CLINICAL PRACTICE

Food Allergy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 3-year-old boy with a recent history of hives and wheezing after eating chocolate mousse is evaluated. At 18 months of age, contact urticaria developed after he put his hand into a cake mix containing egg. He also has a history of chronic rhinitis, nocturnal cough, severe eczema, and a previous hospitalization for recurrent wheezing. How should this child be evaluated and treated?

THE CLINICAL PROBLEM

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IgE-mediated food allergies affect between 6 and 8% of children in the United Kingdom and the United States.[1] Although up to 25% of adults report symptoms that may be related to certain foods, the prevalence of food allergies among adults is less than 3%. The major food allergens are water-soluble glycoproteins that are derived from animals and plants; these glycoproteins tend to remain stable during treatment with heat, acid, and proteases. Different foods affect different age groups (Table 1). Cow's milk, hen's eggs, peanuts, tree nuts, and sesame seeds account for most food-induced allergic reactions in young children, and kiwi allergy has been increasingly reported.[2] Wheat and soy allergies, although frequently suspected, are rarely confirmed. Shellfish, fish, peanuts, and tree nuts are the most common causes of food allergies in adults.[3]

Despite geographic differences in the prevalence of IgE-mediated food allergies (e.g., mustard allergy is mainly observed in France[4] and sesame-seed allergy is more commonly observed in Israel than elsewhere[5]), hen's eggs and cow's milk appear to be the most common causes of food allergies among children throughout the world.[3] Population-based studies show that the prevalence of allergy to egg whites among children is between 1.5 and 3.2%.[6-8] A family history of egg allergy or atopy is a risk factor for egg allergy, although the magnitude of the increase in risk is uncertain.

Most food-induced allergic reactions occur on first known oral exposure, especially in the case of eggs and peanuts; although this review focuses on egg allergy, aspects of other food allergies are mentioned. There are allergen-specific differences in the natural history of food allergy (Table 1). Egg allergy has typically been thought to resolve in 66% of children by 5 years of age and in 75% of children by 7 years of age,[9,10] although a recent study from a tertiary allergy center suggests a longer duration of allergy, with persistence in approximately 33% of patients older than 16 years of age.[11] There have been rare cases of a new-onset egg allergy in adults,[12-14] with clinical characteristics that differ from those of egg allergy in children (Table 2). Allergies to peanuts, tree nuts, and sesame seeds are infrequently outgrown.

CLINICAL PRESENTATION

Symptoms of food-induced allergic reactions range from localized hives to life-threatening anaphylaxis (Fig. 1). The organ systems most commonly involved include the skin (e.g., urticaria, flushing, angioedema, and worsening eczema), gastrointestinal tract (e.g., vomiting, abdominal pain, cramping, and diarrhea), and respiratory tract

Table 1. Natural History of Food Allergy and Cross-Reactivity between Common Food Allergies.

Food	Usual Age at Onset	Cross-Reactivity	Usual Age at Resolution
Hen's egg white	6–24 mo	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	6–12 mo	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	6–24 mo	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve by 5 yr)
Tree nuts	1–7 yr; in adults, onset occurs after cross-reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve after 5 yr)
Sesame seeds	6–36 mo	None known; coreactivity with peanuts and tree nuts	Persistent (20% of cases resolve by 7 yr)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat‡	6–24 mo	Other grains containing gluten	5 yr (80% of cases resolve)
Soybeans‡	6–24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

* Recent studies suggest that resolution may occur at a later age.
† Fish allergy that is acquired in childhood can resolve.
‡ Although IgE-mediated allergies to wheat and soybeans are frequently suspected food allergies, in practice these diagnoses are rarely confirmed after evaluation by a specialist.
§ Allergy to apples, carrots, and peaches (oral allergy syndrome) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits and vegetables.

(e.g., rhinitis, asthma, and stridor). In rare cases, egg allergy has caused fatal reactions in children, particularly those younger than 2 years of age.[15] Contact urticaria is a common manifestation of egg allergy in childhood.

Food allergies may also be manifested as a food aversion or as changes in behavior or mood in young children. Status asthmaticus may also be a presenting manifestation in the absence of any other signs or symptoms, and there should be a high index of clinical suspicion when a patient presents with the sudden onset of severe wheezing shortly after eating a meal.[16]

COEXISTING CONDITIONS

Eczema, which generally develops in the first 6 to 12 months of life, is typically the first obvious manifestation of atopy, and it is present in more than 80% of children with egg allergy. More severe eczema is associated with a greater likelihood of allergies to eggs and other foods,[17] and sensitization to foods increases the likelihood of severe, persistent eczema. Respiratory allergies such as asthma and rhinitis are also common and typically are diagnosed well after the appearance of food allergies; respiratory allergies are generally diagnosed after 3 years of age, whereas food allergies are generally diagnosed between 6 months and 2 years of age. However, data show that among children with atopy, respiratory disease may be present in the first year of life.[18] Egg allergy or sensitization is the strongest recognized predictor of respiratory allergies in children and asthma in adults.[18-21] Although eczema and food allergies usually resolve in children, they persist in a substantial number of children, and additional allergies develop in many children. Patients with systemic allergic disease typically have multiple food allergies, eczema, allergic rhinosinusitis, asthma, or a combination of these conditions, which cause considerable illness and impairment in the quality of life.[22] Patients who have both food allergies and asthma are at increased risk for anaphylactic reactions and life-threatening asthmatic reactions.[23-25]

STRATEGIES AND EVIDENCE

The medical history should include the nature of the symptoms and their timing after exposure to the presumed allergen, the consistency of the al-

Table 2. Clinical Syndromes Associated with Egg Allergy.

Presentation	Population	Clinical Manifestation	Natural History	Egg Component	Major Allergens
Egg-white allergy	Young children, predominantly patients with atopy and eczema	Contact urticaria, systemic type 1 hypersensitivity symptoms after ingestion	Resolves by 7 yr of age	Egg white	Ovomucoid, ovalbumin
Bird-egg syndrome*	Adults, predominantly women who have been exposed to birds	Respiratory symptoms after exposure to bird feathers, type 1 hypersensitivity symptoms after ingestion of egg yolk	Persistent	Egg yolk	Alpha-livetin (chicken serum albumin), cross-reactivity with bird feathers
Occupational egg allergy ("egg–egg" syndrome)	Adults in the confectionery and food industry	Respiratory symptoms after exposure to aerosolized egg white, variable type 1 hypersensitivity symptoms after eating egg white — usually mild	Persistent	Egg white	Ovalbumin, ovomucoid, conalbumin, lysozyme

* Oral symptoms that have occurred involve primarily hen's eggs, but respiratory symptoms can occur with exposure to many different types of birds.

lergic response, and the patient's response to treatment (Table 3). The route of exposure to the allergen is also important; cutaneous exposure can lead to contact urticaria, inhalational exposure during cooking can lead to wheezing, and oral exposure usually causes perioral, oral, and gastrointestinal symptoms.

Referral to a specialist for allergy testing is warranted when food allergy is suspected. Skin-prick testing generally has a sensitivity of approximately 90% but a specificity of only about 50%, although these rates vary with different allergens and other factors, including the patient's age, the extract used, and the site of application. Specific IgE testing by means of enzyme-linked immunosorbent assay also has a high sensitivity but a low specificity. The positive and negative predictive values for both these tests are more useful measures in practice; cutoff points indicating a positive predictive value of 95% for allergies to eggs, milk, peanuts, wheat, and fish have been established for both skin-prick test results[26] and specific IgE values.[27] However, positive predictive values vary depending on the prevalence of the condition in a population. The use of likelihood ratios for skin-prick test results and specific IgE values overcomes this problem (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org), and the use of these values combined with the medical history leads to an accurate diagnosis of food allergy in 70% of patients (Fig. 2).

In some patients, food challenges are required to establish allergy or tolerance. The standard is the double-blind, placebo-controlled food challenge,[28] in which incremental doses of the food allergen or placebo are given at 20-minute intervals and the patient is observed for objective signs of food allergy. Patients who tolerate the final dose of this challenge should then undergo an open (unblinded) challenge, in which a regular-size portion of the food is given, in order to establish tolerance. The double-blind challenge, used routinely in research, is recommended in clinical settings in which patients report subjective symptoms, whereas incremental challenges without placebo are commonly used in the assessment of patients with objective evidence of allergy. Food challenges carry a small risk of anaphylaxis and should be conducted in a supervised medical setting where resuscitation equipment is available. These challenges should be performed only in patients whose

allergic symptoms, including asthma, are well controlled before testing.

In children with egg allergy, serial skin-prick testing and IgE measurements are recommended, typically on an annual basis, to assess whether tolerance has developed. A 50% decrease in the titer of specific IgE antibody to egg white over a period of 12 months is associated with a 50% probability of resolution of the allergy[9,25,29]; this probability is generally considered to be sufficiently high to warrant formal reassessment with a food challenge. Tolerance to cooked egg may develop before the development of tolerance to raw egg, and if the latter is not assessed, a premature conclusion that a patient is tolerant to egg may place the patient at risk for anaphylaxis.[30]

Other food allergies such as those to peanuts, tree nuts, and sesame seeds develop in approximately 30% of children with egg allergies.[16] Thus, children with egg allergies should also be evaluated for these other allergies.

Figure 1. A 10-Year-Old Child with Food-Induced Anaphylaxis.
The endotracheal tube and angioedema of the lip are shown.

MANAGEMENT

SHORT-TERM MANAGEMENT

Anaphylactic reactions require prompt treatment of symptoms with rapid-acting antihistamines and intramuscular epinephrine; frequently, inhaled beta-agonists and systemic corticosteroids are required.[31] Patients should be immediately transported to the hospital, and oxygen and intravenous fluid support should be given (Fig. 2 in the Supplementary Appendix).

Intramuscular epinephrine should be administered within minutes after the allergic reaction. The lateral thigh is the optimal route of administration. Subcutaneous or inhaled epinephrine provides suboptimal therapeutic levels of the drug.[32]

Delayed use of epinephrine is associated with the risk of a fatal reaction[23] and an increase in biphasic reactions[33] (i.e., reactions in which delayed symptoms follow the early acute symptoms[31,33,34]) due either to delayed absorption of allergens through the gastrointestinal tract or to a late-phase allergic response. Biphasic reactions are reported to occur in 6% of cases of anaphylaxis; half of these reactions are severe, and 90% occur within 4 to 12 hours after the first signs. Therefore, patients who have severe reactions requiring epinephrine should be monitored in the hospital. It is commonly recommended that patients presenting with respiratory symptoms be monitored closely for at least 8 hours, since most biphasic reactions occur within that period. Patients presenting with hypotension or loss of consciousness should be monitored for at least 24 hours. The use of oral prednisone (at a dose of 1 to 2 mg per kilogram of body weight per day for 3 days) is recommended to prevent the late phase of the reaction.[31,34]

LONG-TERM MANAGEMENT

The cornerstone of the management of food allergies is avoidance of the relevant food allergens. The management of multiple food allergies is more complex than the management of single food allergies; the greater the number of food allergies, the higher the likelihood of subsequent allergic reactions.[35] Consultation with a trained dietitian is critical in developing a plan to avoid relevant food allergens and in preventing secondary dietary deficiencies with potentially adverse nutritional consequences, such as rickets, iron-deficiency anemia, and impaired growth in children[36] and osteoporosis due to a dairy-free diet in adults.

A multidisciplinary approach involving specialist physicians, nurses, and dietitians has been shown to markedly improve patient and family knowledge of the management of allergic reactions to food,[36] and it has been associated with a reduction in the number of subsequent allergic reactions.[37] Even with careful dietary advice, patients have reactions on average every 3 years; family members and other caretakers should be

Table 3. Medical History in a Workup for Food Allergies.

Question	Possible Significance
What is the suspected food allergen?	Consider whether the allergen is typical for the patient's age and population.
Was the suspected food allergen ingested, inhaled, or touched?	A proportion of patients have a reaction after inhalation of or contact with the allergen.
Does the patient have an aversion to the suspected allergen?	Generally patients dislike and refuse food containing the allergen.
How soon after exposure to the suspected food allergen did the symptoms occur?	IgE-mediated allergic reactions usually occur within 20 minutes after the exposure and certainly within 2 hours after the exposure.
What are the specific symptoms and how severe are they?	If the symptoms are not typical of food allergy, consider a differential diagnosis; if the symptoms are severe, alteration of the emergency management plan may be necessary.
How long did it take for the symptoms to resolve?	The typical time to symptom resolution after reaction to food is 4–12 hours.
How reproducible are the symptoms with previous or subsequent ingestion?	A patient is unlikely to have a reaction to a food just one time, although reactivity may vary depending on factors such as preparation (e.g., depending on whether the egg is raw or cooked and how much antigen it contains).
Does exercise precipitate the symptoms?	Exercise that precipitates symptoms may suggest a diagnosis such as food-dependent, exercise-induced anaphylaxis.*

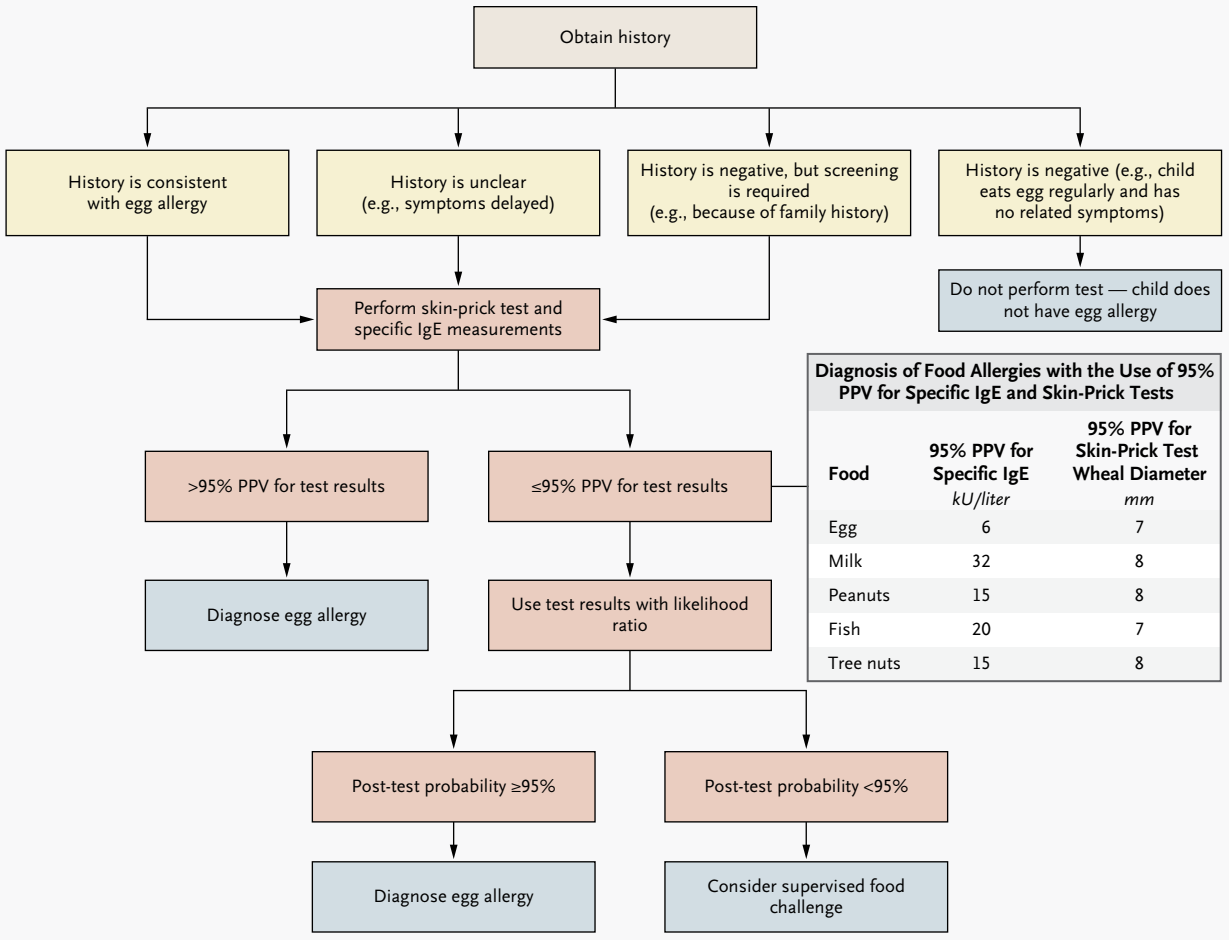
* In food-dependent, exercise-induced anaphylaxis, a patient tolerates a specific food without a clinical reaction and separately tolerates exercise. If the food is eaten within 2 hours before or after exercise, anaphylaxis may occur.

trained to recognize early symptoms of food allergy and to administer the necessary medications if an allergic reaction occurs. Medications for the treatment of anaphylaxis should be kept readily available. On the basis of clinical experience, it is recommended that these medications should include a rapidly acting antihistamine and — especially in all patients with a history of severe reactions or asthma — a device for self-injection of epinephrine. All patients with food allergy and coexisting asthma should have an inhaled bronchodilator. European guidelines also recommend the use of glucocorticoids in patients who have required epinephrine or have had bronchospasm[31] (Table 1 in the Supplementary Appendix).

Given the frequent coexistence of multiple allergic diseases, children with egg allergy should be tested for other food allergies and evaluated for other atopic diseases, and those presenting with moderate-to-severe eczema at a young age should undergo testing for food allergies. The identification of other allergies will minimize the risk of a subsequent severe allergic reaction. Moreover, the management of one allergic disease may improve the outcome of other allergic diseases. For example, some studies have shown improvement of childhood eczema after the elimination of egg and other food allergens, although the relative contribution of such a diet to management is unclear. In a review of elimination diets,[38] the greatest amelioration in eczema was noted to be in children younger than 2 years of age in whom a specific diagnosis of food allergy had been confirmed. As noted above, given the risks of nutritional deficiencies, elimination diets should not be undertaken without a clear diagnosis of food allergy and supervision by a dietitian.

IMMUNIZATION

Common vaccines that are cultured in egg fibroblasts may contain small amounts of egg-protein allergen, and immunization with these vaccines might cause anaphylaxis in children with egg allergies. Thus, the American Academy of Pediatrics recommends that influenza vaccines produced in egg cultures not be used in patients with severe systemic allergic reactions to egg. This group also recommends that before vaccination, children with egg allergy and asthma undergo skin-prick testing with any influenza vaccine containing egg.[39] If either an epicutaneous or an intradermal skin test is positive, the vaccine should be administered in multiple, graded doses under supervision.[40] Skin-prick testing is not required before measles–



Diagnosis of Food Allergies with the Use of 95% PPV for Specific IgE and Skin-Prick Tests

Food	95% PPV for Specific IgE *kU/liter*	95% PPV for Skin-Prick Test Wheal Diameter *mm*
Egg	6	7
Milk	32	8
Peanuts	15	8
Fish	20	7
Tree nuts	15	8

Figure 2. Diagnostic Algorithm for Egg Allergy.

This treatment algorithm can be used for other food allergies if the test result associated with a positive predictive value (PPV) of 95% or higher is known for the population and if the likelihood ratio is known for a given test result. A double-blind, placebo-controlled food challenge should not be performed if the patient has a history of severe anaphylaxis. In the skin-prick test, the mean wheal diameter obtained depends in part on the age of the patient, the extract used, the method of performing the test, and the site on the body where the test is performed. Values for specific types of tree nuts have not been validated. See Figure 1 of the Supplementary Appendix for a nomogram.

mumps–rubella (MMR) vaccination in children with egg allergy. Allergic reactions to the MMR vaccine appear to be due to other components of the vaccine, such as neomycin and gelatin.[39]

AREAS OF UNCERTAINTY

PREVENTION OF FOOD ALLERGIES

The premise that early exposure to food allergens may cause an immature immune system to produce IgE has led to recommendations for delayed weaning as a means of preventing the development of allergies.[41] Although some data suggest that exclusive breast-feeding and the use of extensively hydrolyzed formula may prevent the development of eczema,[42] there is insufficient evidence that such dietary interventions prevent the development of IgE-mediated food allergy. Randomized, controlled trials of the elimination of food allergens from the diet during the first year of life or from the diet of mothers during pregnancy and breast-feeding have not shown reductions in the risk of IgE-mediated food allergies in children at 7 years of age.[43,44]

In contrast, in mouse models, early exposure to high doses of food antigens such as ovalbumin and peanut has been shown to result in oral toler-

ance and to prevent the development of allergies to these foods.[45] Recent studies suggest that infants who are exposed to food allergens early through the oral route are less likely to have food allergies than infants without such exposure,[46,47] but such observational cohort studies are subject to confounding and the possibility of reverse causality. An ongoing randomized trial (ClinicalTrials.gov number, NCT00329784) involving infants at high risk for food allergy is comparing early exposure to high doses of food allergens with complete avoidance of these allergens during infancy (www.leapstudy.co.uk).

Some data indicate that the route of exposure to allergens may affect the development of food allergy. In mouse models that showed tolerance to food allergens after early oral exposure to high doses of these allergens, exposure to low doses of the same proteins through abraded skin led to IgE sensitization to these foods.[48] Allergic sensitization in humans may also occur through transcutaneous exposure (i.e., through inflamed skin). Early severe eczema and exposure to emollients containing peanut oil have been reported to be independent risk factors for the development of peanut allergy.[49]

NEW TREATMENTS FOR FOOD ALLERGIES

Although subcutaneous immunotherapy is highly effective in patients with allergies to grass pollen and insect stings, this therapy has been shown to be unsafe in patients with food allergies. However, oral desensitization with egg white[50] and other foods has shown some efficacy. This strategy appears to increase the threshold dose of reactivity to the food, although it is unclear whether long-lasting oral tolerance is maintained after treatment has been discontinued. Recombinant vaccines for food allergy and other immunomodulatory strategies are under development.[51]

Treatment with monoclonal anti-IgE antibody markedly increases the threshold reactivity to peanuts in adults with peanut allergies,[52] and it has also proved to be effective in treating allergic rhinitis and asthma. This form of treatment might be used for other food allergies, but ongoing treatment is required, and treatment with monoclonal anti-IgE antibody is associated with high attendant costs. Studies are needed to assess the efficacy of treatment with anti-IgE antibody in combination with allergen-specific subcutaneous immunotherapy in desensitizing patients with high doses of food allergens.

GUIDELINES FROM PROFESSIONAL SOCIETIES

The American Academy of Allergy, Asthma and Immunology has issued recommendations for the management of food allergy (www.aaaai.org/members/resources/practice_guidelines/food_allergy.asp), and the European Academy of Allergology and Clinical Immunology has issued recommendations for the management of anaphylaxis.[31] The recommendations provided here are generally consistent with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The child in the vignette has egg allergy and associated conditions, and he requires management of his food allergy and other allergic disorders. The diagnosis of egg allergy should be made on the basis of a detailed history, skin-prick testing, specific IgE tests, and, if necessary, a food challenge in a medically supervised setting. Management should involve education and the prescription of supplies for the treatment of anaphylaxis. This treatment includes a short-acting antihistamine, self-injected intramuscular epinephrine, a beta-agonist inhaler with a spacer device, and — in Europe, although not routinely in the United States — oral corticosteroids. The child and his parents and caregivers should be educated in the use of these medications and should keep them readily available. He should wear a medical-alert bracelet detailing his food allergies. This bracelet should state that he carries epinephrine.

Involvement of a dietitian is warranted to assess the patient's nutritional status and to provide advice on foods that should be avoided and dietary supplements as needed. A history of egg allergy is not a contraindication to the MMR vaccine, but skin testing is recommended before administration of the influenza vaccine.

Children with a known food allergy should be routinely evaluated for other food allergies, with particular testing according to the patient's geographic location, since typical allergies vary among

countries. Children should also be tested for sensitivity to inhalant allergens in order to minimize the risks of allergic reactions and asthma and other associated atopic disorders. Detailed strategies for the management of eczema,[53] allergic rhinitis,[54] and asthma[55] are described elsewhere. Once adequate symptom control has been achieved, annual follow-up is recommended to assess children both for resolution of the egg allergy and for the emergence of coexisting allergic disorders.

Resources for patients with egg allergies include the American Academy of Allergy Asthma and Immunology (www.aaaai.org), the Food Allergy and Anaphylaxis Network (www.foodallergy.org), and the Anaphylaxis Campaign (www.anaphylaxis.org.uk).

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An audio version of this article is available at www.nejm.org.

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