

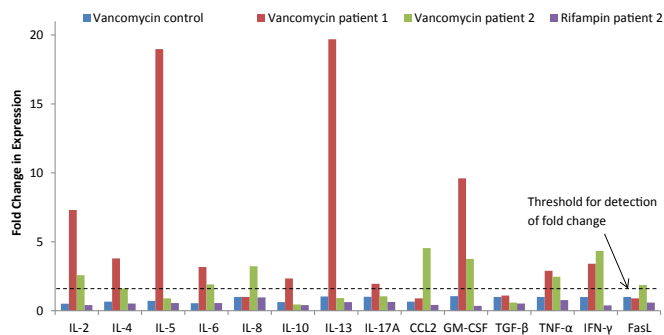


Figure 1. Lymphocyte cytokine expression profile. Relative expression of genes in peripheral blood mononuclear cells (PBMCs) from a patient incubated with vancomycin (vancomycin patient 2), a patient incubated with rifampin (rifampin patient 2), a different patient with drug reaction with eosinophilia and systemic symptoms syndrome (vancomycin patient 1), and a control receiving vancomycin (vancomycin control) shown as a fold change. FasL indicates Fas ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon γ ; IL, interleukin; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α .

may be heterogeneity within eosinophilic T-cell responses; however, the end result of eosinophil activation provides a similar clinical picture. Differential cytokine responses is not surprising because there is already described heterogeneity in the clinical and histological patterns of DRESS.^{6,7} Furthermore, it is possible that there could be features of T_H1 responses in DRESS syndrome, as evidenced by the increase in IFN- γ in our patient, and possibly a component of $CD8^+$ T-cell stimulation as well, given the increase in FasL expression and the skin exfoliation observed clinically. Alternative explanations include the possibility of disease progression from DRESS syndrome to epidermal necrolysis reactions or an overlap syndrome between the two.⁸ Lastly, knowledge of cytokine profiles might help distinguish which patients would be candidates for emerging therapies, such as intravenous immunoglobulin.⁹

This case highlights the heterogeneity of T-cell-mediated drug hypersensitivity reactions and supports the utility of PBMC gene expression testing as a potentially useful tool to identify causative drugs and characterize the mechanism of drug reactions. Furthermore, the observation of vancomycin-induced DRESS syndrome in multiple patients raises the question of whether this drug may play a larger role in these drug hypersensitivity reactions than previously appreciated. A review by Young et al¹⁰ in 2014 found only 19 cases of vancomycin-induced DRESS syndrome in the literature; however, 9 of these were reported after 2012. Included within this

review was an 18-month review of DRESS syndrome cases at Massachusetts General Hospital, where 5 of the 6 cases of DRESS syndrome were attributable to vancomycin.¹¹ We believe these speak to vancomycin-induced DRESS syndrome as an emerging player in drug hypersensitivity reactions. As more cases are described, we believe there will continue to be heterogeneous presentations of the disorder, and perhaps the use of PBMC gene expression will help distinguish different phenotypes with DRESS that ultimately may help with prognosis and treatment for patients.

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Approach to food allergy diagnosis and management by nonspecialty practitioners



In the United States, food allergy affects as many as 8% of children.¹ Pediatricians are often the first health care professionals to encounter these patients. National Institute of Allergy and Infectious Disease–sponsored guidelines for the management of food allergy advise the appropriate use of diagnostic tests, allergen avoidance education, epinephrine autoinjector (EAI) prescription and training, and provision of anaphylaxis emergency action plans (EAPs).² Previous studies^{3,4} have found a lack of adherence with these guidelines. Another study⁵ also found that only 20% of

pediatricians felt comfortable interpreting food allergy test results, and others felt inadequately prepared to care for food allergic children. This study assesses parental report of physician management before referral to an allergy specialist for evaluation of food allergy.

An anonymous questionnaire (Fig 1) was distributed to all English-speaking families presenting for an initial consultation with a pediatric allergist at the Icahn School of Medicine at Mount Sinai between March 2014 and February 2015. The study was conducted in 2 pediatric allergy practices that differ in type of insurance plans accepted (commercial vs state). Statistical analysis was performed with GraphPad (GraphPad Software, La Jolla,

Age of child:

Gender (circle): Male Female

Was your child referred for possible food allergy? Yes No

What food(s) are you or your doctor worried about? _____

Who referred you to see an allergist?

1. Pediatrician
2. Emergency room physician
3. Allergist
4. Other: _____

Why were you referred?

1. My child had an allergic reaction to a food.
2. My child has positive test results for foods.
3. We have a family history of food allergy.
4. I am worried about food allergies even though my child has not had a reaction.
5. I am not sure why I was referred.
6. Other: _____

Did the referring physician advise your child to avoid specific foods? Yes No

Did the referring physician discuss how to avoid the specific food(s)? Yes No
(For example, read ingredient labels, cross-contamination issues)

Did the referring physician suggest substitutes for the foods avoided? Yes No

Did the referring physician prescribe an EpiPen or Auvi-Q? Yes No

If yes, did you fill this prescription? Yes No

If it was prescribed, were you or a guardian trained in how to administer it? Yes No

Did the referring physician provide a written emergency plan
to describe how to manage allergic reactions? Yes No

Did the referring physician perform testing for food allergies? Yes No

If testing was done, which ones were performed?

1. Skin testing
2. IgE testing
3. Component testing (for example, UKnow peanut)
4. I don't know

If the referring physician sent blood tests for allergy, which foods were tested?

1. Only foods that we were concerned about were tested.
2. Tests were performed for many different foods.
3. I don't know.

Figure 1. Questionnaire distributed at initial food allergy consultation.

California). Comparison of categorical data was performed with the Fisher exact test with a 2-tailed *P* value. This study was deemed exempt from Mount Sinai Institutional Review Board approval because no identifying information was collected as part of the survey.

The parents of 120 children completed the questionnaire. Most were referred with a history of reaction to a food allergen (85%), with 34.2% having concerns for more than one food. Pediatricians provided most of the referrals (93%) (Table 1).

Of the 48 patients (40%) who underwent diagnostic testing before referral to an allergy specialist, 88% had food specific IgE levels drawn. Of these, 83% were tested to many different foods, including foods other than those in question and some foods the child was already tolerating regularly.

Eighty percent were advised by their referring physician to avoid the food(s) in question. Half recalled receiving specific instructions on how to avoid the allergenic food(s), with 18 patients receiving food substitute recommendations.

Table 1
Patient Characteristics^a

Characteristics	Findings, n = 120 (%)
Sex	
Male	63 (52.5)
Female	57 (47.5)
Age, median (range)	3 y (8 mo–17 y) (n = 87)
Reason for referral	
History of reaction	102 (85.0)
Positive test results	6 (5.0)
Family history of food allergy	5 (4.2)
Eczema/rash	3 (2.5)
Other ^b	4 (3.3)
Concern for multiple food allergies	41 (34.2)
Food allergies of concern	59 (49.2)
Milk	15 (12.5)
Egg	31 (25.8)
Soy	10 (8.3)
Peanut/tree nut	59 (49.2)
Fish/shellfish	34 (28.3)
Other	44 (36.7)
Referring person	
Pediatrician	111 (92.5)
Emergency department physician	5 (4.2)
Self (parent)	4 (3.3)
Prior management	
Food avoidance advised	96 (80.0)
Substitutions suggested	18 (15.0)
Prescribed epinephrine autoinjector	80 (66.7)
Milk	6 (40.0)
Egg	18 (58.1)
Soy	6 (60.0)
Peanut/tree nut	44 (74.6)
Fish/shellfish	26 (76.5)
Other	33 (75.0)
Provided with emergency action plan	19 (15.8)
Underwent diagnostic testing	48 (40.0)
(serum specific IgE or skin prick testing)	

^aData are presented as number (percentage) of patients unless otherwise indicated.^bWorried even though no history of reaction, need for MMR vaccine, and previously told child was allergic.

Referring physicians prescribed EAI for 67%, and nearly all (94%) filled the prescription. Only 63% of those receiving a prescription recalled having been trained in how to use the device. A few (16%) recalled being provided with an EAP outlining appropriate management of allergic reactions. Those prescribed an EAI were more likely to have also received an emergency action plan ($P = .003$). There was no difference between those reporting a history of reaction compared with those who did not in terms of receiving a prescription for EAI or provision of EAP. Patients with state insurance were more likely than patients with commercial insurance to have received an EAP (21.0% vs 5.1%, $P = .03$); there was no difference in terms of EAI prescription.

Children referred for a peanut or tree nut allergy more often had allergy testing performed before referral (50.9% vs 29.5%, $P = .02$), but they were no more likely to have had broad testing compared with those without nut allergies. If the concern was a nut or seafood allergy, referring physicians more often prescribed an EAI (74.7% vs 48.6%, $P = .007$). Conversely, significantly fewer physicians prescribed an EAI for milk allergy as opposed to other foods (40% vs 70%, $P = .04$). No differences were seen in prereferral management of children with concerns for single compared with multiple food allergens. For patients whose referring physician initiated diagnostic testing, there was no significant difference in the rates of EAI prescription (72.9% vs 62.5%, $P = .32$) or provision of an EAP (18.8% vs 13.9%, $P = .61$).

Our data indicate that there continues to be a need for further education for primary care physicians on food allergy management. Many are testing a wide range of food allergens (including those already tolerated). When food allergy is a concern, referring

physicians often advise the patient avoid the food(s) in question; however, specific guidance on how to do is not always provided. For those who are prescribed EAI, most do not concurrently receive a written EAP to provide guidance on when the EAI may be indicated.

Potential factors that influence physicians' management of potential food allergies were explored. It is notable that having a history of a reaction prompting the referral to an allergy specialist did not appear to influence whether the patient was prescribed an EAI or provided an EAP by the referring physician. Rather, the results suggest that the type of food allergen in question affects a physician's management because those with nut allergies are more likely to have testing initiated before referral, and children having concerns for allergy to nuts and/or seafood were more likely to receive EAI prescriptions. This finding suggests that there is a greater awareness by referring physicians of the potential for severe reactions in those with nut and seafood allergies but that history of reaction is not identified as a risk factor.

Limitations of this study include the small sample size from a single tertiary care center, that this was not a validated survey, and that the survey was offered only in English. This study was performed from the patient perspective and is subject to parental recall bias. The survey did not explore the symptoms or severity of reactions, which limits the ability to ascertain whether these historical facts influenced referring physicians' actions. Furthermore, we did not inquire about the length of the time lapse between referral and arrival for the specialist appointment.

Studies have suggested that 40% to 80% of information provided by medical practitioners is forgotten immediately and more is forgotten overtime.⁶ Certainly, if a parent does not recall receiving food allergen avoidance instructions, prescription for EAI, or provision of an EAP, then this highlights several potential areas for improvement. Ultimately, the knowledge and attitude of the parent have the greatest effect on the day-to-day life of a food allergic child. Thus, efforts should be made to minimize discrepancy between physician education and parental understanding and recall.

The study additionally highlights the potential effect of the specific allergen in question on referring physicians' actions with respect to the management of pediatric food allergy. Specifically, those with concern for nut or seafood allergies are more often prescribed EAI, whereas those with concern for milk allergy are not. This finding is similar to the findings of the study by Blumenstock et al,⁴ which found that parents of patients with egg and milk allergy were significantly less likely than those with peanut allergy to receive education on epinephrine use. This finding highlights a common misperception that severe allergic reactions occur only for nuts and seafood; thus, physicians may incorrectly minimize the potential danger of other allergens. Severe allergic reactions may occur to any food, and EAI are indicated for those who are at risk for anaphylaxis.⁷ In fact, one study⁸ reported that milk accounted for up to 13% of fatal food-induced anaphylaxis. In a prior study,⁹ only 72% of surveyed primary care physicians recognized that fatal reactions can occur with milk allergy. The data from this study indicate that management provided by referring physicians appears to be more influenced by the food in question than the patient's history of reaction. Whether this finding indicates gaps in food allergy training and/or a lack of comfort in managing food allergies remains to be seen. These management differences may also be due to variations in physicians' motivations or barriers in terms of workflow that are impeding the provision EAI prescriptions or EAPs to patients. Future studies exploring these possibilities would be beneficial. Ultimately, a more seamless and unified approach to food allergy management will benefit food allergic children and their families.

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A case of vibratory anaphylaxis



Vibratory angioedema and urticaria are rare conditions that have been well documented in the literature.¹ Hereditary, acquired, and occupational forms of vibratory angioedema exist.² Identified stimuli include massage, toweling, motorcycling, lawn mowing, horseback riding, or jackhammer use.¹ Although vibration is a well-known cause of physical urticaria and angioedema, there is no clear published report of vibration as a primary cause of anaphylaxis.

There have been several previous case reports documenting vibratory angioedema with associated systemic symptoms. A 1972 report described an episode of vibratory angioedema associated with the systemic symptoms of headache and generalized erythema.² Another report documented a case of angioedema precipitated by exercise or vibration that was accompanied by dizziness, tachycardia, and hypotension.³ Most recently, a single case of venom-dependent, vibration-induced anaphylaxis was described.⁴ This was a case of severe anaphylaxis 18 hours after a wasp sting with a large local reaction. In this letter, we report a case of vibration as the primary cause of anaphylaxis.

A 53-year-old woman with hypertension, diabetes mellitus type 2, and hyperlipidemia used a vibratory massage bed for 10 minutes. The massage bed used water pressure to create vibration without any physical water contact. The massage bed was heated and had a latex-free plastic covering. Within minutes of stopping the massage bed, she developed diffuse pruritus, followed by diffuse flushing, nausea, vomiting, and presyncope. The patient was immediately brought to the emergency department (ED).

The patient had no history of anaphylaxis, food, or latex allergies. She also denied any new foods, medications, or substance ingestions. There was no exposure to Hymenoptera. This episode occurred in January in Minnesota, not in a season with stinging insects or in an area endemic for fire ants. She had been taking lisinopril for the past 3 years. She was taking aspirin, 81 mg/d, but no other nonsteroidal anti-inflammatory drugs or pain medications. The patient used the massage bed at work, where it was available to employees. Approximately 1 hour 21 minutes after symptom onset, her blood pressure was 64/32 mm Hg, heart rate was 59/min, oxygen saturation was 96% on room air, respiratory rate was 20/min, and temperature was 36.4°C. She had a witnessed syncopal episode and emesis while in the ED. Her physical examination revealed diffuse skin flushing and 1-mm papules in the interdigit spaces, but findings were

otherwise unremarkable. She had a history of pustular psoriasis vs dermatitis on her hands, which may have facilitated allergen entry across the epithelial barrier. She was treated with intramuscular epinephrine, 0.3 mg; intravenous methylprednisolone, 125 mg; intravenous diphenhydramine, 25 mg; intravenous ondansetron, 4 mg, and 2 L of intravenous 0.9% sodium chloride for suspected anaphylaxis. She responded to treatment appropriately with an increase in blood pressure and improvement of symptoms. Her heart rate was low on presentation at 59/min, with a subsequent increase to 91/min with treatment. Her baseline rate was 64/min. It is unknown whether there was any tachycardia preceding her presenting heart rate of 59/min. The patient was observed overnight in the intensive care unit without recurrence of symptoms. Treatment with lisinopril was discontinued, and hydrochlorothiazide therapy was used for hypertension management.

On the basis of the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network anaphylaxis diagnostic criteria, this patient met the clinical criteria for anaphylaxis.⁵ She had acute onset of skin involvement (flushing) associated with persistent gastrointestinal symptoms and documented hypotension.

Her serum tryptase level 8 hours after the event was 8.29 ng/mL (reference range, <11.5 ng/mL). Subsequent tryptase levels at 3 and 9 months were normal at 4.25 ng/mL and 2.98 ng/mL, respectively. In view of the 2011 consensus proposal regarding the definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes, which specified a significant change in serum tryptase as an “increase in serum total tryptase by at least 20% above baseline plus 2 ng/mL,” the serum tryptase level of 8.29 ng/mL was considered significantly elevated when compared with the convalescent baseline values.⁶

On further workup, the results of serum specific IgE antibodies to all foods ingested the evening of her anaphylaxis episode and latex were negative. Skin prick test results to a panel of foods and latex were negative 3 months after the anaphylactic event. These results did not reveal food or latex as a cause of anaphylaxis. No Hymenoptera sting was reported. The levels of *N*-methylhistamine and β -prostaglandin $F_{2\alpha}$ collected in the urine 9 months after the anaphylaxis episode were within normal limits. Mastocytosis was considered to be of a low probability based on these results.

The patient experienced 2 subsequent episodes of vibration-induced angioedema with symptoms that included hand and foot