

Conditional Logistic Regression Models Predicting Odds of Food Allergy by Tacrolimus Exposure and Age at Transplantation

Variable	No. of patients	No. of food allergies (%)	Odds ratio (95% CI)	P value ^a
Tacrolimus exposure (model 1)				
No	25	2 (8)	NA	NA
Yes	127	36 (28)	9.1 (1.1–72.8)	.04
Age at transplantation (model 2)				
Age at transplantation	152	38 (25)	0.91 (0.8–1.0)	.04

Abbreviation: NA, not applicable.

^aComparisons made using χ^2 , Fisher exact, and Wilcoxon rank-sum tests.

account for these differences.^{2,3,6} In addition, general population estimates include younger individuals transiently allergic to egg and milk, which will increase prevalence compared with older populations. In our study, patients with PTFA were younger at transplant compared with matched controls, and solid organ transplant recipients exposed to tacrolimus were at particular risk for PTFA. These findings build on previous smaller studies, most of which do not compare BMT with solid organ transplants.^{3,5,7} Although donor data were not available for this study, solid organs may harbor antigen-specific lymphocytes that transmit allergy risk.² Other allergic diseases were not investigated in this study; however, other cohort studies have found acquired asthma, eczema, allergic rhinitis, and eosinophilic gastrointestinal disorders after solid organ transplantation.⁶ Our findings also confirm the limitations of EMR-based cohorts, as noted in studies in other chronic diseases.⁸

In this cross-sectional, retrospective, case-control study, age at transplantation and tacrolimus exposure were risk factors for PTFA. These findings require further validation in a large, prospective cohort study. Future work should focus on which organ transplantation recipients exposed to tacrolimus are at highest risk. Increased attention should be paid to PTFA as a diagnosis in this patient population.

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Supplementary Data

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References

1. Legendre C, Caillat-Zucman S, Samuel D, et al. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med*. 1997;337(12):822–824.

- Hosakoppal SS, Bryce PJ. Transplant-acquired food allergy: current perspectives. *J Asthma Allergy*. 2017;10:307–315.
- Needham JM, Nicholas SK, Davis CM. Food allergies developing after solid organ transplant. *Pediatr Transplant*. 2015;19(8):827–835.
- Hernandez-Ojeda A, Rojas N, Barriga F, Wietstruck MA, Morales PS, Borzutzky A. Incidence and risk factors of food allergy after umbilical cord blood transplantation in children. *J Allergy Clin Immunol Pract*. 2017;5(6):1789–1791.
- De Bruyne R, Dullaers M, Van Biervliet S, et al. Post-transplant food allergy in children is associated with liver and not with renal transplantation: a monocentric comparative study. *Eur J Pediatr*. 2013;172(8):1069–1075.
- Marcus N, Amir AZ, Grunebaum E, et al. De novo allergy and immune-mediated disorders following solid-organ transplantation: prevalence, natural history, and risk factors. *J Pediatr*. 2018;196:154–160.e152.
- Ozbek OY, Ozcaý F, Avci Z, Haberal A, Haberal M. Food allergy after liver transplantation in children: a prospective study. *Pediatr Allergy Immunol*. 2009;20(8):741–747.
- Snyder AB, Lane PA, Zhou M, Paulukonis ST, Hulihan MM. The accuracy of hospital ICD-9-CM codes for determining Sickle Cell Disease genotype. *J Rare Dis Res Treat*. 2017;2(4):39–45.

The clinical presentation of alpha-gal allergy among pediatric patients with food allergy in southwest Missouri



Alpha-gal allergy is associated with immunoglobulin E (IgE) antibodies to galactose- α -1,3-galactose (alpha-gal), a carbohydrate found in beef, pork, and lamb. First described in the adult population in 2009 by Commins et al,¹ this syndrome is associated with delayed anaphylaxis, angioedema, and urticaria with symptom onset 3 to 6 hours after eating red meat.^{1–3} Bites from ticks, namely the Lone Star Tick (*Amblyomma americanum*) in the United States, are associated with production of IgE antibodies to alpha-gal, resulting in an immune system primed to react to foods containing the antigen in patients who previously tolerated meat without symptoms.^{3,4}

The epidemiology and clinical features of alpha-gal syndrome in pediatric patients are not well studied. Lack of awareness for this allergy may lead to a delay in diagnosis and failure to avoid the offending agent, thus increasing the patient's risk of a severe systemic reaction.^{4–6} This study aimed to determine the clinical presentation of alpha-gal syndrome among pediatric patients with documented food allergy in southwest Missouri. A greater understanding of the prevalence and clinical presentation will help physicians determine when to test patients for IgE to alpha-gal as a potential cause of their symptoms.^{4–6}

Using Healthe Analytics by Cerner, we recruited patients retrospectively for the study from one of southwest Missouri's largest health care systems with a catchment area spanning from northern Arkansas toward the central region of Missouri. The study determined the total number of pediatric food allergy patients ages 0 to 18 years based on food allergy ICD10 codes. Similarly, we used Healthe Analytics to generate an initial list of pediatric patients with alpha-gal sensitization based on an IgE level greater than 0.35 kU/L from 2014 to 2018. From this list, we accessed each patient's chart to confirm the presence of a true alpha-gal allergy based on clinical presentation consistent with a delayed allergic reaction 3 to 6 hours after red meat consumption in addition to elevated IgE levels against alpha-gal.^{1,2}

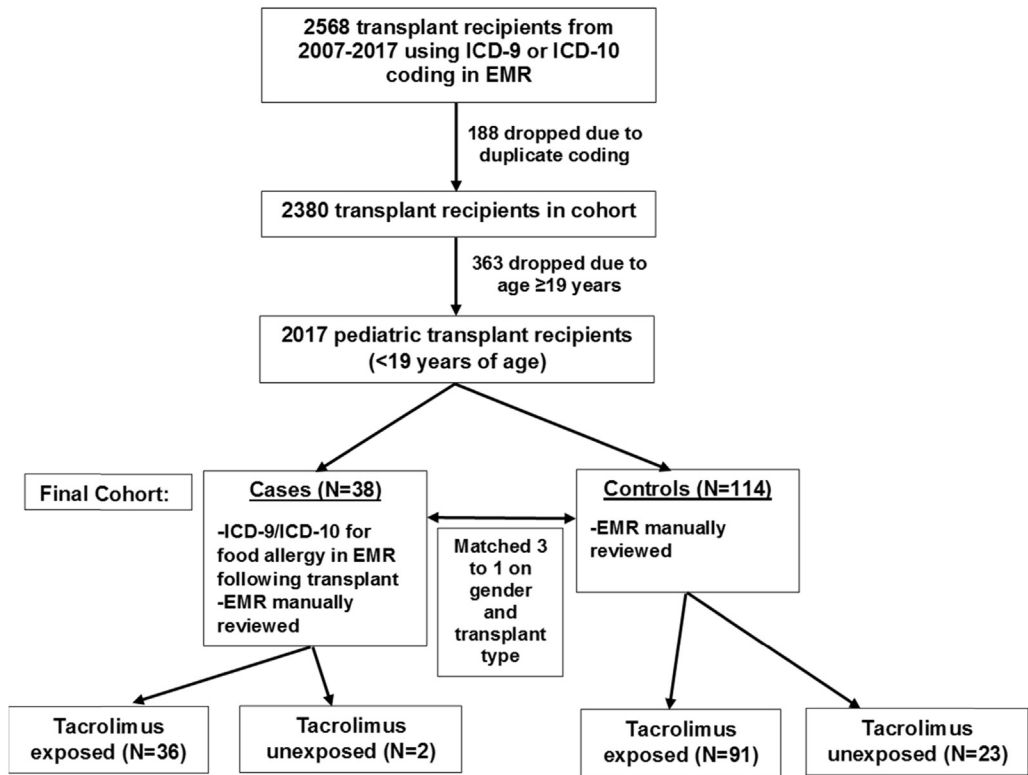
We used this information to determine the prevalence of alpha-gal syndrome among pediatric patients with documented food allergies. With the earliest diagnosis recorded in November 2014 in our system, our prevalence calculation includes all reported alpha-gal diagnoses from 2014 to 2018 among patients currently 18 years of age or younger from multiple clinics in southwest Missouri. We determined incidence based on new diagnoses from January 1, 2018 to December 31, 2018. Alpha-gal patient charts were accessed individually to identify sex, age of diagnosis, clinical presentation, history of emergency room management, and prior physician diagnosis of allergic rhinitis, eczema, and asthma (Table 1).

A total of 1268 patients with documented food allergy between the ages of 0 and 18 years in southwest Missouri were included in the study. Of these patients, 42 were diagnosed with alpha-gal syndrome based on elevated IgE levels against alpha-gal as well as a history of a delayed allergic reaction after red meat consumption. The prevalence of alpha-gal syndrome in southwest Missouri among pediatric food allergy patients was 3.31%, with an incidence of 0.87% during 2018. The mean age of diagnosis was 9.95 years with a range from 3 years to 17 years of age. Slightly more patients were male at 57.14% (24 of 42).

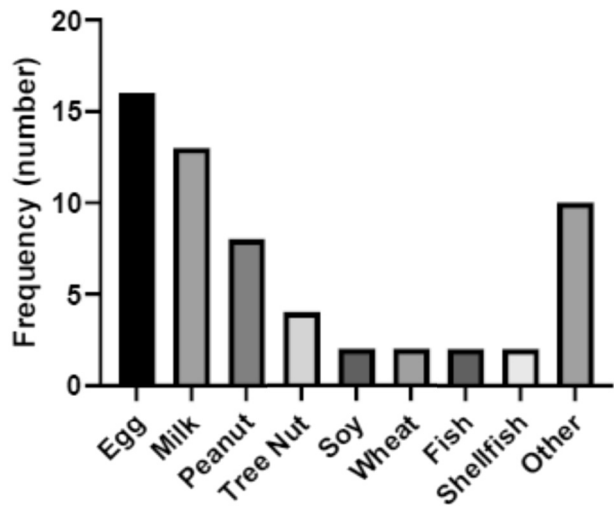
Urticaria was the most common presentation, accounting for 78.05% (32 of 41) of cases. From most to least prevalent, other presentations included anaphylaxis, angioedema, and gastrointestinal symptoms. Many of these reactions were severe with 32.5% (13 of 40) of patients requiring emergency room management for their symptoms. Levels of IgE antibody ranged from 0.38 to 67.7 kU/L with a geometric average of 2.94 kU/L. Most alpha-gal patients at 78.05% (32 of 41) reported a history of eczema, allergic rhinitis, or asthma with allergic rhinitis reported in 68.39% (28 of 41) of cases. Approximately 19.5% (8 of 41) of alpha-gal patients reported asthma and 9.76% (4 out of 41) reported eczema.

No prior studies have reported the prevalence of alpha-gal syndrome in the pediatric population to our knowledge. Our study found a prevalence of 3.31% among pediatric patients with a documented food allergy in southwest Missouri. The range of clinical presentation of our alpha-gal patient population showed similar results to prior studies with urticaria as the most common symptom.³ Compared Wilson et al,³ fewer patients in our study presented with gastrointestinal symptoms. This may be attributable to a lower level of suspicion among clinicians for alpha-gal syndrome as well as greater consideration of alternative diagnoses in pediatric patients presenting with gastrointestinal symptoms compared with those presenting with more typical presentations of food allergy, such as urticaria or anaphylaxis. While almost half of patients required emergency room management in Kennedy et al,⁴ only one-third of patients in our study presented to the emergency room. Although our study focuses on pediatric cases, our results show similar prevalence of allergic conditions compared with Wilson et al,³ with 68.3% of patients diagnosed with allergic rhinitis and 19.5% diagnosed with asthma.

Although we accessed each alpha-gal patient's chart to determine the presence of true alpha-gal allergy, a drawback of our study was using Healthe Analytics to generate an initial list of pediatric food allergy patients based on ICD10 codes and age. We did not access these patients' charts individually to determine the presence of a true food allergy based on allergic symptoms in response to consumption of a specific food. This may dilute our calculated prevalence of alpha-gal among pediatric patients. Future



eFigure 1. Flowchart outlining generation of the final cohort. EMR, electronic medical record; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, 10th Revision.



*Allergens implicated for N=36; N=16 with clinical reactions to multiple allergens.

eFigure 2. Overall frequency of food implicated in posttransplantation food allergy clinical reactions. Allergens were implicated for 36 patients, with 16 with clinical reactions to multiple allergens.