The Truth Behind *Allergies*

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While many people believe they may be allergic to specific foods, the term allergy tends to be used too loosely. Adverse reactions to foods may be true immunologic reactions, but most reactions are non-immunologic, due to various forms of food intolerance. A proportion of the population will experience true immunologic reactions to specific foods. The immunologic mechanisms may give rise to either immunoglobin E (IgE) mediated manifestations or non-IgE mediated immunologic disease. Examples of the former include anaphylaxis, urticaria and angioedema, and oral allergy syndrome. Specific forms of non-IgE mediated food-induced disease include dermatitis herpetiformis and protein-induced enterocolitis. Some conditions, such as atopic dermatitis and eosinophilic gastroenteritis, are the results of a combination of both IgE-mediated and non-IgE mediated immunologic mechanisms.

Who's most at risk?

True food allergy is more common in infants and children, with a prevalence of 6% to 8%.[1,2] The prevalence decreases with age (1% to 2% of adults are affected).

Eight specific foods account for the preponderance of food allergies in the North American population. These include peanut, tree nuts, fish, shellfish, milk, egg, wheat, and soy and cow's milk. Sesame seed is assuming an increased importance in North America as a major cause of severe reactions.

Ryan's illness

Ryan, 35, presented with a life-threatening allergic reaction following a meal of sushi and sashimi. Part way through his meal, Ryan developed a feeling of warmth and itching in his palms, axillae, and groin. He then developed generalized hives, periorbital edema, progressive throat constriction with dysphagia, hoarse voice, and inspiratory stridor. He became dizzy and lightheaded, and passed out for about three minutes. He was noted to be hypotensive by the paramedics before administration of epinephrine. Manifestations of anaphylaxis gradually resolved with treatment.

Afterwards, he recalled having eaten crab meat shortly before the onset of symptoms. Prick skin tests with commercial and freshly prepared extracts of crab were non-reactive. A capacity radioallergosorbent (Cap-RAST) test for specific immunoglobin E antibody to crab was negative. However, a skin test and supervised graded oral challenge with surimi (Alaskan pollock) were positive. Alaskan pollock is often used as an inexpensive substitute for crab meat.

While genetic susceptibility clearly predisposes to food allergies, societal eating patterns are an important determinant in the prevalence of food allergy. In North America, approximately 2.5% of infants have true allergies to cow's milk, and about 1.1% of the general population is allergic to peanuts and tree nuts.

The diminishing prevalence of food allergies with age suggests some food allergies are "outgrown." About 85% of food-allergic individuals will, in fact, gradually outgrow their allergies to cow's milk, egg, wheat, and soy by about three years of age. Non-IgE-mediated forms of gastrointestinal immunologic disease typically resolve by about three years of age. However, allergy to peanuts, tree nuts, and seafood typically persists for a lifetime.

Diagnosis of food allergy

A detailed history will often yield clues as to the specific food trigger responsible for the allergic manifestations. The nature of the acute reaction, manifestations, rate of onset and duration, will point to either an IgE-mediated reaction or a non-IgE-mediated mechanism. Occasionally, food diaries are required to better establish the cause of specific reactions, by demonstrating a pattern of foods ingested before the onset of typical symptoms. A knowledge of both the specific food trigger and the type of immunologic mechanism involved is essential for further investigation and management. IgE-mediated reactions to foods may be confirmed by means of prick skin testing or in vitro RAST testing. However, neither of these methods will be informative in non-IgE-mediated forms of food intolerance. In these latter cases, biopsy of the gut or skin may be required. Elimination of the suspect food or, alternatively, a restricted (so-called oligoantigenic) diet may be helpful in certain individuals. Confirmatory oral challenging, either open or blinded, may be required for unequivocal confirmation of a suspect food trigger.

Elimination of the offending food is currently the only accepted approach to management of food allergy. If the patient has a potential for life-threatening reactions with accidental exposure to a food trigger, they should be trained to use an epinephrine autoinjector and encouraged to carry one at all times. Medical identification bracelets should be recommended.

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What is food-induced anaphylaxis?

Multisystem allergic reactions to foods are potentially life-threatening. The onset may be rapid (within moments of ingestion) or manifestations may be delayed by as much as one to two hours. While any food is capable of causing life-threatening manifesta-

Table 1

Reasons food allergy fatalities have doubled over the past five years

- Denial of the potential severity of food allergy (particularly prevalent amongst teenagers)
- The presence of asthma (especially when poorly controlled)
- Delayed administration of epinephrine
- Prior history of severe reactions to foods

tions in susceptible individuals, a few foods are responsible for the majority of anaphylactic fatalities to foods. These include peanuts, tree nuts, and seafood.

Some individuals may experience anaphylactic reactions to specific foods only when they exercise within two to six hours of ingesting a specific food. Food-dependent, exercise-induced anaphylaxis is most commonly associated with allergy to wheat, celery, chicken, peanuts, and shellfish.

Over the past five years, fatalities due to food allergies have doubled. A number of reasons have been identified (Table 1).

Most individuals experiencing food-induced anaphylaxis will have cutaneous manifestations, such as hives or angioedema. However, those individuals destined to have the most severe or potentially fatal reactions seldom have any cutaneous manifestations at all. While both patients and physicians often rely on the presence of urticaria and angioedema to make the diagnosis of food allergy, the absence of typical cutaneous manifestations makes diagnosis harder, and actually portends more severe reactions.

What are the patterns of anaphylaxis?

Food-induced anaphylactic reactions may follow specific patterns. Most reactions are uniphasic with rapid intensification of symptoms followed by gradual resolution, either spontaneously or with treatment. About 15% to 20% of anaphylactic reactions may be biphasic with an immediate phase which resolves, followed by a recrudescence of symptoms four to eight hours later. The second phase of this reaction may be more severe than the early phase. Without adequate warning of the potential for a biphasic reaction, patients may be discharged from an emergency department when their initial symptoms have resolved, only to be confronted by a more severe reaction after their return home.

Individuals rarely experience a very severe form of anaphylaxis (known as a protracted anaphylactic reaction). Protracted reactions are invariably life-threatening and may require cardiopulmonary support for as long as three weeks.

What is oral allergy syndrome?

In contrast to anaphylaxis, oral allergy syndrome tends to be mild and localized. Whereas other forms of food allergy arise from primary sensitization to a specific food, in the case of oral allergy syndrome, the primary sensitization is to plant pollens, such as birch or ragweed. Foods are immunologically related to the corresponding pollens that give rise to symptoms due to the presence of cross-reactive proteins in the foods. Symptoms are typically restricted to the oropharynx, with itching and occasionally mild swelling of the lips. The cross-reactive proteins in the foods are heat labile. Heating, cooking, or microwaving typically denatures the offending proteins in the foods causing oral allergy syndrome. For this reason, fresh fruits and vegetables are allergenic, whereas cooked or microwaved counterparts are well-tolerated. Management is either avoidance, cooking, or briefly microwaving of the offending food.

Reasons for allergy referral

Referral to an allergist with expertise in investigation and management of food allergy may be helpful in identification of the causative food

trigger, institution of an elimination diet, education on strategies for food avoidance, development of an action plan in the event of an acute reaction following accidental exposure, and for prevention of other allergies.

What about the patient with urticaria and angioedema?

Urticaria and angioedema are typically subdivided into acute forms which last for hours or days, but generally less than six weeks, and chronic urticaria which recurs daily for more than six weeks.

Urticaria and angioedema are common manifestations of allergic disease with a cumulative lifetime prevalence of about 20%. All age groups are affected, although chronic urticaria is more commonly seen in young or middle-aged women.

Numerous triggers of urticaria and angioedema are known. Some triggers, however, are characteristically associated with acute, self-limited urticaria, whereas others more typically predispose to chronic urticaria. Foods, drugs, insect stings, and viral infections often give rise to hives. The hives may persist for a few hours or days. In contrast, collagen vascular diseases, neoplasms, physical urticarias, genetic types of urticaria and angioedema, and autoimmune forms of urticaria will typically cause hives which recur daily for weeks, months, or years.

Causes of chronic urticaria

Autoimmune urticaria is typically due to the presence of autoantibody against the high affinity IgE receptor on mast cells, or against IgE itself. These autoantibodies induce mast cell degranulation and histamine release, leading to the formation of hives. Like other autoimmune diseases, autoimmune urticaria is more common in women.[3]

Many genetic types of urticaria and angioedema have been characterized. Some of these manifest in conjunction with other abnormalities, such as urticaria with deafness and amyloidosis. Hereditary angioedema, or C1 esterase inhibitor deficiency, may be either familial or sporadic. The physical urticarias, including vibratory angioedema, aquagenic urticaria, delayed-type localized heat urticaria and delayed cold-induced urticaria, all show familial inheritance patterns.

Physical urticaria

A number of physical agents may produce recurring urticaria in predisposed individuals. These physical factors include cold (*e.g.*, cold-urticaria, cold-induced cholinergic urticaria, systemic cold urticaria), heat (*e.g.*, cholinergic urticaria), pressure (*e.g.*, immediate-pressure urticaria, delayed-pressure urticaria, dermographism), and solar urticaria (*e.g.*, idiopathic, IgE-related, and associated with protoporphyria).

Frequently Asked Questions

1. What is the typical response to allergen immunotherapy?

It is estimated that 80% to 85% of patients show a good therapeutic response.

2. Of the patients who have a reaction to immunotherapy, what proportion will have a biphasic reaction?

In the neighbourhood of 15% to 20%. This means that patients should be observed for four to six hours following a systemic reaction, and discharged with an epinephrine autoinjector.

3. Do allergic reactions to foods get progressively worse with exposure?

About one-third of reactions will worsen upon re-exposure.

4. Is it true that patients with allergy to radiocontrast agents will also be allergic to seafood?

The premise behind this falsehood is that radiocontrast agents contain iodine (as do saltwater fish). This type of cross-reactivity has not been seen in clinical practice.

5. What is the accuracy of skin tests for food allergies?

Skin tests are highly reliable at ruling out food allergies. In contrast, positive result skin tests are not nearly as accurate on their own, but must be interpreted in the context of the patient's ability (or inability) to tolerate a specific food.

Urticarial vasculitis

The lesions of urticarial vasculitis are atypical, as compared to other forms of urticaria. Individual lesions typically last for days rather than hours. The individual lesions tend to sting or burn rather than itch, and resolution of individual lesions leaves residual "bruising" or areas of atrophy. Urticarial vasculitis may be associated with constitutional symptoms and abnormal laboratory investigations, including positive antinuclear antibody, elevated erythrocyte sedimentation rate, and abnormalities on urinalysis.

What is the management?

Efforts should be made to identify causative triggers in order to minimize exposures. Therapy with non-sedating antihistamines should be initiated. This may require a high dose of antihistamine for control of symptoms. Hives refractory to antihistamines may require addition of second or third-line agents, including anti-leprosy drugs, anti-malarial drugs, and corticosteroids. Typically, topical steroid agents are not effective. If systemic steroids are to be used, alternate day protocols are preferred to daily dosing.

Allergen immunotherapy

Currently, allergen immunotherapy is the only modality available by which to modulate the natural history of allergic disease. Avoidance measures should be implemented to the extent possible to minimize ongoing exposures. Pharmacotherapy for management of allergic rhinoconjunctivitis is often very helpful. However, in those situations in which pharmacotherapy is either not well-tolerated or provides suboptimal relief, allergen immunotherapy will prove to be very helpful. However, immunotherapy may be associated with systemic reactions which can potentially be life-threatening or fatal. Patients should be made aware of the potential, local, and systemic complications of allergen immunotherapy. Certain risk factors

are recognized, which predispose to systemic reactions, and efforts should be made to modify these risk factors so as to minimize attendant risk.

Large local reactions

Local reactions are commonplace during the course of immunotherapy. These manifest with redness, induration, discomfort, and heat at the injection site. Pretreatment of the patient with non-sedating antihistamines one or two hours before receiving their immunotherapy injection will minimize the size of the local reaction. Cold compresses on the injection site will also help to alleviate discomfort.

Occasionally, the immunotherapy dose will need to be altered, or repeated injections of the same dose may be required before dose escalation resumes.

Systemic reactions

Some notable patterns have been documented in studies of fatalities associated with immunotherapy. Individuals with a high degree of allergen sensitivity are prone to experiencing systemic reactions. This is particularly true in those individuals who receive injections during the season when their allergy sensitivity is heightened.

Symptomatic asthma is a clear risk factor predisposing to systemic reactions. Individuals with asthma should first be stabilized before immunotherapy is initiated. The degree of asthma control should be ascertained before allergy injections are given.

Over the course of time, allergens will degrade by enzymatic and non-enzymatic mechanisms leading to loss of potency. When new vials are used, they are considerably more potent than vials of extract which have been stored in the refrigerator for weeks or months. Appropriate dosing adjustments should be made when switching to a new vial.

Dosing errors remain a common cause of systemic reactions. Protocols should be developed in the office by which to double-check patient identifiers against extract labels, and to check extract dosages before administration.

Certain drugs, particularly beta blockers and angiotensin-converting enzyme (ACE) inhibitors, predispose to anaphylaxis. Beta blockers also interfere with the action of epinephrine, which is used to treat acute systemic reactions to immunotherapy. Patients planning to receive immunotherapy should be switched from beta blockers or ACE inhibitors to alternative agents. Therapy with beta blockers and ACE inhibitors should not be initiated in patients on immunotherapy regimens.[4,5]

Pregnancy and immunotherapy

Smooth muscle organs are targets of the action of mediators of anaphylaxis. In pregnancy, systemic reactions may cause uterine contractions, leading to a miscarriage.

Immunotherapy should not be initiated during pregnancy because of the risk of systemic reaction. However, immunotherapy may be continued at stable maintenance doses during pregnancy, except in those individuals who have experienced systemic reactions in the past.

Since systemic reactions are an ever-present risk in patients receiving allergen immunotherapy, it is important to have appropriate resuscitative equipment and medications on hand in medical offices and clinics that administer allergen immunotherapy. CME

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Take-ho messag

- True food allergy is more common in infants and children; its prevalence decreases with age.
- Eight specific foods account for the preponderance of food allergies in North America (peanut, tree nuts, fish, shellfish, milk, egg, wheat, and soy and cow's milk). Sesame seed is assuming an increased importance in North America as a major cause of severe reactions.
- Some individuals may experience anaphylactic reactions to specific foods only when they exercise within two to six hours of ingesting the food.

t Readings

1. National Institute of Nutrition: *www.nin.ca/public_html/Consumer/food_allergies.html*
2. The Lung Association: *www.lung.ca/asthma/nutrition/intolerance.html*

www.stacommunications.com

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