Approach to evaluation and management of a patient with multiple food allergies

J. Andrew Bird, M.D.

ABSTRACT

Background: *Diagnosing food allergy is often challenging, and validated testing modalities are mostly limited to immunoglobulin E (IgE)-mediated reactions to foods. Use of food-specific IgE tests and skin prick tests in individuals without a history that supports an IgE-mediated reaction to the specific food being tested diminishes the predictive capabilities of the test.*

Objective: *To review the literature regarding evaluation of patients with a concern for multiple food allergies and to demonstrate an evidence-based approach to diagnosis and management.*

Methods: *A literature search was performed and articles identified as relevant based on the search terms "food allergy," "food allergy diagnosis," "skin prick test," "serum IgE test," "oral food challenge", and "food allergy management."*

Results: *Patients at risk of food allergy are often misdiagnosed and appropriate evaluation of patients with concern for food allergy includes taking a thorough diet history and reaction history, performing specific tests intentionally and when indicated, and conducting an oral food challenge in a safe environment by an experienced provider when test results are inconclusive.*

Conclusion: *An evidence-based approach to diagnosing and managing a patient at risk of having a life-threatening food allergy is reviewed.*

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INTRODUCTION

Clinical Scenario

Christopher was a 4-year-old boy who was brought to an allergist's office for an initial visit with a diagnosis of multiple food allergies. His mother reported that Christopher was born *via* caesarean section without any complications and was initially breastfed. She tried giving him a cow's milk–based formula at 6 months of life and noticed vomiting and "hives" all over his face and chest within 10 minutes of ingestion of the formula. She gave him diphenhydramine, and the "hives" resolved. Shortly after this incident, the patient was taken to his primary care physician, who told his mother to avoid giving Christopher any cow's milk products.

By 18 months of life, Christopher's mother had avoided giving any food that she considered "allergenic" based on information that she had gathered from the Internet. In addition to milk avoidance, she had not given Christopher egg, peanuts, tree nuts, wheat, soy, fish, or shellfish. The mother asked Christopher's primary care physician to order food allergy tests. A panel of food allergens was obtained, and the results are shown in Fig. 1. Christopher's interim health history was remarkable for no immediate reactivity to any foods since the initial reaction to milk at 6 months. He had moderate atopic dermatitis that was well controlled with topical emollients and occasional use of topical steroids. Diet history is as follows:

- Milk. The mother reports that Christopher had successfully avoided milk and all milk-containing products until the past weekend when he was given a piece of cheese pizza. She states that he tolerated the cheese pizza without incident.
- Egg. He had never eaten any egg product, including baked egg products (*e.g.*, cake, cookie, muffin).
- Peanut and tree nuts. He had never had a peanut, tree nut, or product derived or containing either peanuts or tree nuts (*e.g.*, peanut butter, candies).
- Wheat. The mother stated, "We avoid wheat completely. He eats white bread."
- Soy. He had not had any known ingestion of edamame, tofu, soybean, soy flour, soy milk, or soy yogurt.
- Corn. He did not eat kernels of corn, but he had eaten popcorn, corn tortillas, corn chips, and corn bread made from corn meal without problems.
- Sesame. He had never eaten sesame seed on a hamburger bun, but he did eat foods that contained tahini (*e.g.*, hummus).

From the Division of Allergy and Immunology, Department of Pediatrics, University of Texas Southwestern Medical Center, and the Food Allergy Center at Children's Medical Center, Dallas, Texas

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Address correspondence to J. Andrew Bird, M.D., Children's Medical Center 1935 Medical District Drive, F6.04 Dallas, TX 75235-7794

E-mail address: drew.bird@utsouthwestern.edu

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Food Allergen	Specific IgE Result (kU/L)
Egg white	2.27
Peanut	2.30
Wheat	2.21
Walnut	9.98
Codfish	<0.35
Milk	0.51
Soybean	2.62
Corn	5.26
Shrimp	<0.35
Scallop	<0.35
Clam	<0.35
Sesame seed	3.87

Figure 1. *Christopher's laboratory test results.*

Case Discussion

A patient such as Christopher is commonly seen in the allergist's practice, and unraveling which foods are likely to be harmful and which will be safely tolerated often requires more attention than simply ordering an additional test. This review walks through a reasonable approach to evaluating a child diagnosed with multiple food allergies, interpretation of and indications for food allergy testing, and considerations before offering and performing an oral food challenge (OFC).

Food allergy affects ~15 million Americans,[1] and self-reported prevalence of allergy varies from 0.2% to 7% for egg and from 1.2% to 17% for milk.[2] Challenge-proven allergy, however, is much lower, ranging from 0% to 1.7% for egg and 0% to 3% for milk.[2] Factors that contribute to misdiagnosis of food allergy include misinterpretation of currently available testing modalities[3] and underutilization of office-based OFCs to more accurately define clinical reactivity to food allergens of concern.[4] More than 85% of practicing allergists report performing OFCs, but <6% perform >10 per month.[5] Deciding which foods may be reintroduced or liberalized at home and which deserve further investigation starts with dissecting the patient's history.

Clues from the Diet History

Gleaning useful information from the diet history starts with taking each food of concern individually and considering relevant aspects of what we know about the allergen to determine if additional testing is warranted. Christopher's initial reaction followed cow's milk ingestion; however, his mother noted that he recently ingested cheese pizza without having an immediate reaction. As many as 70% of individuals with milk allergy may tolerate baked milk.[6] Extensively heating milk leads to denaturation of conformational epitopes, which makes them unrecognizable by epitope-specific immunoglobulin E (IgE).[7] Cheese cooked on pizza is considered a less-heated form of milk than milk baked into a wheat matrix (*e.g.,* muffin or cake), so it may be assumed, based on Christopher's history, that he tolerates baked milk. Children with milk allergy who tolerate baked milk products and incorporate baked milk into their diets on a regular basis are 16 times more likely to develop a tolerance to uncooked cow's milk,[8] so, in addition to positively affecting Christopher's quality of life, ingestion of baked milk products is likely to accelerate acquisition of tolerance to uncooked milk. Further investigation regarding the likelihood that Christopher remains allergic to uncooked milk products is warranted.

Egg, peanuts, and tree nuts have never been ingested according to Christopher's mother. Sicherer and Wood[9] recently published a comprehensive review regarding interpretation of food-specific allergy testing. As mentioned in their review, established predictive values that indicate a likelihood of reacting with ingestion rely on a history of reactivity after ingestion.[9] The pretest probability diminishes in the absence of a history of reactivity, and OFCs are often warranted to determine if the food is likely to be tolerated. Skin-prick testing (SPT) and OFCs will need to be considered to better understand the likelihood of Christopher reacting to egg, peanuts, or tree nuts.

The mother stated that, "Christopher is avoiding wheat altogether, and he eats white bread frequently." Foods that contain white flour or wheat flour contain wheat protein; therefore, Christopher was ingesting wheat on a regular basis and would not be considered allergic to wheat. Further testing for wheat allergy was not warranted.

Soy ingestion is often difficult to determine. Many families do not regularly or intentionally feed foods, *e.g.,* edamame (soy beans), or other foods with known soy protein, *e.g.,* soy milk or soy yogurt. However, families often think that their child eats soy because many foods contain soybean oil or soy lecithin. Soybean oil and lecithin do not commonly contain soy protein; therefore, it is not appropriate to determine an individual's ability to tolerate soy based on ingestion of soybean oil or lecithin. Further investigation into soy allergy will be required.

Clinical reactivity to corn is not often seen, but specific IgE to corn is commonly detected.[3] Studies that looked at alteration of corn protein have not been performed. Popcorn, corn meal, corn flour, and corn flakes are lesser-processed forms of corn and likely retain allergenicity (S. L. Taylor, Ph.D., written communication, March 2014). Processing may affect corn chips and corn tortillas, although this has not been studied. Corn syrup does not typically contain corn protein; therefore, corn tolerance cannot be safely judged based on ingestion of corn syrup. The patient mentioned in this case had safely ingested a variety of

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Table 1 **The 95% PPVs for specific foods by using ImmunoCAP specific IgE tests***

Age Group	Food	Serum IgE (kU/L), ~95% react	Serum IgE (kU/L), ~50% react
Mean age 5 years	Egg white#	≥7	2
≤2 y		≥2	
Mean age 5 years	Milk#	≥15	2
≤2 y		≥5	
Mean age 5 years	Peanut	≥14	2, 5§

PPV = positive predictive value; IgE = immunoglobulin E.
**From Refs. 10–13.*
#Egg white and milk predictive values were derived based on reactivity to uncooked or lightly cooked egg and milk products; 95% PPVs have not been well established for baked egg or baked milk product reactivity.
§Fifty percent of 5-year-old children will react to peanut at a level of 5 kU/L if there is no history of a previous reaction.
ImmunoCAP, Phadia AB, Uppsala, Sweden.

corn products, and it was unlikely that he was allergic to corn.

Sesame seed is often found on hamburger buns and more significantly present in commercially produced hummus in the form of tahini, which is ground sesame seed. The mother reported that Christopher ate commercially purchased hummus that contains tahini on a regular basis without problems. He was not allergic to sesame seed.

Serum-specific IgE Testing and SPT

Serum IgE testing is easily obtained, and it is often performed in clinical practice. As already mentioned, in the absence of specific symptoms, test results lose their predictive capabilities.[9] Established predictive parameters that indicate a 95% positive predictive value (PPV) have been established for foods such as egg, milk, and peanut (Table 1).[10–12] It is important to remember that 95% PPVs are based on predictive curves, and a resulting value of <95% PPV does not indicate the absence of allergy. As the value decreases, the likelihood of reacting decreases, but the PPV does not fall to 50% for foods such as milk, egg, and peanut until a value of 2 kU/L is reached.[12,13] It is at this point that some practitioners may choose to offer an observed food challenge.[13,14]

It is recommended to order food-specific IgE serum tests based on the patient's history rather than ordering a panel of food-specific IgE tests.[15–17] A recent review of 274 patients seen in a tertiary referral center who were evaluated for concern for food allergy based on results from food panels showed that the PPV of food panel IgE testing fell to 2.2% when testing was ordered in patients who did not have a history that warranted testing for food allergies.[3] Eighty-nine percent of children in the studied population who were avoiding a food that they perceived as an allergen based on testing were able to safely reintroduce the avoided food. Similar results were reported by Fleischer *et al.*,[4] who showed poor predictive capabilities for food-specific IgE testing in children with atopic dermatitis. Their cohort yielded similar results, with 84–93% of the foods being avoided returned to the diet after OFC, which underscored that food-specific IgE tests must be interpreted in light of the patient's history. In circumstances in which test results are not clear, OFC is often necessary and important in providing appropriate dietary recommendations.

SPT may also help to further define the likelihood of a patient having an IgE-mediated reaction to a food. As with serum-specific IgE testing, panels of SPTs may yield a large number of clinically irrelevant results. The overall positive predictive accuracy for SPTs to foods such as soy, milk, egg, and peanut may range from 29 to 80%.[18] The larger the SPT wheal diameter, the more likely that the test result is a clinically relevant positive result for some allergens, such as milk, egg, and peanut[19]; however, SPTs for foods, *e.g.*, soy, have traditionally shown poor positive predictive accuracy.[18,20] A negative SPT result has been reported to be highly suggestive for ruling out the presence of immediate food hypersensitivity[21]; however, investigators reported varying results, with several reporting reactivity on OFC even with a negative SPT result.[18,22] SPT, in general, may aid in the diagnosis of food allergy, but it does not take the place of a thorough diet history. If there is any question in interpreting the SPT results, even with a negative SPT result, then an OFC is often needed to safely verify whether or not the patient is tolerant.

Additional testing, such as component-specific IgE testing and basophil activation testing, has been shown in some studies to improve predictive capabilities for food allergy diagnosis. Component testing was not indicated in the patient discussed in this scenario, and its applicability may be limited to very specific circumstances. Basophil activation testing is not currently

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commercially available and is limited to research settings.

OFC

An OFC is often necessary to clearly define whether a patient does or does not have a clinical reaction to a food after ingestion. In a survey of 1483 Dutch adults, 12.4% claimed that they had a food allergy, but, after double-blind, placebo-controlled food challenge, only 12 of 73 actually had evidence of reactivity.[23] This study demonstrates the disagreement between the perception and presence of food allergy. An OFC will not only confirm existing allergy, but, in the absence of allergy, it allows for the removal of unnecessary dietary restrictions and the negative impact on quality of life imposed by those restrictions.

When considering OFC in the office setting, it generally is prudent to perform low-risk rather than high-risk challenges,[24] although there are circumstances when higher-risk challenges are warranted. Examples of low-risk challenges would include the following:

- Patients who have recently eaten the food in question without a reaction,
- test results (*e.g.,* SPT and/or serum IgE tests) that indicate a >50% probability of passing the challenge,
- no history of a severe reaction, and
- the patient does not have asthma.

Higher-risk challenges include the following:

- A history of reactivity to the allergen within the past 6–12 months,
- test results that indicate a high likelihood of reacting,
- a history of a severe reaction and/or a severe reaction to trace amounts of the allergen,
- the presence of asthma, and
- coexisting medical conditions that may affect resuscitation.

Although a double-blind, placebo-controlled food challenge is considered the criterion standard for diagnosing food allergy, open OFCs are more easily performed and more commonly conducted in an office setting. An open OFC involves feeding an age-appropriate serving size of the allergen divided into five or more servings over a period of 60 to 90 minutes and by observing the patient for an additional 2 to 3 hours.[24] With an open OFC, both the provider and the patient are unblinded, and no placebo is offered.

Regardless of risk assessment before OFC, proper precautions for treating a reaction should be in place to appropriately treat a reaction should one occur. To safely perform an office-based OFC, the following safety requirements may be considered at a minimum[24]:

- Perform challenge in a monitored space. A physician or a nurse under a physician's supervision should monitor the patient throughout the OFC.
- Medications that may interfere with interpretation of the OFC should be discontinued (Table 2).
- Obtain baseline vital signs (weight, respiratory rate, heart rate, and blood pressure) and perform a physical examination, including the oropharynx, lungs, and dermatologic examinations, before starting the OFC.
- Emergency medications must be readily available and appropriate doses calculated before starting the challenge. Medications to have on hand include epinephrine, albuterol, supplemental oxygen and supplies, H1 antihistamine, and intravenous fluids.
- Anaphylaxis practice parameters recommend having an oxygen source; pulse oximeter to monitor

Table 2 **Medications that may interfere with interpretation of OFC***

Medication	Last dose before OFC
Cetirizine	5 d
Cyproheptadine	10 d
Diphenhydramine	3 d
Fexofenadine	3 d
Hydroxyzine	7 d
Loratadine	7 d
Oral H2 receptor antagonist	12 hr
Oral, intramuscular, intravenous steroids	3 d to 2 wk
Short-acting bronchodilator (*e.g.,* albuterol)	8 hr
Long-acting β-agonists	8 hr
Inhaled cromolyn sodium	48 hr
Antidepressants	3 d to 3 wk, drug dependent and dose dependent
Medications that may be continued	
Antihistamine eye drops	
Inhaled, intranasal corticosteroids	
Topical steroids	
Topical pimecrolimus, tacrolimus	

OFC = oral food challenge.
**From Ref. 24.*

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oxygen saturation; sphygmomanometer; appropriate-size nasal cannulas, masks, bag valve mask, and oropharyngeal airways present or readily available for treatment of anaphylaxis.[25]

- Intravenous access may be decided at the discretion of the provider.

Preparation for OFC

Before scheduling an OFC, talk with the family about the food challenge process, signs and symptoms of a reaction, and treatment of a reaction. It is also important to discuss the family's plan for food introduction after challenge. Failure to incorporate peanut into the diet after passing challenge has been reported to result in recurrence of peanut allergy[26]; therefore, it is important to have the family reincorporate the challenged food into the diet. If the food is not incorporated into the diet, then ongoing follow-up should be maintained with the patient's allergist to consider whether or not repeated evaluation for reactivity is warranted.

Medications that may interfere with interpretation of the OFC outcome should be held before the OFC (Table 2). Recommend no meal or only a light, low-fat snack (*e.g.*, half of the typical amount) to be eaten no less than 2 hours before the OFC.[24] Stomach contents may interfere with allergen absorption, so it is preferred to perform an OFC on an empty stomach. Ensure that all atopic diseases (*e.g.*, asthma, allergic rhinitis, urticaria, atopic dermatitis) are under optimal control before commencing challenge. Concomitant illness may also interfere with test interpretation, and, if present, the OFC should be delayed. It is also prudent to calculate doses of emergency medications and have those medications readily available at the patient's bedside.

Conducting the OFC

The OFC should consist of five to seven portions of a standard serving of the food allergen in question fed over 60 to 90 minutes.[24] The first dose is typically 1% of the total portion. Successive doses typically constitute 4%, then 10%, followed by equal portions of the remaining quantity divided over four to five servings. It is recommended to wait at least 15 to 20 minutes between feedings.

The OFC should be stopped at the first sign of an objective reaction, and the patients should be treated appropriately. Objective signs of an allergic reaction typically involve the respiratory tract (sneezing, congestion, and/or rhinorrhea, hoarse voice, dyspnea, cough, wheezing), gastrointestinal tract (nausea, vomiting, abdominal cramping, diarrhea), or skin (flushing, urticaria, and/or angioedema), and, in rare cases, may include hypotension or cardiovascular collapse. Lower respiratory tract symptoms, cardiac symptoms, repetitive emesis, reactions that involve two or more organ systems, and reactions that appear to be progressing are considered indications for giving epinephrine.[24,27–29] Signs in nonverbal children (*e.g.*, young age or developmental delay) may include ear picking, tongue rubbing, grabbing at the mouth, neck scratching, change in demeanor, and becoming quiet or withdrawn.

Subjective symptoms may create a more challenging scenario. Subjective concerns from younger children may include statements such as, "There is a bug in my throat," or "My mouth feels funny." In cases such as these, the medical provider may wish to wait for symptoms to resolve before proceeding to the next dose. If the reaction is not clear-cut, then a blinded challenge at another time might be prudent.[24]

Postchallenge Guidance

A positive challenge (*i.e.*, patient reacts to the food) should be treated, and the patient should be observed for 2 to 4 hours at a minimum.[24] At discharge from the clinic, ensure that family members have two autoinjectable epinephrine devices with them and that they know how to use them. Provide and review a food allergy action plan. Food allergen avoidance education should also be provided, and consultation with a registered dietitian may be considered, especially for children who avoid milk or who are allergic to two or more foods.[30–32] Educational materials and a food allergy action plan may be found at the Food Allergy Research and Education Web site.[33]

A negative challenge result (*i.e.*, the patient does not have a reaction after completing challenge) typically indicates tolerance of the food allergen. It is recommended to instruct the patient to continue avoidance of the food for the remainder of the day of challenge in case of a rare, delayed reaction. If a reaction does not occur, then the food may be reintroduced into the diet, and regular ingestion is encouraged.[24]

CONCLUSION

A patient such as the one in this case study often presents to his or her primary care physician, and initial evaluation may be restricted to ordering limited specific IgE tests based on the child's history. In this case, ordering milk-specific IgE alone would have been reasonable, or, in addition, evaluating egg- and peanut-specific IgE based on an increased risk of sensitization to egg and peanut in food allergic infants might be considered. Broad panel screening is not recommended.[3,4,15–17] Understanding which foods will likely trigger a clinical reaction and which test results are not meaningful requires careful clinical investigation, starting with a thorough diet history. Additional testing with SPT or serum-specific IgE testing may be

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required, and, when results are in question, an OFC performed by a board-certified allergist may help to elucidate the presence of allergy or tolerance of the allergen in question.

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